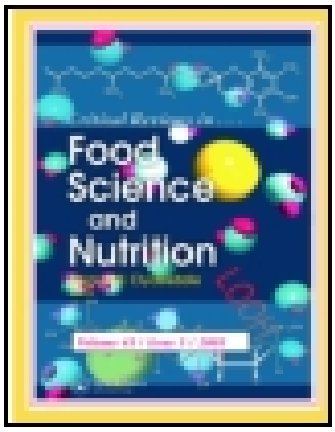

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Iodine Deficiency and the Brain: Effects and Mechanisms

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Iodine deficiency and the brain: effects and mechanisms

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Iodine is an essential micronutrient needed in human diets. As iodine is an integral component of thyroid hormone, it mediates the effects of thyroid hormone on brain development. Iodine deficiency is the most prevalent and preventable cause of mental impairment in the world. The exact mechanism through which iodine impacts the brain is unclear, but is generally thought to begin with genetic expression. Many brain structures and systems appear to be affected with iodine deficiency, including areas such as the hippocampus, microstructure such as myelin, and neurotransmitters. The clearest evidence comes from studies examining cognition in cases of iodine deprivation or interventions involving iodine supplementation. Nevertheless, there are many inconsistencies and gaps in the literature of iodine deficiency, especially over the lifespan. This paper summarises the literature on this topic, suggests a causal mechanism for iodineôs effect on the brain, and indicates areas for future research (e.g. using MRI and fMRI to examine how iodine supplementation facilitates cognitive functioning).

Iodine deficiency and the brain: effects and mechanisms

Iodine is a trace element, first discovered in 1811 (Zimmermann, 2008). It is an essential nutrient required in small quantities in the human diet. The amount of iodine in food is dependent on the levels in the environment from which the food is derived (World Health Organisation, 2007). Iodine is often leeched out of soil by rain and glaciation so that many parts of the world often contain little iodine in the soil. This results in low amounts of iodine in the diet and subsequent iodine deficiency in the population (Zimmermann, 2009). Iodine deficiency is one of the most common micronutrient deficiencies, yet is easy to prevent (World Health Organisation, 2007). It produces a wide range of symptoms that may be classified as iodine deficiency disorders (Hetzel, 1983), including hypothyroidism, hyperthyroidism, goitre, increased sensitivity of the thyroid to nuclear radiation, as well as mental impairment (World Health Organisation, 2007).

Iodine status can be monitored by determining urinary iodine concentration (UIC). UIC is a measure of the amount of iodine excreted in urine, and is an indirect index of dietary iodine intake. As urinary iodine is associated with large inter- and intra- individual variation (König et al., 2011), the median UIC is used to diagnose the iodine status of a population. A UIC of <20µg/L represents a severe iodine deficiency, 20-49µg/L moderate iodine deficiency, and 50-99µg/L represents a mild iodine deficiency. An adequate iodine status is defined by a median UIC between 100-299µg/L, and a value over 300µg/L is classified as excessive (World Health Organisation, 2007).

Iodine is converted by the thyroid gland into the thyroid hormones, thyroxine (T4) and triiodothyronine (T3). These are necessary for metabolism in almost all body tissues (Ahmed et al., 2008), but are especially important for brain development (Delange, 2001). It is well known that iodine deficiency can severely impair brain structure and subsequent function (Hetzel, 1983), and iodine deficiency is one of the most prevalent, preventable sources of intellectual disability in the world (World Health Organisation, 2007). What is unclear, however, are the mechanisms by which thyroid hormones influence brain development. The consequences of severe iodine deficiency (including cretinism, characterised by profound mental retardation; Hetzel, 1983) have been the most comprehensively researched. However, there is emerging research that less severe iodine deficiency (i.e. mild and moderate) can also affect cognition (Zimmermann, 2009).

BIOLOGICAL MECHANISMS

Cognition is a general term to describe an array of processes within the brain. These include executive functions or higher-order cognitive functions such as mental flexibility, planning, and inhibition (Isaacs and Oates, 2008), memory, attention, language, psychomotor ability (i.e., movement including both gross and fine motor skills that are associated with mental performance), and perception (Schmitt et al., 2005). An impairment in brain development may lead to functional deficits seen in lowered cognitive ability (Casey et al., 2000). Thus, an understanding of how brain development can be influenced by thyroid hormones, and therefore iodine status, may help prevent cognitive dysfunction in people who are iodine-deficient. Thyroid hormones are needed for the development and metabolism of the mammalian brain

(Delange, 2001). Although the precise ways in which thyroid hormones impact on brain function are poorly understood (Erlanger et al., 1999), thyroid hormone affects processes such as myelination, cell migration and differentiation, synaptogenesis, dendrite structure, transcriptional regulation, and synaptic plasticity (Koibuchi, 2008; Rivas and Naranjo, 2007; Thompson and Potter, 2000).

Studies with animals indicate that lower concentrations of thyroid hormones result in decreases in brain weight, synaptogenesis, cortical neuron size, as well as white matter (Loosen, 1992). For instance, mice born to iodine-deficient mothers experienced reduced brain weights relative to mice born to iodine-sufficient mothers (Farsetti et al., 1991). The offspring of iodine-deficient sheep have malformed heads, as well as reductions in the number and size of neurons in the cerebellum and cerebral hemispheres. Pregnant sheep injected with iodised oil at day 100 (late in gestation) showed recovery of brain structure, although not to the same extent as controls on an iodine-rich diet (Potter et al., 1984). Similar results have been found in marmosets, where offspring of severely iodine-deficient pairings had reduced growth, cell size, and cell numbers in the brain (Mano et al., 1987).

Studies with humans indicate that the timing of iodine deficiency is particularly important, especially when considering critical periods, such as fetal development (Bernal, 2009). During the fetal period most of the brain structures become formed; this vulnerable time is characterised by critical and sensitive periods for development (Monk et al., 2013). In the first eight weeks (known as the embryonic period), major compartments and structures are established, such as the neural tube and the ventricles (Stiles & Jernigan, 2010). At week five cellular changes begin and neuronal precursor cells proliferate, and at week eight the neural

progenitor cells start to differentiate (Tau & Peterson, 2010). Starting at week 12, neuronal migration begins and continues into week 29, whereby differentiated cells move along the scaffolding formed by radial glial cells to target sites (Stiles & Jernigan, 2010). Synaptogenesis results when axons and dendrites form between neurons, creating neural circuits (Tau & Peterson, 2010). These circuits may also be regulated by apoptosis, or programmed cell death, in order to create effective circuits as well as remove errors and transient cell populations (Stiles & Jernigan, 2010). Other processes start later in gestation, for example myelination, which continues during postnatal development (Rice & Barone, 2000). The processes involved in prenatal development are dynamic and complex, often overlapping and are influenced by both genetic and environmental factors (Tau & Peterson, 2010). Deficits, insults or injury to the developmental processes, particularly during the early stages, can result in impairments to further development with irreversible consequences for cognitive function (Rice & Barone, 2000).

When the mother is severely iodine-deficient during pregnancy, the result is profound and irreversible mental impairment (Hetzel, 1983). This makes sense given that the first eight weeks after gestation is critical to brain development (as described above). Furthermore, within the fetal period, different degrees of neurological impairment may result due to the timing of iodine deficiency. For example, consider the two types of cretinism. Neurological cretinism occurs when there is insufficient maternal thyroid hormone in the first half of pregnancy, resulting in severe mental impairment of the child as well as a multitude of other symptoms (deaf-mutism, squint, spasticity, motor rigidity). Children born with myxedamatous cretinism, however, experience mental impairment to a lesser degree, and their physical symptoms (short stature, hypothyroidism, dry skin and hair, thyroid gland atrophy, immature facial feature

development; Zimmermann, 2009) often differ from those of neurological cretinism. Iodine supplementation in the latter stages of pregnancy will not prevent neurological cretinism, but may be beneficial in preventing myxedamatous cretinism (Bernal, 2009). Myxedamatous cretinism results in thyroid gland dysfunction of the fetus or infant, within the last trimester of pregnancy, whereas neurological cretinism results from low *maternal* thyroid hormone concentration (Bernal, 2009).

