2 Macronutrient Deprivation
Biological Mechanisms and Effects on Early Neurodevelopment

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CONTENTS

2.1 INTRODUCTION

Macronutrient deficiency during the prenatal and early postnatal period is related to poorer cognitive and motor development in both animal models and humans, and these effects can last through adolescence and adulthood. Overall, children and adolescents who suffer severe malnutrition in early life demonstrate IQ deficits and poorer school performance compared to individuals who are not malnourished, especially for those experiencing chronic life stress (Grantham-McGregor 1995). Supplementation trials generally indicate improvements in outcomes depending on the timing of the intervention; specifically, prenatal and early postnatal (aged 0–3 years) interventions have the

biggest effects (Christian et al. 2010, 2011; Cusick & Georgieff 2012; Gillespie & Allen 2002). The timing of macronutrient deprivation and subsequent outcomes is in line with the literature on brain development such that many of the effects of macronutrient deprivation in early life parallel the brain structures and circuits rapidly developing during this time period. These findings will be reviewed to understand the specific impact of macronutrient deprivation in the context of early brain development.

The focus of this chapter is to outline the neurodevelopmental effects of pre- and postnatal macronutrient deprivation and biological mechanisms of action, utilizing evidence from preclinical models, infants with intrauterine growth restriction (IUGR), and young children experiencing growth stunting. Supplementation trials will be reviewed to understand timing effects and potential reversibility of deficits due to nutrient deprivation. These findings will be compared and contrasted with other at-risk groups to understand macronutrient effects in groups experiencing high levels of stress.

2.2 BIOLOGICAL MECHANISMS OF MACRONUTRIENT DEPRIVATION

The macronutrients include the two major sources of energy, fat and carbohydrates, and protein. They constitute the major nutritional building blocks which provide the foundation for structure and function during brain development. Reduced availability of these substrates results in changes in brain development that range from profound to subtle and from global to highly specific. Much is known about macronutrient requirements for the developing brain through careful experiments across multiple levels of evidence from cell cultures to whole animals. These experiments are typically developmentally sensitive with respect to approximating human brain development in order to provide biologic plausibility to observations made in human studies (discussed in the following).

2.2.1 Protein

Although the brain has a high fat and water content, amino acids are the building blocks for neuronal architecture, neurotransmitters, and growth factors. Ultimately, much of brain performance is related to neuronal complexity (e.g. dendritic fields in hippocampal area CA1) which relies heavily on appropriate amounts of amino acid substrates, neurotransmitter stimulation within developing circuits, and adequate amounts of cellular energy. Several interacting signalling cascades regulate critical aspects of the neuronal cellular development, for example, neurite extension and retraction, and actin polymerization, by sensing the extra- and intracellular availability of critical metabolites including amino acids. Foremost among these is the mammalian target of rapamycin (mTOR) pathway which senses various availabilities of amino acids, growth factors, iron, oxygen, and energy and, through a complex feedback and feedforward system of kinase-driven reactions, regulates actin polymerization, protein translation rates, cell size, and autophagy (Fretham et al. 2011; Wullschleger et al. 2006). Amino acids regulate the pathway through multiple pathways directly affecting Rheb and mTOR complex 1 (mTORC1) expression and

indirectly through regulating the synthesis of growth factors such as insulin-like growth factor (IGF-I) that signal through the PI3K subpathway (Jewell et al. 2015; Wullschleger et al. 2006; Zheng et al. 2014). mTOR also plays an important role in regulating amino acid carriers in the placenta, thus ensuring the appropriate substrate for protein synthesis in the fetal brain (Larque et al. 2013). Growth factors are small-molecular-weight proteins which are necessary for converting a nutritional substrate into growth (via pathways such as mTOR). Without growth factors, such as IGF-I, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell–derived neurotrophic factor (GDNF), neuronal growth is restricted, the dendritic tree is left simplified, and the neuronal performance is compromised. Fetal macronutrient malnutrition reduces IGF-1 expression (Nishijima 1986), which results in a reduction in regional brain volumes (Lee et al. 1999).

The effect of protein restriction has been well studied in multiple animal models including rodents and non-human primates. The findings at the molecular, cellular, and structural level are remarkably consistent and generally reflect the timing, dose, and duration of the deprivation (Dobbing & Sands 1979; Fuglestad et al. 2008; Kretchmer et al. 1996). Effects are evident not only in neurons but also in supporting cells, including oligodendrocytes, microglia, and astrocytes. The brain has a particularly high need for protein during two major phases of its development: from conception through 3 years of postnatal age when the majority of brain neurogenesis and differentiation takes place and then again in the teenage years when a great deal of remodelling and refinement take place. These two epochs in human development are characterized by the highest dietary protein requirements on a per weight basis.

