

Iodine and Cognition in Young Adults: A Randomised, Placebo-Controlled
Trial

By Kahla Fay Redman

A thesis submitted for the degree of
Master of Science

At the University of Otago, Dunedin, New Zealand.

December 2011

Abstract

Iodine is a micronutrient which is essential to the production of thyroid hormones. Thyroid hormone functions are prevalent throughout the human body, but one of the most important functions is the influence on brain development. Central nervous system components such as myelin and neurotransmission are affected by the levels of iodine and thyroid hormone. Iodine deficiency is recognised as the world's most prevalent preventable cause of intellectual disability. The most severe condition resulting from iodine deficiency is cretinism, which is characterised by severe cognitive impairment. However, even milder forms of iodine deficiency may result in some cognitive impairment. Iodine supplementation in individuals with iodine deficiency has been shown to result in improvements in cognitive scores. The majority of the work has investigated children, with the effect on the young adult population largely unknown. Potential mechanisms by which iodine affects cognition include enhancing neurotransmitters and assisting myelination (white matter maturation), both of which facilitate neurotransmission and are malleable in this age group. The present study investigated the effect that iodine supplementation has on the cognitive scores of mildly iodine-deficient *young adults*. It was hypothesised that individuals who took iodine supplements would show an improvement in cognitive scores above that of the placebo group. Participants were aged 18 to 30 years, and were given either iodine supplements or a placebo, in this double-blind, randomised-controlled trial. Seven subtests from the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) were used including: Block Design, Digit Span Backwards, Matrix Reasoning, Symbol

IODINE AND COGNITION IN YOUNG ADULTS

Search, Visual Puzzles, Coding, and Letter-Number Sequencing. Cognitive scores were measured both prior to and after a 32-week period during which participants took iodine or the placebo. The results showed that at baseline, the participants were mildly iodine-deficient. The results did not support the hypothesis that iodine would facilitate cognition however, as there were consistent non-significant associations with iodine, both when comparing treatment groups and across all participants within examined time points. Thus, iodine supplements, while improving the iodine status of the supplement group, were not associated with an increase in cognitive scores. Furthermore, I speculated that this may have been because iodine facilitates cognition primarily through enhancing myelination, and the process of myelination is more complete in adulthood compared to childhood, and therefore less malleable. These speculations are in need of future research however. Future research could further investigate the differences between child and adult myelin development, as well as the impact of mild iodine deficiency in adults, to determine whether iodine does, in fact, have an effect on adults' cognitive ability.

Acknowledgements

Thank you to my supervisor, Professor Ted Ruffman, for being an invaluable source of guidance. I also wish to thank my co-supervisor Sheila Skeaff, who has invested a great deal in this project.

Thank you to Penelope Fitzgerald, who has always worked so hard and was a great companion throughout this project. I would not have wanted to do this project with anyone else.

I also want to thank my mum, Adeline Redman, who has always been an ear for my troubles and a tireless advocate for my studies. Thank you too, to my Grandma and Grandad, who took the time to write to me every week and who I am very grateful to for their support.

Thank you to Nick, Kelly, Vanessa, and Emma, who among others were always ready to have a chat and kept me sane in stressful times.

Finally, a big thank you to all of the participants who enrolled in the Think2 Project. This could have never been possible without your time and commitment.

IODINE AND COGNITION IN YOUNG ADULTS

Table of Contents

Abstract	ii
Acknowledgments.....	iv
Table of Contents.....	v
List of Tables.....	viii
List of Figures	ix

Introduction

Iodine and Thyroid Hormone.....	1
Iodine Deficiency	3
Neurobiology of Cognition.....	7
White matter development and cognition	7
Neurotransmitter development and cognition	10
Iodine and Cognition	12
<i>Myelin and iodine</i>	<i>13</i>
<i>Neurotransmitters and iodine</i>	<i>14</i>
Iodine Deficiency and Cognition	15
Iodine Supplementation	18
The Present Study.....	23

Method

Participants	26
Materials.....	27
Cognitive Assessment	27
<i>Block Design</i>	<i>28</i>

IODINE AND COGNITION IN YOUNG ADULTS

<i>Digit Span Backwards</i>	28
<i>Matrix Reasoning</i>	29
<i>Symbol Search</i>	29
<i>Visual Puzzles</i>	29
<i>Coding</i>	30
<i>Letter-Number Sequencing</i>	30
Biochemical Measures	30
Supplements	31
Questionnaire	31
Procedure	32
Results	34
Participant Demographics	34
SF-36	39
Biochemical Samples	41
Compliance	46
Cognitive Scores	48
Discussion	60
Biochemical Measures	60
Iodine and Cognition in Adults	63
Biological Basis of Iodine and Cognition	66
Implications	68
Strengths, Limitations, and Future Research	69
Conclusion	71