After birth and into adulthood, thyroid hormone deficiency may lead to mood disorders and cognitive impairment (Smith et al., 2002). Whether this is due to the same mechanisms as those during earlier periods of development is unknown. While iodine deficiency *in utero* can lead to irreversible mental impairment, the effects of thyroid hormone on cognition in adults can generally be treated with thyroid hormone replacement, especially in older adults (Bernal, 2009, Miller et al., 2006).

So *how* does thyroid hormone affect the brain? Although there is currently no definitive answer to this question, due to the many potential and complicated interactions thyroid hormone has on the brain (for reviews, see Anderson, 2001; Bernal, 2009; Williams, 2008; and especially for fetal development see Patel et al., 2011), the first step begins at a molecular level with genetic expression. The path to genetic expression starts at the site of target cells, where T4 (considered a prohormone) becomes converted to the active form T3 (Mohácsik et al., 2011). Deiodinase enzymes (D1, D2, and D3) are responsible for the conversion of thyroid hormones, and are important regulators of thyroid hormone homeostasis (for a review see Bianco and Kim, 2006). T4 is converted to T3 by D2 (Mohácsik et al., 2011). D2 action increases the level of cellular T3, and when levels start to become excessive, D3 converts T3 back into the inactive form, T4

(Bianco and Kim, 2006). Thyroid hormone transporters, located in the membranes of target cells, allow T4 and T3 to enter the cell (Bernal, 2009), where transcription of genes can be regulated by thyroid hormone receptors in the cell nucleus (Anderson, 2001; for a review see Visser et al., 2011). The specific genes and nuclear thyroid hormone receptors that thyroid hormone *directly* act on are largely unknown (Lasley and Gilbert, 2011; Visser et al., 2011). However, the location of thyroid hormone receptors can help in identifying potential sites of thyroid hormone action. Thyroid hormone receptors are found throughout the brain, and in all major cell types (Anderson, 2001), which indicates that thyroid hormones are involved in many brain processes. The resulting gene expression controls cellular activity, which has impacts on the structure and function of the brain (Vara et al., 2002) as previously discussed.

Thyroid hormones may affect the brain through multiple means, and at different levels of central nervous system functioning including the macrostructure (e.g. the hippocampus), microstructure (e.g. myelin production), and neurotransmitters (Wachs, 2000) as shown in Figure 1. Each of these examples is discussed in more detail below.

Hippocampus

The hippocampus is part of the limbic system, located in the medial, temporal lobe of the brain, and is known to mediate aspects of memory (Gilbert and Sui, 2006). It is composed of specific cell layers including CA1, CA2 and the dentate gyrus (West 1993). Thyroid hormone is important for the formation of many brain structures but the hippocampus has been well studied, perhaps due to the fact that the cell types and circuitry are relatively well understood (for a review see Koromilas et al., 2010).

Neuronal migration, synaptic plasticity, and neurogenesis are processes that are essential for brain maturation (Bernal, 2009). In the hippocampus, these processes are known to be influenced by thyroid hormone. In animal models of neurological cretinism caused by low iodine diets, there is disruption of both cell differentiation and migration in the hippocampus (Martinez-Galan et al., 1997). In the hypothyroid rat, the weight and density of the hippocampus was reduced (Howdeshell, 2002). This is possibly due to impaired neuronal migration, and thyroid hormone has been shown to influence specific proteins (e.g. reelin and Dab1) in the central nervous system that are important for neuronal migration (Alvarez-Dolado et al., 1999).

Learning and memory are supported by two processes: long-term potentiation and synaptic plasticity. Long-term potentiation is a long-lasting facilitation in signal transmission between two neurons that have previously fired together and is thought to underlie synaptic plasticity (e.g. the strengthening of synapses between neurons), and therefore learning and memory. Synaptic plasticity works by altering the magnitude of neurotransmitter release, or the number of receptors on the postsynaptic cell (Drever et al., 2011). A reduction in synaptic plasticity affects cognitive function, and is generally shown in animals through impaired spatial memory (Gilbert and Sui, 2006). Thyroid hormone action can be experimentally blocked by propylthiouracil (PTU). When PTU is given to pregnant rats, the hippocampus of the offspring shows impairment in synaptic plasticity, spatial memory and learning (Gilbert, 2011), the effects of which may last through to adulthood (Gilbert and Sui, 2006). Thyroid hormone has been demonstrated to influence both long-term and short-term plasticity in the hippocampus (Fernandez-Lamo et al., 2009; Gilbert and Sui, 2006; Opazo et al., 2008).

Similar processes may also be present in the human brain. Using functional magnetic resonance imaging (fMRI) during a visuospatial memory task, Wheeler et al. (2011) showed that individuals with congenital hypothyroidism had increased activation of brain areas in the hippocampus. They suggested that congenital hypothyroidism may impair the optimal functioning of the hippocampus, such that the brain must compensate, by recruiting additional brain areas, in order to avoid cognitive deficits. Consistent with this idea, increased activation is also observed in the early stages of Alzheimerôs disease after neurological impairment has begun but before clinical symptoms arise, and is hypothesised to stem from generally increased effort due to decreased neurological functioning (Mondadori et al., 2006).

Neurotransmission

Neurotransmitters such as noradrenaline, dopamine, acetylcholine, serotonin, and amino acids, are chemicals released at the synaptic terminals of axons, and function to signal between neurons. The role of neurotransmitters changes over the lifespan (Dratman and Gordon, 1996). In fetal brain development, neurotransmitters appear to be important for cell migration, differentiation, and proliferation (Nguyen et al., 2001), promoting brain growth prior to the development of actual neurotransmitter systems (Dratman and Gordon, 1996).

Although thyroid hormones appear to have a complex and poorly understood relation with neurotransmitter systems, there is some evidence that thyroid hormones may influence the probability of neurotransmitter release during fetal development (Vara et al., 2002), and may even function as neurotransmitters themselves (Dratman and Gordon, 1996). In addition, thyroid hormones have been shown to interact with several neurotransmitter types including

acetylcholine (Kundu and Ray, 2010), norepinephrine (Dratman and Gordon, 1996), and dopamine (Overstreet et al., 1984) in a way that facilitates neural communication.

In childhood, neurotransmitters are thought to be necessary for the development of cognitive functions such as learning, memory, psychomotor ability, and attention (Herlenius and Lagercrantz, 2004). In human adults, thyroid hormones play a role in cognition, mood, and affective disorders (Bauer et al., 2008). Indeed, thyroid hormone has been shown to interact with serotonin systems, which have been linked to mood and depressive disorders (Bauer et al., 2002), and insufficient thyroid hormone can result in cognitive impairment, sometimes appearing as pseudo-dementia (Koromilas et al., 2010).

Studies using rat models have demonstrated that, compared to control rats, hypothyroid rats have a reduction in the expression of neurotransmitters including synapsin I, synaptotagamin I, syntaxin, and Ŭ-Ca^{2+}/calmodulin kinase II at synapses (Vara et al., 2002). Similarly, adult rats on low iodine diets have increased numbers of dopamine receptors, as well as impaired memory function (Overstreet et al., 1984), with too little or too much in the way of neurotransmitters, resulting in impaired cognitive performance (Li et al., 2010). Acetylcholine is another neurotransmitter that may be linked to cognitive function and thyroid hormone. In one study, adult rats were administered a thyroid hormone treatment, and then had cognitive deficits chemically induced prior to a spatial memory task (Morris water maze). Both acetylcholine concentration and cognitive performance increased with thyroid hormone treatment. Furthermore, rats given chronic thyroid hormone treatment experienced reduced cognitive impairment (Smith et al., 2002).