The consequences of protein malnutrition to the brain include reduced DNA, RNA, and protein content and reduced mRNA for neuronal and glial proteins which provide scaffolding for the fatty acids of myelin (Morgane et al. 2002; Schober et al. 2009). The reduction in myelin is in part mediated through oxidative stress–mediated upregulation of brain morphogenetic protein-4 (BMP-4) expression (Reid et al. 2012). IUGR reduces neuronal cell numbers in the hippocampus and cerebellum accompanied by retarded dendritic and axonal growth (Mallard et al. 2000). mRNA expression for growth factors is also reduced, resulting in lower concentrations of IGF-I and BDNF (Dieni & Rees 2005; Lee et al. 1999). At the structural level, IUGR results in a reduction of dendritic elongation, simplification of the dendritic arbor, and altered synaptic spine density in the hippocampus, which likely has negative effects on learning and memory function (Dieni & Rees 2003). The synthesis of neurotransmitters and their receptors (e.g. glutamate, gamma-aminobutyric acid [GABA], monoaminergic, cholinergic) is compromised (Schober et al. 2009; Wiggins et al. 1984). The combined structural and neurochemical abnormalities likely underlie the brain's compromised electrical potential (Pinto et al. 1981). Overall brain weight and volume are reduced, most likely reflecting both reduced cell number and complexity. These molecular, cellular, electrophysiologic, and anatomic changes manifest as abnormal behaviours, the specificity of which depends on which brain circuits were most rapidly developing and had the highest requirements at the time of the insult. For example, protein malnutrition during late gestation and early postnatal life compromises the hippocampus, an area of the brain that

subserves recognition and spatial memory. Abnormalities in spatial memory induced by early life protein malnutrition extend into adulthood and support the concept of a 'critical period' for protein with respect to hippocampal development (see Georgieff et al. 2015 for a discussion of critical periods and nutrition).

2.2.2 Energy

Energy can be derived from any of the macronutrients: carbohydrates, fats, or amino acids. The developing human brain has the highest energy metabolism of any mammal at any time of life (Kuzawa 1998). Sixty percent of the human neonate's total body oxygen consumption occurs in the brain. This figure compares to 20% in the adult human, 10% in the neonatal sheep, and 2% in the adult sheep and rodent (Kuzawa 1998). This enormous energy 'sink' reflects the high demands of rapid neuronal and glial growth and development in our species. Thus, the human brain is highly dependent on a constant source of energy, and, while it highly prefers glucose as a substrate, it has adapted to utilize other energy sources including lactate, amino acids, and ketone bodies derived from fat (Erecinska et al. 2004; Prins 2011; Rao et al. 2010). During gestation, carbohydrate delivery is facilitated from maternal plasma to the fetus by the GLUT transporter and facilitative diffusion (for a review, see Hay 1994). Transport from the fetus' or infant's plasma across the blood–brain barrier is achieved by GLUT1 and 3 (Khan et al. 1999).

The peculiarly high energy demand of the human brain makes modelling of the effects of substrate deprivation (e.g. hypoglycaemia) in animal models quite difficult (Hay et al. 2009). Nevertheless, the effects of early life hypoglycaemia on the developing brain are striking. The cingulate and occipital regions of the cortex, the hippocampus, and the striatum are vulnerable during the neonatal period, while more extensive cortical injury is seen with postnatal hypoglycaemia (Burns et al. 2008; Ennis et al. 2008; Yamada et al. 2004). Early life hypoglycaemia in rats increases fear-related behaviour and alters stress reactivity that persists into adulthood (Moore et al. 2010). Early life hypoglycaemia leads to neuronal death and cell injury through glutamate hyperexcitation and activation of A1 adenosine receptors that promote excessive calcium influx (Turner et al. 2004). Cholinergic and GABAergic neurotransmitter systems are also affected by neonatal hypoglycaemia, as evidenced by a reduction in muscarinic receptors and reduced M1, M2, and M3 receptor gene expression and decreased GABA receptor gene expression in the hippocampus of rats following neonatal hypoglycaemia (Anju & Paulose 2015; Sherin et al. 2012). In cell culture, hypoglycaemia reduces oligodendrocyte precursor cell proliferation, maturation, and migration, while in cerebellar slice culture, hypomyelination occurs. These findings are consistent with a hypomyelination effect (Yan & Rivkees 2006). Thus, neurons are not the only brain cells at risk for the loss of this energy substrate. Ultimately, hypoglycaemia leads to apoptosis, cell loss, and abnormal dendritic structure in vulnerable brain regions. The vulnerability of brain regions is largely dictated by their relative metabolic rates at the time of the insult (Ennis et al. 2011).

Energy can also be derived from fat and utilized by the brain through ketone production, but this process is usually reserved for the neonatal brain in extreme energy crises, for example, hypoglycaemia and hypoxaemia (Ennis et al. 2011; Prins 2008).

Under homeostatic conditions, certain fatty acids are transported from the mother to fetus by direct transport mechanisms. In addition, lipids can also be derived from maternal lipoproteins which are metabolized by the placenta and released as fatty acids into the fetal plasma (for a review, see Hay 1994).

The neurodevelopmental consequences of energy restriction are well described in rodent and monkey models (Schober et al. 2009; Xie et al. 2013). It is useful to consider models of broad profile fatty acid deprivation, as would be seen in generalized malnutrition in humans, and of specific essential fatty acids. The literature on neurodevelopmental effects of deficiency of 'fish oils' is well described and covered in Chapter 3.

The brain needs fats to generate myelin and cell membranes, including synaptosomes. Fatty acid composition of the latter affects their ability to merge with the external presynaptic cell membrane to release neurotransmitters (reviewed in Georgieff & Innis 2005; Uauy & Dangour 2006). Thus, fats play a role in synaptic efficacy beyond myelin's effect on increasing the speed of processing. Fatty acid deficiencies reduce the brain's speed of processing, render neurons more susceptible to membrane disruption and cell death, and profoundly affect cognitive behaviours such as learning and memory (Yehuda et al. 1998, 2005).