References	72
-------------------------	-----------

Appendices

A	Poster Advertisement for Participant Recruitment.....	87
B	Questionnaire for Demographic Information	88
C	Short-Form Health Questionnaire (SF-36)	93
D	Information Sheet	97
E	Consent Form	99
F	Introductory Verbatim for Cognitive Testing	100

List of Tables

Table 1	<i>Baseline frequencies for participant demographic information for iodine and placebo groups.....</i>	36
Table 2	<i>Mann-Whitney U scores comparing participants in the iodine group to those in the placebo group at baseline and 32 weeks.....</i>	37
Table 3	<i>Participant health and diet information at baseline and 32 weeks for iodine and placebo groups.....</i>	38
Table 4	<i>Median and mean (standard deviation) scores on the eight categories of the SF-36 for baseline and 32 weeks for iodine and placebo groups</i>	40
Table 5	<i>Median (Mdn) and Mean (standard deviation) for biochemical measures at baseline and 32 weeks for iodine and placebo groups</i>	43
Table 6	<i>Frequency of compliance in the iodine group as determined by difference in iodine status over 32 weeks</i>	48
Table 7	<i>Median and mean (standard deviation) of cognitive test scores at baseline and 32 weeks for placebo and iodine groups.....</i>	49
Table 8	<i>Cognitive scores at baseline and 32 weeks for iodine and placebo groups</i>	50
Table 9	<i>Spearman's correlations between differences in cognitive scores and intervention (n = 172)</i>	52
Table 10	<i>Spearman's correlations between iodine difference scores and cognitive difference scores within the iodine group.....</i>	53
Table 11	<i>Spearman's correlations between cognitive scores and urinary iodine concentration (UIC) at baseline for iodine group (n = 102)</i>	55
Table 12	<i>Spearman's correlations between cognitive scores and thyroglobulin concentration (Tg) at baseline for the iodine group (n = 102).....</i>	56
Table 13	<i>Spearman's correlations between cognitive scores and urinary iodine concentration (UIC) at 32 weeks for iodine group (n = 64)</i>	57
Table 14	<i>Spearman's correlations between cognitive scores and thyroglobulin concentration (Tg) at 32 weeks for iodine group (n = 55).....</i>	58

List of Figures

<i>Figure 1</i>	Classification of iodine status (severe: <20 µg/L, moderate: 20-49 µg/L, mild: 50-99 µg/L, sufficient: 100-299 µg/L, and excessive: >300 µg/L) as measured by urinary iodine concentration (UIC) for iodine and placebo groups at baseline and 32 weeks	44
<i>Figure 2</i>	Classification of iodine status (sufficient: <10 µg/L, mild: 10-19 µg/L, moderate: 20-39 µg/L, and severe: >40 µg/L) as measured by thyroglobulin for iodine and placebo groups for baseline and 32-week	45

IODINE AND COGNITION IN YOUNG ADULTS: A RANDOMISED, PLACEBO-CONTROLLED TRIAL

Iodine is a micronutrient found in numerous body tissues (Patrick, 2008), and is an essential component of thyroid hormones (TH; Mattson Porth & Matfin, 2009). TH, and therefore iodine, are important for an array of biological functions, including brain development (Delange, 2001). When iodine is severely deficient, developmental abnormalities may arise (Bleichrodt, Drenth, & Querido, 1980). Iodine deficiency is recognised by the World Health Organisation (2007) as being the most prevalent cause of preventable cognitive impairment. It may affect individuals at any stage of life, starting *in utero* and continuing into adulthood (Zimmermann, Jooste, & Pandav, 2008). Even mild iodine deficiency may be associated with mental impairment (Zimmermann, 2009). Correcting these deficiencies with iodine supplementation or food fortification has the potential to improve iodine status (Untoro, Timmer, & Schultink, 2010). While most of the research has examined school children, from a public health perspective it is important to know whether the effects of iodine deficiency on cognition extend to adults. Below, iodine's effect on the body and cognitive ability is examined.

Iodine and Thyroid Hormone

Iodine is absorbed through the food people eat, and the amount of iodine is influenced by the environment in which food grows and is sourced (World Health Organisation, 2007). Seafood (including seaweeds such as kelp) is particularly high in iodine, whereas crops grown in mountainous regions may become low in iodine due to iodine depletion in the soil (Zimmermann, 2009).