Myelination

Myelin is a white fatty sheath that surrounds some neuronal axons, the component that gives brain white matter its name. Myelin functions to insulate the axon, promoting conduction of action potentials, allowing more rapid communication between cell regions (Filley, 2010). In the central nervous system, myelin is produced by glial cells called oligodendrocytes. Iodine and thyroid hormone are essential for myelin development and maintenance, including control of myelin composition and metabolism (Dussault and Ruel, 1987). In hypothyroidism, there is a reduction in myelin, whereas in hyperthyroidism there is an increase in myelin (Bernal, 2009). The precise mechanisms of thyroid hormone action on myelin are unknown, but are likely linked to the expression of genes that code for components of myelin, including: myelin basic protein (MBP), proteolipid protein (Plp), 2´-, 3´-cyclic nucleotide 3´-phosphodiesterase (CNPase), and myelin associated glycoprotein (MAG; Thompson and Potter, 2000). For instance, hypothyroid mice showed decreased expression in MBP, indicating that thyroid hormone is required for optimal action, but is not essential for initiating myelin gene expression (Farsetti et al., 1991).

Thyroid hormone also influences both oligodendrocyte maturation (the cells that wrap myelin around axons of neurons) and the level of myelin production from the oligodendrocyte (Anderson, 2001). Induced hyperthyroidism in newborn rats increases the number of oligodendrocytes present in the optic nerve, and oligodendrocyte progenitor cells cultured from rats do not develop into oligodendrocytes in the absence of thyroid hormone (Barres et al., 1994). Thyroid hormone regulates oligodendrocyte differentiation not only during fetal development, but also in adult animals (Fernandez et al., 2004).

In summary, thyroid hormones affect the mammalian brain on several levels, and by multiple mechanisms. The specific biological mechanisms through which thyroid hormones act are still under investigation, however, several processes are integral to the relation between thyroid hormone and brain development. In iodine deficiency, inadequate thyroid hormone is produced and the resulting impairment in brain morphology may correspond to impairments in cognitive function. Brain volume in regions such as the hippocampus, myelination, and neurotransmitter systems have all been shown to be influenced by thyroid hormone, and each has been linked to brain development and cognitive function.

WHITE MATTER AND COGNITION THROUGH THE LIFESPAN

One of the most likely ways in which iodine affects cognition is through its effect on thyroid hormone and white matter. As described above, myelin development relies on thyroid hormone, and in turn white matter development is essential for cognitive function. The importance of white matter to cognitive function is clearly illustrated in both normal functioning (e.g. Fields, 2008; Fjell et al., 2011), and when normal myelination is disrupted, such as in autism (Wolff et al., 2012), Alzheimerôs disease (Benes, 2004), schizophrenia, bipolar disorder, and attention deficit hyperactivity disorder (Paus, 2010). Likewise, when myelin development is impaired in demyelinating diseases, cognitive function is also impaired (Fields, 2008). As thyroid hormone plays an important role in the formation of myelin, there is a potential link between cognitive ability and pathology in humans and thyroid hormone function. Yet again, there is insufficient research directly addressing this relation.

Myelin acts by increasing the speed of conduction of neural impulses and improved conduction speeds may then influence cognitive abilities including attention and processing speed (Filley, 2010). These cognitive abilities may in turn influence other cognitive functions (for example, increased processing speed may improve memory and fluid IQ; Kail and Salthouse, 1994). In humans, myelination begins primarily after birth (Baumann and Pham-Dinh, 2001). The first two years of life involve rapid myelin development (Hayakawa et al., 1990), after which myelin continues to increase throughout brain regions. Myelin still develops and increases in adulthood (e.g., Bartzokis, et al., 2001; Bartzokis et al., 2010; Ge et al., 2002), peaking around age 40 (Courchesne et al., 2000), and then declines in the sixth decade of life (Bartzokis et al., 2001).

There have been several studies investigating age-related changes of white matter and the corresponding changes in cognitive measures (e.g., Bava, et al., 2010; Olesen et al., 2003; Nagy et al., 2004; Zahr et al., 2009). These studies investigated myelin maturation using diffuse tensor imaging (DTI), a neuroimaging tool that images water diffusivity in body tissues. Using this method, fractional anisotropy (FA) is calculated, showing the direction of water diffusivity across tissue, and may be used to estimate white matter maturation (anisotropy increases with increased myelination, axonal thickness, or organisation of axons; Paus, 2010). Olesen et al. (2003) imaged brain areas of children aged 8 to 18 years, and found that the degree of FA positively correlated with working memory and was lateralised to the left hemisphere of the brain. Although this correlation disappeared when age was controlled for, Nagy et al. (2004) also found a significant positive correlation in working memory and FA in children aged 8 to 18, which was present even when controlling for age differences. The brain regions were also not

restricted to the left hemisphere but also the anterior of the corpus callosum, a major white matter tract in the brain.

Bava et al. (2010) examined participants in late adolescence over two time periods. Participants were on average 18 years at time 1 and average of 19 years at time 2. There was a significant difference in FA between the two time points, as well as a positive correlation between FA and cognitive function (including executive functioning, verbal fluency, recall, and recognition memory). These results indicate that the maturation of white matter was not only increasing in late adolescence but was also relevant to cognitive ability. Likewise, Zahr et al. (2009) examined both young (average 26 years) and older (average 78 years) adults using DTI. A wide range of cognitive tests were used to examine cognitive function in the two age groups, including tests of working memory, motor ability, and problem solving. As predicted, young adults consistently performed at a higher level compared to older adults, and a significant positive correlation was found between cognitive functioning and FA. Bendlin et al. (2010) also examined cognition and white matter maturation in adults. Neurologically healthy young adults, aged 20 to 80 years, were assessed on white matter microstructure using DTI. A range of cognitive tests were given to participants and were used to assess processing speed, working memory, executive function, verbal achievement, and episodic memory. Performance on these cognitive tasks was significantly and positively correlated with age and white matter maturation in specific brain regions. Together, these studies support the idea that myelin is central to cognition throughout the lifespan.

One factor crucial to the issue of iodineôs effect on the brain is the rate of brain change over development. Diffusion tensor imaging indicates that the process of myelination is more

rapid in childhood than later in life. Thus, white matter increases rapidly from 5 to approximately 20 years (including in frontal areas that mediate the higher cognitive functions). After this time it increases more gradually, and eventually peaks and begins to decline (Imperati et al., 2011; Lebel et al., 2012; Westlye et al., 2010). A similar pattern is found with regard to neurotransmitters. For instance, dopamine production and sensitivity increases over adolescence (Spear 2000). Furthermore, whereas subcortical dopamine peaks in the teenage years, cortical dopamine does not peak until early adulthood, after which it declines (Li, 2012). Not only do neurotransmitters increase, but they also have a direct effect on the development of white matter (Li et al., 2006). They can stimulate dendritic growth, or at higher levels can halt axonal or dendritic growth, or at still higher levels can result in dendritic pruning (Lipton and Kater, 1989).

These findings have very important implications. Levels of white matter and neurotransmitters are intricately related to cognitive indices such as working memory, processing speed, block design, and matrix reasoning (see above). In turn, iodine and thyroid hormones enhance white matter and neurotransmitters (also see above) either because iodine enhances both white matter and neurotransmitters independently, or because it enhances neurotransmitters, which then facilitates white matter growth. The obvious implication in either case is that any intervention with iodine will be more effective earlier in development when there is greater plasticity.