2.2.3 Neurodevelopmental Consequences of Intrauterine Growth Restriction in Animal Models

As noted in the following section, human populations rarely have pure deficiencies of single macronutrients. Instead, a combination of protein energy malnutrition with accompanying micronutrient deficiencies is often seen, particularly in the context of intrauterine growth restriction. Multiple models of IUGR exist. IUGR can be induced by food deprivation, protein deprivation, energy deprivation, or restriction of maternal–fetal blood flow. The latter can be accomplished in multiple ways, including via surgical ligation of the uterine arteries, administration of vasoconstrictive chemicals, or increasing maternal body temperature. IUGR has been induced in rodents, sheep, and non-human primates. Overall, the anthropometric phenotype of a small-for-gestational-age (SGA) newborn with loss of muscle and fat mass along signals macronutrient malnutrition. The presence of microcephaly (or low brain weight/volume at necropsy) indicates severe brain involvement, although it must be noted that the lack of microcephaly does not necessarily indicate brain sparing at the microstructural level.

Models of IUGR have elucidated fascinating mechanisms of altered brain form and function including epigenetic modifications of synaptic plasticity genes (Caprau et al. 2012; Fung et al. 2012). The latter findings may be important for understanding the long-term brain/behaviour consequences of early life nutrient deficiency in spite of adequate postnatal growth (Pylipow et al. 2009). It is certainly possible that the long-term behavioural abnormalities following IUGR in humans are a function of abnormal construction of the brain during its critical period and that no amount of postnatal rehabilitation will completely reverse the consequences. An alternative, but not mutually exclusive, possibility is that crucial regulatory set points for genes controlling energy metabolism may be epigenetically modified as the nutrient-restricted brain attempts to maintain a thrifty phenotype (Hanson & Gluckman 2014).

The resultant downregulation of energy utilization may promote brain cell survival but result in more simple cells with less capacity (and less demand on the expected limited resources). The developmental origins of adult health and disease (DOHaD) posit that the fetus and young organism 'make the metabolic assumption' that nutrient availability across the lifespan is likely to be similar to their present condition and set their metabolism accordingly (Gluckman & Hanson 2004). One mechanism to accomplish this is to modify the expression of genes that control metabolic rate with the positive and negative consequences noted earlier. Recent studies demonstrating that IUGR in the rodent model alters the chromatin structure of the hippocampal IGF-1 receptor gene and alters hippocampal neuroprogenitors strongly not only support this possibility but also beg the question whether therapies (e.g. methyl diets; HDAC modifiers) which can alter the epigenetic landscape can rescue the adult brain/behaviour phenotype if proper postnatal macronutrient substrates are provided (Caprau et al. 2012; Fung et al. 2012).

2.3 HUMAN STUDIES

2.3.1 Protein–Energy Malnutrition

Fetal protein–energy malnutrition, which is often the result of maternal malnutrition or hypertension, can result in growth retardation of the fetus (Low & Galbraith 1974). In postnatal life, preterm infants may become malnourished if they are fluid restricted, thereby limiting their nutrients. Protein energy is necessary for global brain cell proliferation and differentiation, synaptogenesis in the cortex, and growth factor synthesis in the hippocampus (Georgieff 2007). Protein intake is generally most important during gestation for global brain development and myelination, as well as for the specific development of the hippocampus, striatum, and cerebellum (Georgieff 2007). Another important sensitive period for protein consumption is 4–12 postnatal months, which is especially important for prefrontal cortex development and myelination (Georgieff 2007). Growth restriction during these periods can result in the failure of the head to grow properly, which is linked to poorer developmental outcomes (Strauss & Dietz 1998; Winer & Tejani 1994). Even when head growth is not severely stunted, around 15% of infants with IUGR have mild cognitive abnormalities (Spinello et al. 1993), and memory systems, especially explicit recognition and working memory, appear especially vulnerable to the effects of macronutrient deprivation during fetal development (Georgieff 2007; Gottlieb et al. 1998; Pollitt and Gorman 1994). Protein–energy malnutrition also has significant effects on motor development which can be detected in infancy (Georgieff 2007).

2.3.2 Intrauterine Growth Restriction

IUGR involves limitations on fetal nutrition often due to poor placental nutrient transfer, poor maternal nutrition, or both at a time when the brain is developing rapidly. The physical manifestations (e.g. low weight for age, low length for age, loss of somatic muscle and fat stores) are due to protein and energy malnutrition. Nevertheless, the syndrome represents a general restriction of nutrients when there is poor placental