IODINE AND COGNITION IN YOUNG ADULTS

For mammalian bodies, iodine is essential for synthesising thyroid hormones (TH; Mattson Porth & Matfin, 2009). There are two relevant thyroid hormones: triiodothyronine (T3) and thyroxine (T4; Ahmed, El-Gareib, El-Bakry, El-Tawab, & Ahmed, 2008). T4 acts mainly as a pro-hormone and is converted locally in cells to T3, the active form of TH (Bernal, 1999). T4 and T3 are necessary for most tissue growth in the body, as well as influencing metabolism and brain development (Delange, 2001). TH accelerate myelination, influence maturation of certain neuronal populations, as well as cell migration and differentiation in the brain (Rivas & Naranjo, 2007). This makes iodine an essential micronutrient for humans (Hollowell & Hannon, 1997).

Thyroid hormone release is controlled in part by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus, which in turn stimulates the anterior pituitary gland to release thyroid-stimulating hormone (TSH; Magner, 1997). TSH functions to stimulate the thyroid gland to synthesise T4, the precursor to T3. This system works on a negative feedback loop such that when T4 levels increase or decrease, TSH secretion is decreased or increased, respectively (Magner, 1997). Iodine status can be assessed in several ways, although the main methods used include measures of TSH, thyroglobulin (Tg) and urinary iodine concentration (UIC; Zimmermann et al., 2008). Urine samples are used to indicate recent changes (i.e., over days) in iodine intake, as 90% of ingested iodine is excreted through urine (Andersson & Zimmermann, 2010). Tg indicates changes from weeks to months (Zimmermann et al., 2008). Tg is a protein produced by the thyroid gland, and levels in blood circulation increase with TSH stimulation (Zimmermann, 2008). Serum Tg, taken from small blood samples, is a good

IODINE AND COGNITION IN YOUNG ADULTS

indicator of recent iodine status in children and adults (Andersson & Zimmermann, 2010). In adults, TSH is a relatively insensitive measure of iodine status (Zimmermann, 2008). Thyroid hormones themselves (T3 and T4) are also considered to be insensitive measures of iodine status except in situations of very severe iodine deficiency (Zimmermann, 2008). Total thyroxine (TT4), the biologically active form of thyroid hormone, may be influenced by other factors such as pregnancy or the intake of oral contraceptives (Schatz, Palter, & Russell, 1968). To control for this, a free thyroxine index (FTI) may be calculated, by multiplying TT4 and uptake of T3 (by calculating levels of thyroid binding globulin). The FTI is considered a clinically reliable indicator of thyroid function (Schatz et al., 1968).

Iodine Deficiency

The World Health Organisation (2007) recommends a dietary intake of iodine of 150 µg/day for adolescents and adults. In childhood the range is from 90 µg/day (0-5 years) to 120 µg/day (6-12 years). Infants typically need more iodine than children (110-130 µg/day), while pregnant and lactating women need the most iodine, at 250 µg/day (World Health Organisation, 2007). If not enough iodine is ingested, iodine deficiency may result in suboptimal levels of TH, the effects of which are more focused on brain development than the thyroid (Delange, 2001). Insufficient iodine intake may lead to a series of adverse health effects called iodine deficiency disorders (Hetzel, 1983). Iodine deficiency disorders reveal the impact that TH have on a wide range of functions in the body, and iodine deficiency is one of the leading causes of preventable developmental delay (World Health Organisation, 2007). Iodine deficiency disorders are common and reported around the world, not just in

IODINE AND COGNITION IN YOUNG ADULTS

remote mountain areas, but also in Asia, Europe and Africa (Melse-Boonstra & Jaiswal, 2010). More economically developed countries such as Australia and New Zealand, also have reported a re-emergence of iodine deficiency (McElduff & Beange, 2004; Skeaff, Thomson, & Gibson, 2002).

In order to categorise samples as iodine-*deficient*, or iodine-*sufficient*, biochemical results may be used to place samples into ranges of iodine status. Urinary iodine concentration (UIC) ranges of iodine status for adults are: severe, <20 µg/L; moderate, 20-49 µg/L; mild, 50-99 µg/L; sufficient, 100-299 µg/L; and excessive, >300 µg/L. For thyroglobulin (Tg) measures the adult ranges are: iodine sufficient, <10 µg/L; mild, 10-19 µg/L; moderate, 20-39 µg/L; and severe, >40 µg/L (World Health Organization, 2007).