THYROID HORMONE AND COGNITION THROUGH THE LIFESPAN

Due to the link between thyroid hormones and brain development (Delange, 2001), it is important to know how iodine deficiency may impact brain and cognitive function over a

lifetime. Originally, researchers claimed that fetal development occurred without maternal thyroid hormone due to the placenta blocking the exchange of hormones between mother and child, but more recently it has been demonstrated that there are mechanisms in place to allow transfer of maternal thyroid hormone to the fetus (Morreale de Escobar et al., 2004). Indeed, maternal thyroid hormones appear to play an important role in fetal brain development from the first trimester until birth (Patel et al., 2011). For instance, in cretinism, the very small amounts of thyroid hormone produced by severely iodine-deficient mothers indicates that less maternal thyroid hormone is transferred to the fetus, which subsequently results in gross fetal impairment (Zimmermann et al., 2008).

Studies on maternal hypothyroxinemia (characterised by low T4 and normal thyroid stimulating hormone; TSH) in pregnancy have examined the effect of low thyroid hormone on neurocognitive development in children. Work by Pop et al. (1999; 2003), Kooistra et al. (2003), and Finken et al. (2013) demonstrated that maternal hypothyroxinemia affected neural development in children, with significant cognitive impairments observed in children aged 10 (Pop et al., 1999), 12, and 24 (Pop et al., 2003) months. However, the effects of maternal hypothyroxinemia appear in infants as early as 3 weeks after birth (Kooistra et al., 2003), and up to 5 years of age (Finken et al., 2013).

The timing of hypothyroxinemia in gestation was also important for the neurodevelopment of the children. In particular, recent studies indicate that untreated hypothyroxinemia in early gestation leads to more severe impairments compared to later in gestation. For instance, the Generation R study examined a cohort of over 2000 women and children. Measures of maternal blood TSH and T4 in early pregnancy indicated that a small

percentage of mothers were hypothyroxinemic. Measures of cognitive development were given to infants from 18 to 30 months of age, with children born to mothers with severe hypothyroxinemia in pregnancy more likely to have a delay in both verbal and nonverbal ability. For mothers diagnosed with mild hypothyroxinemia, some delay was seen for verbal ability of the offspring, although nonverbal cognition was not affected (Henrichs et al., 2010).

The Millennium Cohort study assessed infant hypothyroxinemia in preterm infants (Ò34 weeks gestation) and neurodevelopment later in childhood. Hypothyroxinemia was defined as a T4 concentration less than the 10^{th} percentile, and euthyroid as a T4 concentration between the 10^{th} and 90^{th} percentile at day 7,14, and 28, corrected for gestational age. Neurodevelopment was assessed using the commonly used McCarthy scales (measuring fine and gross motor and cognitive development) when children were a mean age of 5.5 years. The authors found that hypothyroxinemic infants scored lower than euthyroid infants on almost all McCarthy scales, even after adjusting for potential confounds such as neonatal illness, maternal health, parental depression, and parental intellect. The authors concluded that there was no developmental ócatch-upô for hypothyroxinemic children (Delahunty et al. 2010).

As stated previously, these recent studies have focused on the effect of thyroid hormone concentration on neurodevelopment. However, the studies did not report iodine status, so that the cause of low T4 could be the result of factors other than iodine deficiency. Other factors, including deficits of nutrients such as selenium (Duntas, 2010) as well as maternal stress (Monk et al., 2013), may account for some of the effects found on child neurodevelopment from maternal hypothyroxinemia. Nevertheless, these studies do provide a model of the effects of low thyroid hormone on neurodevelopment that may result from iodine deficiency. In particular, if

low thyroid hormone is associated with compromised cognition, then it seems logical to expect thyroid hormone and iodine supplementation to alleviate these effects. However, results regarding supplementation are somewhat contradictory. For instance, Lazarus et al. (2012) found that treatment for pregnant mothersô hypothyroidism did not improve the cognitive development of children at 3 years of age relative to a control group of mothers whose hypothyroidism went untreated. In this study, pregnant women were tested for T4 and TSH at their first antenatal visit (about 13 weeks). For women in the screened group, results were analysed immediately and treatment (levothyroxine) was given at 20 weeks of gestation if levels of T4 were low. For the control group, the results of the blood tests were not investigated until full term, meaning that no treatment for hypothyroxinemia was given during gestation. When the children reached 3 years of age, they were assessed using the Wechsler Preschool and Primary Scale of Intelligence. Children born to women with low T4 and high TSH showed no difference in cognitive scores whether they underwent treatment or were not treated. Thus, maternal thyroxine treatment before 20 weeks gestation provided no benefit for cognitive function in children born to mothers with hypothyroxinemia, perhaps as suggested by the authors, because treatment was too late in gestation.

Two observational studies have increased support for the effect of iodine on cognition by examining the association between maternal mild iodine deficiency and the cognitive development of the offspring (see Table 1). In a UK study using participants from the Avon Longitudinal Study of Parents and Children, iodine status was measured for women in their first trimester of pregnancy. Iodine status was established through urinary iodine-to-creatinine ratios (to control for urine volume), and the median UIC of the sample was 91.1 µg/L, indicating mild-

to-moderate iodine deficiency. The sample was classified as iodine deficient (<150 µg/g creatinine) or iodine sufficient (Ó150 µg/g) as per World Health Organisation criteria (World Health Organisation et al. 2007). The children were assessed on verbal IQ using the Wechsler Intelligence Scale for Children at eight years of age, and reading ability using the Neale Analysis of Reading Ability at nine years of age. After adjusting for 21 factors (including maternal age, maternal education, life event scores, as well as child factors including weight at birth, and gender) there was a significant association between maternal iodine status and cognitive performance in the offspring. More children performed at suboptimal levels of verbal IQ, reading comprehension, and reading accuracy when the mothers had been mildly iodine deficient during the first trimester of pregnancy. Although not statistically significant, the cognitive deficits appeared to be more pronounced when the maternal iodine deficiency was more severe (Bath et al. 2013), indicating a potential dose-response relationship.

Similar results were found in a recent Australian study. Maternal iodine status was assessed through UIC during the first trimester of pregnancy. Iodine status in the sample was also classified as iodine deficient (<150 µg/g) or iodine sufficient (Ó150 µg/g). Offspring were tested at age nine using Australiaôs standardised National Assessment Program - Literacy and Numeracy (NAPLAN). Children born to mothers with mild iodine deficiency had lower educational performances for spelling and grammar, compared to mothers who were iodine sufficient during pregnancy. Writing and numeracy scores were not significantly different between groups, leading the authors to propose that processing speed and working memory may play a role in the mechanism for iodine effects on cognitive ability (Hynes et al. 2013).

There are also three studies that have examined the effect of iodine on cognition, using iodine supplement interventions for pregnant women (see Table 2). Berbel et al. (2009) supplemented pregnant women in a mildly iodine-deficient area of Spain. At 18 months of age, the children of women who were given iodine supplements in the first trimester of pregnancy had significantly improved gross and fine motor coordination, and social adaptive ability (as measured by the Brunet-Lézine Scale) compared to children whose mothers were not given iodine supplements until full-term. Children of mothers given supplements in the second trimester also showed an improvement in performance, however, not to the same extent as those who were supplemented in the first trimester of pregnancy.

Velasco et al. (2009) also studied the effect of iodine supplements in pregnant women living in an iodine-deficient area of Spain and the development of subsequent offspring. Pregnant women were given an iodine supplement from the first trimester of pregnancy, while the control group were women who did not receive iodine supplements in pregnancy. Children were assessed using the Bayley Scales of Infant Development between 3 and 18 months of age, measuring mental development, psychomotor development, and qualitative behaviour. Although the mental development and behaviour ratings of the children of women who had received the iodine supplement did not differ from those of the control group, the psychomotor development of the iodine group was significantly better.