transport, and thus, micronutrient malnutrition also exists. For example, 50% of infants with IUGR are iron deficient (Chockalingam et al. 1987). Micronutrient malnutrition early in life also negatively affects brain development (see other chapters in this volume). IUGR has frequently been studied in developing countries where maternal undernutrition is more common, with approximately 16% of births being low birthweight (most are IUGR) and up to 27% in South Asia (Walker et al. 2011). Studies of IUGR infants demonstrate that the effects of this early nutritional deprivation can be observed from infancy to adulthood (Strauss 2000). As early as 12 months, IUGR infants in Brazil demonstrate lower developmental quotients than infants of normal birthweight (Grantham-McGregor et al. 1998), and this same result is observed at age 2 and 3 years for IUGR infants in Guatemala (Gorman & Pollitt 1992). Further, Jamaican infants with IUGR showed delays in problem-solving at 7 months (Gardner et al. 2003) and lower developmental quotients at both 15 and 24 months compared to normal birthweight infants (Walker et al. 2004). One study of very-low-birthweight (VLBW) infants reported that being SGA alone was not associated with lower developmental scores compared with appropriate-for-gestational-age (AGA) infants (Latal-Hajnal et al. 2003). Instead, growth by age 2 years was predictive of motor and physical development. SGA children who remained below <10th percentile in weight showed poorer psychomotor development than SGA children who showed greater catch-up growth (Latal-Hajnal et al. 2003). In contrast, AGA children who fell below the 10th percentile at age 2 showed lower mental development scores than AGA children who remained above the 10th percentile (Latal-Hajnal et al. 2003). As a result, it appears that catch-up growth may be more important for determining neurodevelopment than gestational size for age (discussed further in Section 2.3.4. However, Pongcharoen and colleagues (2012) reported that linear growth at birth and in the first year has stronger associations with IQ than weight and growth between ages 1 and 9 had no effect on IQ.

IUGR appears to be associated with persistent deficits in weight and height catch-up growth in childhood, with approximately 0.5 standard deviation (SD) lower weight-for-age and height-for-age z-scores than children born without IUGR (Strauss & Dietz 1998). In addition, children with IUGR scored lower on measures of IQ and motor development. However, within sibling pairs discordant for IUGR, there were no differences on these measures (Strauss & Dietz 1998). There were differences, however, when siblings with IUGR had significant deficits in head circumference (Strauss & Dietz 1998). As a result, it appears that children with IUGR demonstrate the greatest impairment when head growth is reduced.

Infants born with low birthweight have less positive affect, are less active, and vocalize less than normal birthweight infants (Gardner et al. 2003; Grantham-McGregor et al. 1998). Low-birthweight infants are more likely to develop behavioural problems reported by both teachers and parents during adolescence than those born with a normal weight (Liu et al. 2001). Difficulties with emotion and behaviour may extend into adulthood. Adults who were conceived at the height of the Dutch Hunger Winter (1944–1945) and were thus exposed to severe malnutrition early in gestation showed a twofold greater risk of schizophrenia than those who were not exposed to famine at this early period (Susser et al. 1996). Males who experienced malnutrition during the second trimester of fetal development due to the Dutch

Hunger Winter showed a significantly increased risk of affective psychosis (Brown et al. 1995). These cognitive and affective changes are likely related to the neural circuitry developing at this specific time period, including the patterning of neurons in the embryonic period and the formation of neural structures during the fetal period.

However, evidence for long-term effects of IUGR remains mixed. For example, there were no IQ or behavioural differences reported in 6-year-old Jamaicans (Walker et al. 2010), 8-year old Brazilians (Emond et al. 2006), or 12-year-old South Africans who were with IUGR and born at a normal size (Sabet et al. 2009). In mothers from Jamaica who were generally nourished, weight before pregnancy and the amount gained during pregnancy had no association with their child's cognitive outcomes at age 7 (Walker et al. 2007). This mixed result may follow evidence from the moderately preterm infant literature that early outcomes (before age 2) are associated with prenatal biological insults, while, later into childhood and adolescence, other factors such as parenting, socio-economic status (SES), and education may be more related to long-term outcomes.

In developed countries, adolescents who had IUGR were more likely to be recommended with special education and less likely to be in the top 15% of the class than adolescents who were of normal birthweight (Strauss 2000). Adults who had IUGR had lower weekly pay, were less likely to have professional or managerial careers, and remained shorter during adulthood (Strauss 2000). As most studies in individuals with IUGR do not extend past infancy or early childhood, future longitudinal studies should follow these individuals' development throughout adulthood, with a special focus on specific neurodevelopmental outcomes in this group. Longitudinal studies of interventions to increase birthweight in at-risk infants are also needed to understand long-term cognitive/socio-emotional effects of increasing birthweight beyond improving health at birth.

2.3.3 Postnatal Growth Stunting

Worldwide, growth stunting is present in approximately a quarter of children under 5 years of age (United Nations Children's Fund 2014). Stunting can be the result of severe undernutrition, infectious disease, psychosocial stress, or a combination of these factors, and severity and duration of stunting have been used as indices of the extent of nutritional and/or social deprivation. As with IUGR, stunting rarely represents pure protein or protein–energy malnutrition. The other causes of stunting carry their own independent risks to brain development. Nevertheless, a robust finding in the literature on macronutrient deprivation is that, controlling for socio-economic status, stunting in early childhood is associated with cognitive delays, poorer scholastic performance, less likelihood of enrollment in primary school, and an increased risk of school dropout (Beasley et al. 2000; Chang et al. 2002; Daniels & Adair 2004; Martorell et al. 1992; Mendez & Adair 1999; Walker et al. 2005). In Zimbabwean adolescents, height by age 6 was linked to school grades and age at enrollment in school (Alderman et al. 2006).

Children stunted at 24 months scored 10 points lower on an IQ assessment at age 9 than non-stunted children (Berkman et al. 2002). Children with stunted growth in the first 2 years had lower test scores at ages 8 and 11 years than non-stunted children,

and the effect was the largest for those who were the most stunted (Mendez & Adair 1999). There is evidence that the lower test scores in the stunted group are at least partially the result of delays in school enrollment, more absences, and repeating years of school in the stunted group (Mendez & Adair 1999). Additionally, children who were stunted at 24 months were more likely to drop out of grade school (Daniels & Adair 2004). Over time, the effect of early stunting appeared to decline, as differences between groups were stronger at age 8 than 11 (Mendez & Adair 1999). Overall, stunting that is 1 or more SD below the mean for height between the ages of 12 and 36 months is associated with 0.4–1.05 SD effect size on cognitive development (Grantham-McGregor et al. 2007), indicating that growth stunting may be used as an indicator of poor development or early risk. Duration of stunting may be particularly important for predicting cognitive outcomes, as children who were stunted between 6 and 18 months of age but then showed significant catch-up growth by 4.5–6 years did not differ in verbal and quantitative ability from never-stunted children (Crookston et al. 2010). However, children who were stunted at both time points showed significantly lower verbal and quantitative ability than children who were not stunted at either period (Crookston et al. 2010). The timing of linear growth may also be a key, as linear growth between birth and 1 year was significantly related to IQ at age 9, while growth from ages 1 to 9 was not related to IQ (Pongcharoen et al. 2012).

There has been less work examining the effects of growth stunting in young children, but current evidence from Zanzibar and Nepal suggests that children with greater height for age are more likely to be walking (Kariger et al. 2005; Siegel et al. 2005). Additionally, being stunted during infancy predicts age of walking (Cheung et al. 2001; Kuklina et al. 2004).

Although most research has focused on the cognitive outcomes for malnourished children, social and emotional functioning is also affected. Low weight for height or linear growth stunting in young children is related to less play, less positive effect, greater lethargy, and less likelihood of secure attachment compared to children without growth delay (Gardner et al. 1999; Graves 1978). These problems can translate into difficulties in school, including conduct issues, attention problems, and poorer quality relationships (Chang et al. 2002; Galler & Ramsey 1989, Richardson et al. 1972). A study of Jamaican adolescents demonstrated that stunting in childhood is related to poorer psychological functioning, including greater depression and anxiety symptoms, increased hyperactivity, and lower self-esteem (Walker et al. 2007). A group of stunted children who received psychosocial stimulation in childhood differed from the non-stunted group only in hyperactivity symptoms (Walker et al. 2007). These largely frontal lobe–mediated functions which are impacted by linear stunting are in line with structures developing in the postnatal brain, particularly connections between primary structures such as the hippocampus and striatum to the prefrontal cortex.

The effects of growth stunting can persist into adolescence and adulthood. In late adolescence, verbal, mathematical, cognitive, and general knowledge domains were all related to stunting at 36 months (Martorell et al. 1992). A recent approximation of adult income lost due to the effects of early stunting estimates a 22.2% reduction in adult income for stunted children not living in poverty and 30.1% for children stunted and in poverty (Grantham-McGregor et al. 2007). A study in the Philippines

that followed stunted children into early adulthood reported that those who were stunted early in life were less likely to have formal employment between ages 20 and 22 years (Carba et al. 2009). This evidence suggests that the effect of macronutrient deprivation and stunting on later development may be greater than the independent effect of poverty.

2.3.4 Role of Catch-Up Growth in Determining Neurodevelopment

Further research has indicated that the amount of growth after macronutrient deprivation in IUGR and stunted children may predict cognitive outcomes and motor development better than just being stunted at a certain time point. This finding falls in line with the principle of sensitive periods of brain development, in which the potential for growth early in life may improve developmental outcomes if it occurs before a certain time. The infant brain in these cases often exhibits a great deal of plasticity in response to environmental inputs, even after the insult of macronutrient deprivation. A study of IUGR infants in Guatemala demonstrated delayed development for infants between 6 and 24 months of age, with greater linear growth and weight gain in the first 24 months related to better developmental outcomes at 36 months (Kuklina et al. 2006). Additionally, growth was more closely related to motor than mental development (Kuklina et al. 2006). Birthweight unadjusted for gestational age has been linked to IQ at age 5 as well as grade achieved in high school (Martorell et al. 2010; Santos et al. 2008). Consistent with other studies of early growth, weight gain in the first 2 years is related to more positive school outcomes, but growth between 24 and 36 months of age was not related to developmental outcomes (Martorell et al. 2010; Pongchareon et al. 2012). A Taiwanese study demonstrated that at age 15, small deficits were present in overall academic achievement of adolescents who were IUGR (Wang et al. 2008). There is evidence that catch-up growth following IUGR is associated with differential cognitive outcomes in an inverted J-shaped pattern during middle childhood (Pylipow et al. 2009). Infants gaining the least amount of weight by 16 weeks (1200 g) had the lowest scores on cognitive tests at the age of 7 years (15.5 points lower than the score-maximizing amount of growth; Pylipow et al. 2009). On the other hand, the highest amount of weight gain was also related to lower cognitive scores (2.4 points lower than score-maximizing growth; Pylipow et al. 2009).