Together, the Berbel et al. (2009) and Velasco et al. (2009) studies lend support to the idea that improvements in maternal iodine status via iodine supplementation, especially in the first trimester of pregnancy, has beneficial effects on infant development. The studies are limited however, because neither involved randomized placebo-controlled trials. Thus in numerous

ways, women who chose not to take supplements could have been different from women who took supplements in early pregnancy.

Murcia et al. (2011) used a cross-sectional design to assess the development of children aged 11 to 16 months, again using the Bayley Scales, but in this case found that psychomotor development was *inversely* associated with the use of iodine supplements (and that iodine supplementation was unrelated to performance on the mental development scale or to behaviour ratings). Why iodine would be associated with *worse* motor performance is unclear, as the levels of iodine in this study would not be considered as excessive for pregnant women. However, supplementation was not directly measured, but estimated by participants using a food frequency questionnaire. When viewed together with the studies of Berbel et al. (2009) and Velasco et al. (2009), the findings regarding maternal iodine status and fetal development are inconsistent and inconclusive. There is a need for a well-conducted, randomized, placebo-controlled trial to further study the effect of iodine supplementation in pregnancy on neurodevelopment in infants and toddlers. Another gap in the literature concerns slightly older children. Although the brain is most vulnerable from the first trimester of pregnancy until approximately 2 years of age, brain maturation continues to take place well after this time (Bauman and Pham-Dinh, 2001). Despite the importance of adequate iodine nutrition during early childhood, and the potential for a sustained effect on cognitive performance, to date there are no published studies of children aged 2 to 5 years of age.

Most studies into the effects of iodine and cognition have been undertaken in school-aged children (see Table 3). Observational studies show an association between impairment in mental development and decreased iodine status. Tiwari et al. (1996) compared children from severe-to-

moderately iodine-deficient regions to those from mildly iodine-deficient regions, and found that learning occurred at a reduced rate for children who were more deficient in iodine. Vermiglio et al. (1990) observed children from three iodine-deficient regions of Sicily, and found that the more iodine-deficient children had impairments in motor ability. In addition, there were impairments in visual perception and neuromotor ability in children from more severely iodine-deficient areas. Santiago-Fernandez et al. (2004), examined the intelligence quotients (IQ) of schoolchildren aged 6 to 16 years, residing in a mildly to moderately iodine-deficient province in Spain. Children were divided by UIC, and those with a UIC <100 µg/L had a lower IQ compared to children with a UIC above 100 µg/L.

In summary, observational studies indicate a relation between iodine and cognitive performance. However, observational studies have obvious limitations regarding their interpretation. Comparing populations from different regions is complicated by potential confounding differences in multiple factors such as diet, education, and access to resources.

Intervention studies provide a more powerful indicator of the relation between iodine and cognition. There have been several intervention studies examining the effects of iodine deficiency on the cognitive ability of schoolchildren (see Table 4), although many have failed to find a link between iodine deficiency and cognition (Bauista et al., 1982; Isa et al., 2000; Gordon et al., 2009; Huda et al., 2001; van den Briel et al., 2000, Zimmermann et al., 2006). However, interpretation of these results is also difficult because many of these studies had serious methodological faults. A study using school children in Malaysia found no association between improved iodine status and cognitive ability. In fact, the non-verbal intelligence scores of the control group, who did not receive a dose of iodized oil, actually improved more compared to the

treatment group. Yet, again, interpretation of these results is difficult because the two groups were recruited from different villages within Malaysia, with baseline differences in iodine levels and intelligence scores present between the two groups (Isa et al., 2000).

Other studies have suffered from contamination of the control group (Bauista et al., 1982; van den Briel et al., 2000). Bauista et al. (1982) administered iodized oil to a treatment group of school children in Bolivia, yet found that the control group (who received non-iodized mineral oil) also increased in iodine status. In West Africa, van den Briel et al. (2000) also found that the control group improved in iodine status, possibly due to the introduction of iodized salt into the area during the study. Thus, in neither study was it possible to compare an experimental group who underwent iodine supplementation to a control group without access to iodine.

Another obstacle in studies of iodine intervention concerns identification of the extent of iodine deficiency, especially when there are several measures of iodine status (such as urinary iodine, thyroid hormone levels, and thyroglobulin levels). For instance, Huda et al. (2001) examined school children in Bangladesh, categorizing children as moderately iodine-deficient on the basis of urinary iodine levels, yet after treatment of iodized oil neither the treatment nor control group showed an improvement in iodine status. In addition, serum thyroglobulin levels remained in the normal range at both baseline and 4 months later, indicating that there might be inconsistency between the different measures of iodine status.

In contrast, two well-conducted randomized, double-blind, placebo-controlled trials have demonstrated a link between iodine deficiency and cognition in school-aged children. First, Zimmermann et al. (2006) studied children in villages of south-eastern Albania aged 10 to 12 years who were moderately iodine-deficient. At baseline, the iodine status of the children was

assessed and seven cognitive tests were administered. The children were given either iodised poppy seed oil (containing 400mg of potassium iodate) or a placebo (sunflower oil), and six months later the children were reassessed. The iodine status of the treatment group improved from moderate iodine deficiency to adequate iodine status, whereas the control group remained moderately iodine deficient throughout the trial duration. The control group experienced significant improvements on four of the seven cognitive tests (Ravenôs Coloured Progressive Matrices, rapid target making, symbol search, and rapid object naming) relative to the control group.

A similar study was conducted by Gordon and colleagues (2009) in mildly iodine-deficient children aged 10 to 13 years living in New Zealand. Children were randomly divided into two groups, the treatment group receiving tablets containing 150 µg/L iodine to be taken daily for 28 weeks, and the control group receiving a placebo. At baseline, cognition was assessed using four subtests of the Wechsler Intelligence Scale for Children (Symbol Search, Matrix Reasoning, Letter-Number Sequencing, and Picture Concepts), in addition to iodine status. After the end of the intervention, the treatment group were iodine-sufficient while the control group remained mildly iodine-deficient. There was a significant treatment effect found for two of the four cognitive tests (Picture Concepts and Matrix Reasoning) in the iodine group relative to the placebo group, suggesting that iodine deficiency affects cognitive development up to at least 13 years of age.

There is very little evidence as to whether older adolescents or adults are influenced by iodine status. Hetzel (1983) stated that adults in communities with severe iodine deficiency were apathetic and slow moving. When iodine was introduced into such communities, adults appeared

more animated and the level of activity in the community increased (Chen and Hetzel, 2010). However, without standardized testing to verify such claims, it remains unclear what effect iodine might have on an adult group. When thyroid hormone dysfunction occurs in adulthood, the effects of abnormal thyroid hormone levels are generally reversible (Bernal, 2009). While iodine deficiency *per se* has not been investigated much in older adults, thyroid hormones have been associated with mood, affective disorders, and dementia, and may be related to cognitive functions such as memory and attention (Anderson, 2001). Both healthy older adults with normal thyroid function, and older adults with hypothyroidism, have shown positive associations between thyroid hormone levels and cognitive scores (Bono et al., 2004; Prinz et al., 1999). These studies suggest that brain processes can be influenced after birth, and that brain development is not restricted to critical periods *in utero*. It is likely, however, that these effects will be more pronounced in individuals with severe iodine deficiency, compared to those with moderate-to-mild iodine deficiency, especially as the effects of less severe iodine deficiency are unclear. There have been no intervention studies published to date examining the relation between improvements in iodine status in moderately to mildly iodine-deficient adults and cognition.