In general, early nutritional support and growth are critical factors in medical and neurobehavioural outcomes in premature infants. Stunted linear growth is common in VLBW preterm infants as well, and this linear growth failure is related to poorer scores on cognitive tests at 24 months corrected age even after controlling for increases in weight and head circumference (Ramel et al. 2012). Greater linear growth in VLBW infants has been associated with improvements in cognitive and motor development at 2 years corrected age as well as a decreased likelihood of developing cerebral palsy (Latal-Hajnal et al. 2003). Faster linear growth between term and 4 months corrected age in preterm low-birthweight infants decreases the odds of having an IQ lower than one standard deviation below the mean between 8 and 18 years (Belfort et al. 2013). Linear growth between birth and hospital discharge is also related to higher language scores at 24 months corrected age

(Ramel et al. 2012), and growth after discharge is associated with improvements in motor development for infants born before 33 weeks gestation (Belfort et al. 2011). In addition to gains in height, increased fat-free mass is related to better cognitive performance and faster neural processing (Pfister et al. 2013).

An analysis of 1366 extremely premature infants demonstrated that the amount of energy intake during the first week of life mediated the association between critical illness and adverse outcomes, with greater energy intake related to a greater number of positive outcomes, including faster growth, less likelihood of death, less late-onset sepsis, and more positive neurodevelopment (Ehrenkranz et al. 2011). Providing the macronutrients for healthy development in sick infants proves to be difficult because, compared to the term infant, feeding becomes more challenging, nutritional demand changes, and both inflammatory and stress responses induce catabolic states in the infant (Ramel et al. 2014). While these adaptations may help infants survive in the short-term, long-term growth and neurodevelopment may be put at risk, especially given research on the importance of feeding and growth for healthy neurodevelopment in early postnatal life.

There is also some evidence that birthweight and postnatal growth are not related to IQ or behaviour in preterm children, but in term children both birthweight and postnatal weight gain predict IQ between the ages of 4 and 7 years (Huang et al. 2012). This may be the result of an overwhelming number of risk factors in the preterm group that is minimizing the effect of growth during childhood. An increase of 1 unit (z-score) in birthweight was related to an IQ increase of 1.6 points, and a 1 unit increase (z-score) in postnatal weight gain predicted a 0.46 point increase in IQ (Huang et al. 2012). Likewise, weight for the age of 1 year was not predictive of cognitive functioning at age 7, but the weight change from 1 to 7 years of age was predictive of later cognition, suggesting that weight gain during childhood may be more predictive of cognitive functioning than poor growth in infancy (Cheung 2006). Another study that followed women from birth to adulthood reported that although birthweight did not predict educational achievement in adulthood, greater growth between birth and 2 years predicted higher achievement, while growth after 2 years was unrelated to achievement (Li et al. 2004). Growth also appears to mediate some of the effects of poverty on IQ, along with parental education and home stimulation (Hamadani et al. 2014). In addition, in this rural poverty sample in Bangladesh, growth in the first 2 years of life was more predictive of IQ at 64 months than growth after age 2 (Hamadani et al. 2014).

2.4 SUPPLEMENTATION STUDIES

Much of the literature on growth failure or macronutrient malnutrition and neurodevelopment are observational studies, which are subject to multiple known and unknown confounding variables. However, macronutrient supplementation interventions have consistently demonstrated more positive developmental outcomes for those in the intervention group (Walker et al. 2007). Food supplementation for at-risk pregnant women, infants, and young children has been shown to improve physical, motor, and cognitive development (Behrman et al. 2004; Gillespie & Allen 2002; Pollitt et al. 1993; Schroeder et al. 1995; Walker et al. 2007). Prenatal and

early postnatal interventions are more effective than interventions later on, and postnatal interventions are the most effective and of long-term if delivered during the first 2–3 years of life (Engle et al. 2007; Pollitt et al. 1993). Even during pregnancy, early supplementation may be better than later. A food supplementation study conducted in Bangladesh with undernourished pregnant women suggested that early supplementation (8–10 weeks gestation) is better for problem-solving in the infant at age 7 months than later supplementation (approximately 17 weeks gestation; Tofail et al. 2008). Importantly, food supplementation studies differ from macronutrient supplementation in that the former would include micronutrients, which also aid neurodevelopment.

Food supplementation aimed to improve nutritional status and promote growth has positive effects on cognitive development and motor development (Grantham-McGregor et al. 1991; Husaini et al. 1991; Pollitt & Schurch 2000; Pollitt et al. 1993), with effect sizes of between 6 and 13 developmental quotient points (Walker et al. 2007). The positive effects are likely due to macronutrient and micronutrient supplementation. Decreased behavioural distress and reductions in apathy have been reported for these interventions as well (Mora et al. 1979; Pollitt & Schurch 2000). Evidence is mixed for what domains macronutrient supplementation is most effective at improving. For example, a food supplementation study in Taiwan for pregnant women showed improvements in motor development of the infant at 8 months (Adair & Pollitt 1985). However, no improvements in intelligence were reported in this group at the age of 5 years (Adair & Pollitt 1985), so there may be differences by the age of assessment and domain of functioning. This could be due to the timing of supplementation in relation to the neural structures that are rapidly developing. For example, the striatum develops primarily prenatally and early in the postnatal period. However, IQ may be more influenced by myelination and neural connectivity across diffusely distributed systems, which largely occurs postnatally. Additionally, supplementing Colombian women in the third trimester and infants as old as 6 months showed no benefit on developmental levels between 6 months and 3 years of age (Waber et al. 1981). For socio-emotional and behavioural domains, children who had the largest supplement intake before age 2 showed the greatest behavioural effects between the ages of 6 and 8 years, including less anxiety and greater social interaction (Barrett et al. 1982). Although we see consistent cognitive benefits across studies, the presence of effects on behaviour is variable. However, it could be the case that trials that did not supplement during both the prenatal and early postnatal periods do not see the same effect on behaviour, which would suggest a sensitive period for certain behavioural effects. Thus, the most effective interventions should start as early as possible, particularly in the prenatal period, and supplementation in at-risk groups should aim for the prevention of macronutrient deprivation rather than only the treatment.

A comparison of two nutritional supplements given to mothers, infants, and young children in Guatemala was conducted to determine which was related to better cognitive outcomes (Pollitt et al. 1995). The first supplement, called Atole, contained 163 kcal and 11.5 g protein, and the second, named Fresco, contained 59 kcal and no protein. Both supplements were fortified with vitamins and minerals to ensure that any effects were not due to micronutrient deficiencies. Overall, findings indicated that supplementation that begins during pregnancy and continues

through the first 2 postnatal years has demonstrated both cognitive and emotional benefits into adulthood (Pollitt et al. 1993). In adolescence, those who received the Atole supplement showed faster information processing and performed better on cognitive tests, including both numeracy and verbal tests, than those who received Fresco (Pollitt et al. 1995). Further, in villages receiving the Atole supplement, the typical SES disparities in cognitive outcomes were eliminated (Pollitt et al. 1995). However, in villages receiving Fresco, the expected cognitive advantages of living in a high SES versus a low SES household were observed (Pollitt et al. 1995). Overall, this study suggests that greater macronutrient supplementation, specifically one that involves protein, provides cognitive benefits above the effect of micronutrient supplementation. In a follow-up of this study, individuals receiving the Atole intervention during the first 2 years of life performed better on tests of reading comprehension and cognitive functioning between 25 and 42 years than those who were supplemented later, even after accounting for schooling (Stein et al. 2008). Men who were supplemented with Atole during their first 3 years of life received higher wages as adults (Hoddinott et al. 2008). The increase in hourly wages was approximately 46% for men who were supplemented during the first 2 years of life (Hoddinott et al. 2008). Overall, this series of studies suggests that there are lasting effects of early macronutrient intake and that there may be an early period where macronutrient supplementation is most beneficial. Future studies are needed to examine whether supplementation for mothers before pregnancy further improves birth outcomes and overall functioning throughout childhood and into adulthood.

2.5 TIMING OF MACRONUTRIENT DEPRIVATION

Long-term benefits may be dependent on the timing, duration, and execution of the intervention. For example, a follow-up study of Indonesian children who received a 3-month supplementation between the ages of 6 and 60 months did not show significant differences on a number of cognitive assessments 8 years later compared to the non-supplemented group (Pollitt et al. 1997). However, when the group is restricted to those who received supplementation before 18 months of age, significant benefits were conferred in working memory (Pollitt et al. 1997). Thus, the lack of effects could be due to the specificity of intervention during later infancy rather than during the prenatal or early postnatal periods or to the short supplementation period (3 months). Another follow-up study of 17- and 18-year-olds who participated in a supplementation trial between ages 9 and 24 months showed short-term effects but no long-term effects of the intervention (Walker et al. 2005). All long-term effects on IQ and verbal skills were the result of a psychosocial stimulation intervention rather than supplementation (Walker et al. 2005). It is likely that differences in sensitive periods for nutritional versus psychosocial interventions play a role in later outcomes. For example, nutritional supplementation may be most effective if implemented during the prenatal or early postnatal period, while psychosocial interventions may be most effective during late infancy and early childhood. Thus, multi-faceted interventions must be designed to provide components of care when they will be the most beneficial (Wachs et al. 2014).

It must be noted that the brain is not a single, homogeneous organ. Indeed, its various regions and neural networks develop at different rates across different time periods, and as a result, there are unique growth trajectories and sensitive periods during which environmental influences, including nutrition, may have a particularly large effect (Johnson 2005; Kretchmer et al. 1996). Researchers must consider what brain regions are developing the most rapidly at the time of the insult, the nutritional requirements for that period of development, and what previous insults may have occurred that produce the current phenotype. Macronutrient deficiencies appear to be the most damaging when there is peak growth, and the brain needs nutrients for basic neural metabolic processes (Wachs et al. 2014). Supplementation during or before these rapid periods of brain development is often the most likely to produce large positive effects, and supplementation after these periods often results in failure to correct brain structure and function following earlier deficits. Further, neurodevelopmental outcomes may also differ at different ages and in different domains of functioning (e.g. cognitive, social, motor). Certain macronutrients may be particularly important for the development of particular cognitive outcomes at one period but more important for social development at another time period. Conversely, a number of macronutrient deficiencies likely have impacts on the same regions of the brain, making it difficult to determine the unique contribution of each nutrient. For example, the developing hippocampus needs protein energy, iron, and zinc in order to function properly. Thus, a multilayer combination of human, animal, and cellular models will be needed to understand specific effects of micro- and macronutrient deficiencies. Additionally, there may be differences in the effect sizes of macronutrient supplementation on developmental outcomes between groups of people living in different environments. For example, for those in the Guatemalan cohort who received the Atole supplement, the greatest benefits were derived by children who were in the lowest SES groups and those who achieved higher levels of education (Pollitt et al. 1993). As a result, there can be individual differences in macronutrient needs and later development. For supplementation interventions, the knowledge of macronutrient demands, timing of brain development, and individual differences in supplementation outcomes can be used in order to optimize intervention strategies for children.