In summary, a sufficient supply of iodine is needed to synthesise adequate amounts of thyroid hormones. There is good evidence to suggest that low concentrations of T4, in particular, can adversely affect fetal brain development and subsequently child and adult cognitive function. Understanding the impact of iodine status at different life stages is essential for designing effective prevention strategies, to target at risk populations and to consider the timing of intervention. In addition, understanding the exact cognitive skills that are affected by iodine

deficiency is difficult. The tests used in studies of iodine and cognition, may reflect many complex cognitive abilities. Matrix reasoning is influenced by iodine status in children (Gordon et al., 2009; Zimmermann et al., 2006), yet this assessment may measure fluid IQ, abstract reasoning, spatial reasoning and perceptual organization (Wechsler, 2008). Furthermore, even when a cognitive process is identified as influenced by iodine deficiency, the connection to underlying biological mechanisms in the brain is unclear (Schmitt et al., 2005).

FUTURE DIRECTIONS

Investigation into iodine and the brain has primarily taken place in two separate fields: animal studies that look directly at specific genes, chemicals and brain regions (i.e., Desouza et al., 2011; Gong et al., 2010), and human studies that use behavioural tests to infer brain function. Animal models are useful, but complicate interpretation in humans as there is no guarantee that an animal model will map well to human mechanisms (Babu et al., 2011). There are methods, however, to examine human brain processes *in vivo,* which include imaging tools such as magnetic resonance imaging (MRI), DTI, electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET; Volkow et al., 1997). These techniques use a variety of mechanisms including mapping the cerebral blood flow, and glucose metabolism to image both the structure and areas of functioning in the brain (Sundgren et al., 2004).

Brain network connectivity studies have begun to investigate the relation between brain networks and cognitive function in children. Previous research in adults had shown support for a parietal-frontal network hypothesis for intelligence. Recently, Langeslag et al. (2013)

investigated this link in children aged six to eight years of age recruited from the Generation R study in the Netherlands. Using resting state fMRI and measures of abstract thinking and visuospatial ability, positive correlations were found between the right parietal-frontal network and IQ. These results were supported by additional research whereby children and adolescents from Beijing showed a positive (marginally) significant correlation between IQ and the parietal-frontal network (Li & Tian, 2014). More research is required, especially longitudinal studies, to shed further light on the relation between iodine deficiency and cognitive deficits across the lifespan.

For example, brain imaging may be used to locate biochemical interactions in the brain (Volkow et al., 1997), while DTI is able to investigate changes in white matter (Westlye et al., 2010). Each of these techniques have spatial and temporal advantages and disadvantages. Yet, these techniques have not been widely used for experimental designs as they are only appropriate for short-term monitoring, are expensive, and there is usually limited availability to the needed equipment (Bookheimer, 2000). Subsequently, sample sizes are often small, and these techniques are difficult to utilize with children because they require the participant to be very still throughout the imaging process. An additional challenge is that the brain does not always develop in a linear fashion, making it difficult to make inferences about different age groups, especially as the same imaging techniques are used at all age groups (Sundgren et al., 2004).

As an example of some of the difficulties surrounding the use of such techniques, consider the following study. Akinci et al. (2006) examined hypothyroidism in infants using magnetic resonance (MR) spectroscopy, detecting certain metabolites in the brain. Healthy infants were compared to infants diagnosed with congenital hypothyroidism at 5 to 7 days of age,

and again after thyroxine treatment eight months later. The MR spectroscopy showed that specific ratios of metabolites were reduced in infants with hypothyroxinemia, but after treatment there was no difference in metabolite ratios between the two groups of children. The implications of such findings for other aspects of brain development are unclear. For instance, functional changes in brain metabolism are not always related to structural changes in brain volumes and the relation between brain structure and function is complex and poorly understood (Schmitt et al., 2005). However, this study does show that brain imaging *in vivo* could be a useful tool to investigate changes in brain structure and function over time (i.e., in relation to the effects seen with iodine supplementation). For this reason, the use of MRI, fMRI, etc. *in addition to* behavioral cognitive tests in double-blind intervention studies might make for a powerful combination.

As for behavioral tests measuring aspects of cognition such as problem-solving, reaction time or fluid IQ, these too have limitations. First, there is measurement error on any behavioral test and also potentially when interpreting the results. The researcher, the length of the test, and practice effects may all influence test performance (Isaacs and Oates, 2008; Schmitt et al., 2005). Second, studying cognition during development is not always straightforward because different cognitive processes develop at different rates (Isaacs and Oates, 2008). Third, there may be culture- or language-specific effects that limit the generalizability of results (Isaacs and Oates, 2008). One method of overcoming this limitation is to have cognitive tests that can be used across developmental levels. Such measures have recently been developed in the National Institutes of Health (NIH) toolbox, a publically available source developed to aid longitudinal neurological research. Standardized executive function subtests of the cognitive toolbox were

developed for use from early childhood to adolescence (Zelazo et al., 2013) and up to adulthood (Weintraub et al., 2013). These measures are easily accessible, computerized and short in duration, and should aid research on cognitive development.

The biggest challenge in examining the effect of iodine deficiency on cognitive ability is that little is known about the actual biological mechanisms and potential corresponding functions. Better insight into the cognitive functions that may benefit from improvement in iodine status would aid experimental efforts, so that the appropriate tests were selected. In addition, an understanding of the specific effects of iodine on the brain (i.e., facilitation of myelination, changes in neurotransmitters) would also benefit researchers by providing clear hypotheses as to what cognitive abilities should be affected and at what age. For instance, we have argued that iodine likely improves cognition because it facilitates levels of neurotransmitters and white matter, and that because these processes are more labile in youth, iodine supplementation is likely to have a more beneficial effect prior to adulthood. Thinking about the relation between iodine and cognition would be greatly assisted by additional research examining the different aspects of this hypothesis.

CONCLUSION

Iodine is an important nutrient for the development and maintenance of brain structure and function, the effects of which are mediated through thyroid hormone. While progress has been made in our understanding of this topic over the last decades, there are still many gaps in the literature examining the role of iodine and cognition. These range from the lack of knowledge of the biochemical mechanisms by which thyroid hormone influences brain

development, to deciding which are the most appropriate tests used to assess cognitive function in populations with iodine deficiency. Iodine deficiency *in utero* may have adverse and irreversible effects, and it appears that iodine deficiency also results in cognitive impairments in childhood. Adult cognitive function may also be influenced by iodine status, but the literature on iodine deficiency across the lifespan is incomplete. Both white matter and neurotransmitter levels appear to impact cognitive ability, especially in childhood, yet it is unknown whether iodine affects cognition through either or both of these systems. Understanding how and when iodine affects brain and cognitive development will help in the prevention and treatment of iodine deficiency, and may make it possible to eradicate preventable impairment.

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Table 1. Observation studies investigating the relationship between maternal iodine status and cognitive ability in children

Author (year)	Childôs Age (yrs)	Study design	Maternal Iodine excretion	Cognitive measure	Effect on Cognition
Bath et al. (2013)	8-9	Maternal iodine levels assessed during first trimester of pregnancy. Compared cognitive performance of offspring of mothers classified as iodine deficient (*n*=646), compared to iodine sufficient (*n*=312).	**ID group** <150 µg/g creatinine **Control group** Ó150 µg/g creatinine	WISC (abbreviated form) Neale Analysis of Reading Ability	Children born to mothers with mild-to-moderate iodine deficiency scored significantly lower on verbal IQ (p = .02), reading accuracy (p = .007) and reading comprehension (p = .02), compared to children born to mothers who were iodine sufficient.
Hynes et al. (2013)	9	Maternal iodine status assessed during first trimester of pregnancy. Compared educational performance of offspring of mothers classified as iodine deficient (*n*=162), compared to iodine sufficient (*n*=66).	**ID group** <150 µg/L **Control group** Ó150 µg/L	NAPLAN	Children born to mothers with mild iodine deficiency showed significantly poorer performance on grammar (p = .038), spelling (p = .003), reading (p = .058), and English-literacy (p = .034), compared to children who were born to mothers that were iodine sufficient in pregnancy. No significant differences were found between groups for writing or numeracy.