2.6 ENVIRONMENTAL INFLUENCES ON COGNITIVE DEVELOPMENT

In addition to variability in timing of macronutrient deficiency and brain development, significant variation in early stressful experiences, both infectious and psychological, can occur such that individuals experiencing macronutrient deprivation also undergo additional significant stressors in both pre- and postnatal periods. An example of a group that may experience multiple independent stressors during the prenatal and early postnatal period includes infants born prematurely. Individuals who were born prematurely often show developmental delays in motor abilities, visual motor skills, executive functioning, greater ADHD symptoms, lower IQ, and poorer school achievement than individuals born at term (reviewed in Aylward 2005). In addition, many infants born prematurely experience IUGR (reviewed in

Section 2.3.2), which is an independent risk factor for a number of poorer neurodevelopmental outcomes. Premature infants who are of normal size for gestational age (termed 'macropremie') are still at higher risk for cerebral palsy, hypoxic–ischemic–inflammatory–associated disorders, intellectual disability, hyperactivity, and poorer school achievement in a number of subjects (Amiel-Tison et al. 2002; Huddy et al. 2001), indicating that macronutrient deficiencies are not solely responsible for neurodevelopmental outcomes. Even within infants born prematurely, there is a greater neurodevelopmental risk for infants who had lower weight at birth (Aylward 2005), suggesting that macronutrient effects still account for significant variation in developmental outcomes in this high-risk group. Thus, premature birth and IUGR may be separate 'hits' to development even though they often co-occur, and future research must elucidate the mechanisms between each of these hits and neurodevelopmental outcomes and examine what factors may prevent both premature birth and IUGR to promote optimal development.

Although poor nutrient delivery is often considered to be the primary cause of growth failure, a considerable body of research documents the impact that infection, psychosocial factors, and the environment have on growth. Chronic stress and resulting behaviours can influence metabolism by impacting both feeding behaviours and nutrient absorption (Wachs et al. 2014). A primary example of a group often affected by both psychosocial deprivation and undernutrition includes children living in or adopted from institutional (e.g. orphanage) care. Children often fail to get the nutrients needed to sustain growth or the stress of the institution leads to difficulties with nutrient absorption, causing growth failure even if enough sustenance is provided (Monk et al. 2013). There is also a substantial literature documenting the negative effects of psychosocial deprivation, as is experienced in institutions that often have a high caregiver-to-child ratio and high caregiver turnaround on later physical, cognitive, or socio-emotional development (reviewed in Doom and Gunnar 2016). Internationally adopted children with lower z-scores for head circumference, height, and weight are significantly more likely to have poorer motor development and more severe cognitive and language delays (Miller et al. 1995). Recent work has started to tease apart the impacts of nutrition and psychosocial deprivation on cognitive development and has reported independent effects of nutritional status and psychosocial deprivation (e.g. Doom et al. 2014, 2015). There is even evidence that psychosocial stimulation may play an equal or larger role relative to nutrition. Indeed, after 20 years of psychosocial stimulation study in Jamaica in growth-stunted children, those in the intervention group earned wages that were comparable to non-stunted individuals (Gertler et al. 2014). Psychosocial stimulation thus has independent impacts on the development that may ameliorate later outcomes, even in the context of malnutrition. More work is needed to address independent contributions of macronutrient and psychosocial deprivation on the development of children living in adverse environments to optimize care in institutions and post-adoption. These studies serve to remind that 'supply side' economics are only one side of the coin. Consideration should be given to how nutrients are utilized by the non-stressed growing individual versus the stressed or chronically infected individual. The latter condition results in the release of pro-inflammatory cytokines (which damage the brain themselves), suppression of growth factors, and subsequent repurposing of

macronutrient substrates (glucose, amino acids) for fight or flight responses. While highly necessary for survival, this repurposing is not consistent with an anabolic state and promotion of brain growth (Ramel et al. 2014).

Of course, nutritional factors are not the only determinants of neurodevelopmental outcomes. As environmental enrichment, such as living in a high-resource family, and having sensitive and responsive caregivers have been shown to support optimal cognitive development, it is possible that environmental or family factors may mask some of the effects of macronutrient deprivation. For example, living in an enriched environment with several factors that promote resilience may mitigate deficits in global development and memory. Thus, the environment of the individual must be considered when assessing recovery from macronutrient deprivation and determining what factors best promote cognitive and motor development after an early period of nutrient deprivation.

2.7 CONCLUSION

When considering many factors associated with nutrition and neurodevelopment, one might argue that macronutrient effects are instead due to co-occurring micronutrient deficiencies (e.g. iron or zinc). While most observational studies in humans do not assess all possible micronutrient deficiencies that may co-occur, preclinical studies are especially useful for determining specific effects of macronutrients. Preclinical studies allow researchers to control for micronutrient deficiencies and isolate macronutrient deprivation as the sole experimental factor different between groups, thus making an argument for the beneficial impact of macronutrient supplementation even in the absence of specific micronutrient supplementation. Thus, individuals implementing nutritional interventions in populations experiencing or at risk for prenatal and/or postnatal malnutrition should consider macronutrient supplementation, as macronutrient deficiencies are an independent risk factor for poorer developmental outcomes. With appropriate nutritional supplementation during optimal developmental periods, millions of individuals currently experiencing macronutrient deficiencies can become closer to fulfilling their developmental potential.

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