ID iodine deficient; **IQ** intelligence quotient; **WISC** Wechsler Intelligence Scale for Children; **NAPLAN** National Assessment Program-Literacy and Numeracy

Table 2. Intervention studies investigating the relationship between maternal iodine status in pregnancy and cognitive ability in children

Author (year)	Child Age at testing	Study design	Maternal Iodine excretion (µg/L)	Infant Iodine Excretion	Cognitive measure	Effect on Cognition
Berbel et al. (2009)	18 months	Mothers received supplementation (200mg KI per day) in first trimester (*n*=13), second trimester (*n*=12), or at the term of pregnancy (*n*=18), until end of lactation.	**Treatment 1:** 121 **Treatment 2:** 97 **Control:** 75	Not assessed	Brunet-Lézine scale	Children whose mothers were supplemented in their first trimester showed significantly higher scores overall than mothers who were not supplemented until term ($p < .001$), or until the second trimester ($p < .05$).
Velasco et al. (2009)	**Treatment:** 6 months **Control:** 12 months	Mothers received 300mg KI in first trimester of pregnancy (*n*=133), and were compared to a control group of	**Treatment**: First trimester <10 w: 154 First trimester >10 w: 213 Second trimester:	**Treatment**: 204 µg/L **Control**:115 µg/L	Bayley Scale of Infant Development	No significant difference between groups for motor development of behavioural scales. Psychomotor development was statistically different between groups ($p < .02$).

		mothers who received no supplementation (*n*=61)	252 Third trimester: 263 **Control**: First trimester: -- Second trimester: -- Third trimester: 88			
Murcia et al. (2011)	11-16 months	Mothers completed a food-frequency questionnaire estimating iodine intake (supplements and salt). Subjects were assessed based on the mean estimated dose of daily iodine supplement: <100mg (*n*=169), 100-149 mg(*n*=298), Ó150 mg(*n*=222).	Percentage sample with: **<100**: 34 **100-149**: 21 **150-249**: 25 **≥250:** 20	Percentage sample with: **TSH** **≤ 4 µU/mL**: 96 **> 4 µU/mL**: 4	Bayley Scale of Infant Development	Mothers who reported taking over 150mg per day had children who showed a decreased in psychomotor performance, compared to women who took <100mg of iodine supplements per day ($p <$ .002).

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KI potassium iodine; Iodine excretion measured by urinary iodine concentration; **TSH**: thyroid stimulating hormone, elevated levels indicate issues with thyroid.

Table 3. Observation studies investigating the relationship between iodine status and cognitive ability in children

Author (year)	Age (yrs)	Study design	Iodine excretion	Cognitive measure	Effect on Cognition
Boyages et al. (1989)	7-14	Case control study comparing children from an ID area (*n*=141) with controls from a rural (*n*=51) and two urban (*n*=24, *n*=54) iodine sufficient areas.	**ID area** 154 µg/g creatinine **Control** 428 µg/g creatinine	Griffiths Mental Development Scales Hiskey-Nebraska Test of Learning Aptitude	ID children had a lower mean IQ compared to controls from one rural and two urban areas (72 *vs.* 84, 109 and 106, $p<0.001$). Rural controls had a lower mean IQ compared to urban controls (84 *vs.* 109 and 106, $p<0.001$).
Vermiglio et al. (1990)	6-12	Case-control study comparing children from ID areas with and without endemic cretinism (*n*=719) with age-matched iodine-sufficient controls (*n*=370).	**ID areas** 24 µg/L 31 µg/L **Control area** 82 µg/L	Bender Gestalt test	Greater proportion of ID children had ódefectiveô Bender Gestalt test results (i.e. ' -1 SD from the average of an age-matched reference group) compared to control area (13.8% *vs.* 3.5%, $p<0.001$).
Azizi et al. (1995)	6-16	Case-control study comparing children from severe (*n*=202), moderate (*n*=149), and mild (*n*=694) ID areas, as assessed by prevalence of	**Severe ID area** 20 µg/g creatinine **Moderate ID area** 18 µg/g creatinine	Bender Gestalt test Ravenôs test	Mild ID children made fewer errors on the Bender Gestalt test than children from moderate and severe ID areas ($p<0.001$). Fewer errors were made by moderate ID children compared to severe ID children ($p<0.001$). Mean IQ score was higher in the mild ID children compared with moderate and

		visible goitre and thyroid function.	**Mild ID area** 66 µg/g creatinine		severe ID children (116 *vs.* 96 and 89, respectively; $p<0.001$).
Tiwari et al. (1996)	9-15	Case-control study comparing children from severe ID area (n=100) with age-matched controlõs from mild ID area (n=100).	**ID area** 28 µg/L **Control area** 57 µg/L	Maze, verbal, and pictorial learning tasks	Severe ID children made more errors in the maze learning task ($p<0.01$) and performed less well on the pictorial learning task ($p<0.01$) compared with controls. There was no difference between groups for verbal learning.
Huda et al. (1999)	7-12	Case-control study comparing hypothyroid (n=170) children with school and grade matched euthyroid children (n=170).	**Hypothyroid** 41 µg/L **Euthyroid** 52 µg/L	WRAT, Verbal fluency, Digit span, Visual search, Corsi Blocks, RCPM, French learning test, SSMT, ULSD, Modified stroop, Lafayette peg board	Euthyroid children had a higher mathematics score ($p<0.01$) and reading and spelling score ($p<0.001$) and performed better on the French learning test ($p<0.01$). There were no differences between groups in the other cognitive measures.
Santiago-Fernandez et al. (2004)	6-16	Cross-sectional study (n=1221) looking at the effect of iodine status on IQ in mildly iodine deficient children.	**Mild ID children** 90 µg/L	Cattellõs g factor test of IQ	Children with a UIC Ò100 µg/L had lower IQ scores than children with a UIC > 100 µg/L ($p<0.01$). IQ below the 25th percentile was significantly related to UIC < 100 µg/L (p=0.02) and thyroglobulin > 10 ng/ml (p=0.04).

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Tang et al. (2007)	8-13	Case-control study comparing children from two severe (*n*=225), two moderate (*n*=181), and two mild (*n*=158) iodine deficiency areas	**Severe ID areas** 24; 24 µg/g creatinine **Moderate ID areas** 41; 45 µg/g creatinine **Mild ID areas** 81; 91 µg/g creatinine	Combined Ravenôs test JPB	Mean IQ scores were lower in severe and moderate ID areas compared with mild ID areas (102 and 100 *vs.* 108; $p<0.01$). JPB scores were lower in the severe ID area children compared with moderate and mild ID area children (316 *vs.* 330 and 342; $p<0.01$). Moderate ID children had a lower JPB score than mild ID area children ($p<0.05$).

ID iodine deficient; **IQ** intelligence quotient; **WRAT** Wide Range Achievement Test; **RCPM** Ravenôs Colored Progressive Matrices; **SSMT** Symbol modalities test; **ULSD** Upper limb speed and dexterity; **UIC** urinary iodine concentration; **JPB** Jinyi Psychomotor Test

Table 4. Intervention studies investigating the effect of iodine supplementation on cognitive ability in children

Author (year)	Age (yrs)	Intervention	Iodine excretion (µg/L)			Cognitive measure	Effect on Cognition
Bautista et al. (1982)	5.5-12	Subjects (*n*=200) randomised to receive either a bolus dose 475mg iodine as iodized poppyseed oil, or mineral oil. *Study Duration: 22 months*		**0mo**	**22mo**	Stanford-Binet test Bender Gestalt test	IQ improved and errors on the Bender Gestalt test decreased in both groups with no significant differences in the change between groups (p=0.86; p=0.49, respectively). Analysis of all children found an improvement in IQ with decreased goitre size (p=0.014), especially in girls (p=0.029; *vs.* p=0.088 for boys).
			Treatment	14	53		
			Control	15	32		
			Severe iodine deficiency				
Isa et al. (2000)	5-17	Purposively sampled treatment (*n*=60) and control (*n*=105) groups received single dose iodized poppyseed oil or no treatment, respectively. *Study Duration: 12 months*		**0mo**	**12mo**	TONI-2	Proportion of subjects that obtained a ówery poorô IQ (<70) decreased in both treatment (p<0.0001) and control (p<0.01) groups. Proportion of treatment group scoring an óaverageô IQ (90-110) increased (p<0.0001); proportion of control group scoring an óabove averageô IQ (111-120) increased (p<0.05).
			Treatment	16	40		
			Control	15	28		
			Severe iodine deficiency				
van den Briel	7-11	Subjects		**0mo**	**12mo**	Block design,	All cognitive test z-scores were

et al. (2000)		(*n*=196) randomised to receive either a bolus dose 540mg iodine as iodized poppyseed oil, or non-iodized poppyseed oil. Due to introduction of iodized salt, study design changed post-hoc to compare children with changed (*n*=128) and unchanged (*n*=68) UIC. *Study Duration: 12 months*	**Changed** **Unchanged** Mild-severe iodine deficiency	11 79	86 85	Closure, Concentration, Exclusion, Fluency, Mazes, Hand movements, RCPM	higher in the changed group than the unchanged group at the end of the intervention (*p*=0.044).
Huda et al. (2001)	7-13	Subjects (*n*=305) were randomised to receive either a bolus dose 400mg iodine as iodized poppyseed oil, or non-iodized poppyseed oil.		**0mo**	**4 mo**	Verbal fluency, Digit span, Visual search, French learning test, Corsi blocks, RCPM, SSMT, Modified stroop, ULSD,	Both groups improved scores for all cognitive tests. There was no significant difference between groups on any of the cognitive tests.
			Treatment	35	87		
			Control	36	42		
			Moderate iodine deficiency				

		Study Duration: 4 months				Lafayette peg board	
Zimmermann et al. (2006)	10-12	Subjects (*n*=310) were randomised to receive either a bolus dose 400mg iodine as iodized poppyseed oil, or non-iodine containing sunflower oil. *Study Duration: 24 weeks*		**0wks**	**24wks**	RCPM, Coding, Symbol search, Digit span, Rapid object naming, Bead threading, Rapid target marking	Treatment group had improved scores from baseline for RCPM, rapid target marking, symbol search, coding, and rapid object naming (p<0.0001). At 24 weeks, treatment group performed better than controls on RCPM, rapid target marking, symbol search, and rapid object naming (p<0.0001).
			Treatment	42	172		
			Control	44	49		
			Moderate iodine deficiency				
Gordon et al. (2009)	10-13	Subjects (*n*=184) were randomised to receive either 150 µg iodine or placebo as a daily supplement. *Study Duration: 28 weeks*		**0wks**	**28wks**	Picture concepts, Letter-number sequencing, Matrix reasoning, Symbol search	At 28 weeks, treatment group had improved scores for Picture concepts (p=0.023) and matrix reasoning (p=0.040) compared with controls. Overall cognitive score of the treatment group increased by 0.19 SD compared with controls (p=0.011).
			Treatment	66	145		
			Control	62	81		
			Mild iodine deficiency				

IQ Intelligence Quotient; **TONI-2** Test of Non-Verbal Intelligenceï 2nd ed; **RCPM** Ravens Colored Progressive Matrices; **SSMT** Symbol modalities test; **ULSD** Upper limb speed and dexterity

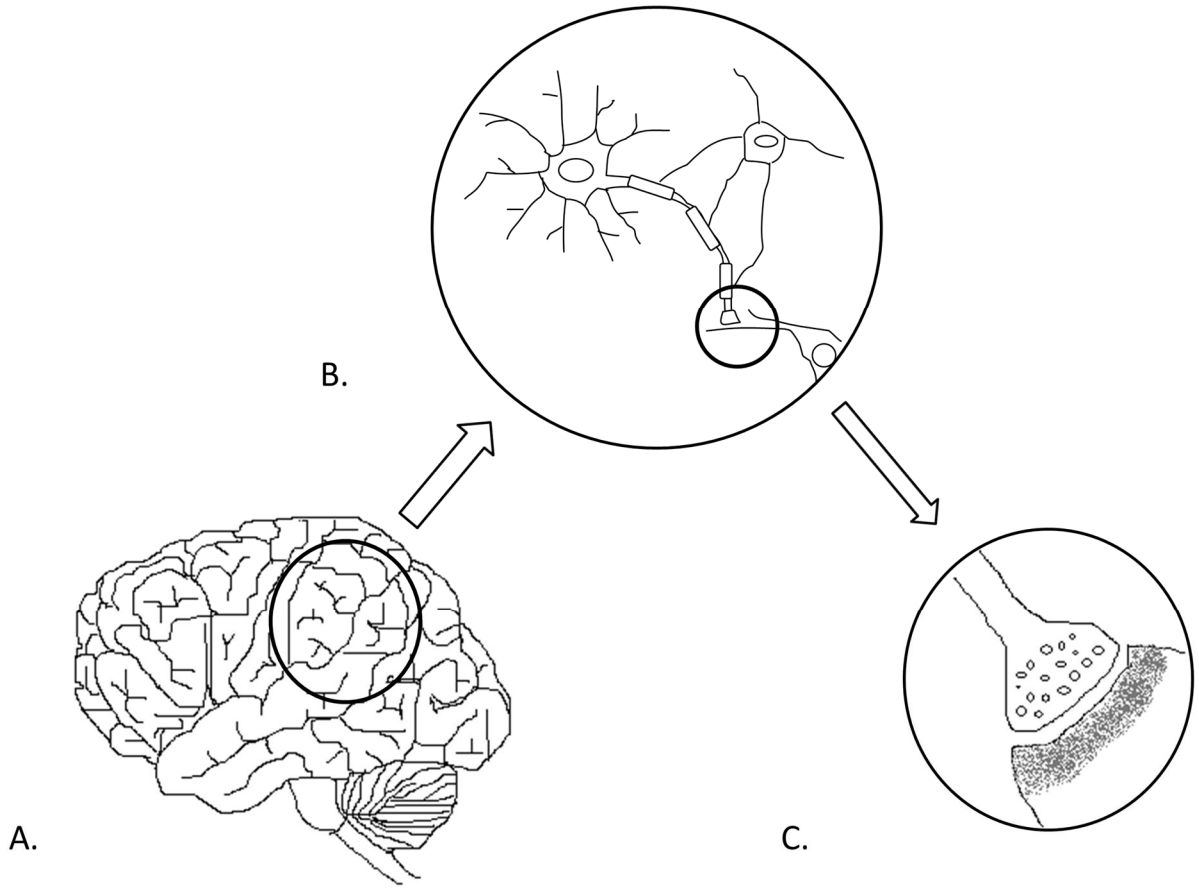

Figure 1. Breakdown of different levels to brain structure. A. Macrostrucure involves whole regions and structures of the brain such as the cerebral cortex, hippocampus, and cerebellum. B. Microstructure makes up the larger components of macrostructure, and includes the cellular level, with structures such as myelin for neuronal axons. C. the axons of nerves end in a synaptic terminal, from which neurotransmitters are released. Neurotransmitters allow the transfer of signals from cell to cell.