Iodine deficiency disorders characterise a range of symptoms across age groups (Hetzel, 1983). Maternal iodine deficiency may negatively impact pregnancy and the growth of unborn children, resulting in congenital abnormalities, while other symptoms include increased risk of morbidity and mortality. Infants born to mothers with severe iodine deficiency in pregnancy may develop cretinism, while children and adolescents may have stunted growth. Adults may be at an increased risk of hyperthyroidism. However, the risk of goitre (thyroid enlargement), hypothyroidism, increased susceptibility of the thyroid to nuclear radiation, and cognitive impairment, are present at all ages (World Health Organisation, 2007). The most severe consequence of iodine deficiency is cretinism. Cretinism is a term for a collection of developmental abnormalities that result from severe iodine deficiency in pregnancy (Hetzel, 1983). The most notable symptom of cretinism is severe intellectual disability (Bleichrodt et al., 1980). Cretinism is the more serious aspect of iodine

IODINE AND COGNITION IN YOUNG ADULTS

deficiency, yet populations are affected by cognitive impairment in lesser forms of iodine deficiency (Zoeller & Rovett, 2004). Moderate and mild deficiencies also result in cognitive impairment, for all ages (Gordon, Rose, Skeaff, Gray, Morgan, & Ruffman, 2009; Zimmermann, 2009). Iodine deficiency in adulthood may result in decreased work productivity (Zimmermann et al., 2008), while iodine-deficient communities may be characterised by low ambition and low productivity (Hetzel, 1983). This is important from a public health perspective, as the general population is most affected by this more subtle impairment (World Health Organisation, 2007).

Iodine is a major constituent in thyroid hormones, so deficiency impairs such activity in the central nervous system (Rivas & Narajo, 2007). The possibility that the effect of iodine on brain development could be independent of TH has been considered in the past. However, studies have shown that the cognition-iodine link appears to be mediated by TH (Bernal, 1999; Mano, Potter, Belling, Chavadej, & Hetzel, 1987). Reductions in TH have been shown to result in decreases in brain weight, synaptogenesis, the size of cortical neurons, and decreased myelination (Loosen, 1992). When mice were born to iodine-deficient mothers, there was an array of detrimental effects including reduced brain weight (Farsetti, Mitsuhashi, Desvergne, Robbins, & Nikodem, 1991). It has been suggested that the body is able to compensate for iodine deficiency (Bleichrodt et al., 1980). However, in a subclinical, hypothyroid animal model, the developing brain does not compensate for lower levels of thyroid hormone (Sharlin, Gilbert, Taylor, Ferguson, & Zoeller, 2010).

IODINE AND COGNITION IN YOUNG ADULTS

Animal studies on the effects of iodine deficiency are not just limited to rats. Sheep have a metabolism for TH that is similar to humans (Potter et al., 1984). This makes sheep a suitable model to investigate the effects of iodine deficiency on brain development. One study used Merino ewes to investigate the effects of iodine deficiency on fetal development (Potter et al., 1984). Thirty ewes were fed a low-iodine diet, whereas 10 of these animals were given a dose of iodised oil to prevent deficiency and to serve as controls. All ewes were then successfully impregnated, but at 100 days of gestation, eight of the iodine-deficient ewes were supplemented with iodised oil. At 140 days of gestation the fetuses were surgically delivered, and their brains were removed and examined. Iodine deficiency had a severe impact on fetal development, with iodine-deficient lambs displaying an absence of wool coat, as well as malformed foot joints and a malformed cranium. The cell numbers in the cerebellum and cerebral hemispheres of the brain were also decreased in animals that were iodine-deficient. The offspring whose mothers had received a dose of iodised oil during the gestation period showed recovery of brain structure although not to the same extent as controls, which had an iodine rich diet (Potter et al., 1984).

While rat and sheep studies have provided considerable evidence for the effects of iodine on brain development, primate models are also useful. Common cotton-eared marmosets are considered to have a close evolutionary relatedness to humans and were used in an investigation into iodine deficiency effects on fetal brain development (Mano et al., 1987). Twenty male-female pairings were used to compare the effects of high- and low-iodine diets. The pairs were divided into two groups and fed either an iodine-rich diet, or a diet low in iodine. The pairs were bred and the offspring surgically delivered 12

IODINE AND COGNITION IN YOUNG ADULTS

hours before natural birth. The results showed that the offspring of parents who were iodine-deficient, had reduced hair growth, reduced strength, and brain regions that showed reduced cell numbers and cell size (Mano et al., 1987).

In summary, iodine is a vital constituent of TH, which in turn is essential for normal brain development. When iodine levels are insufficient, a spectrum of deficits may arise in the organism. Animal studies on iodine deficiency have shown that an iodine-deficient brain may be characterised by impaired myelination, decreased cell numbers and cell size, as well as reduced brain weight. This may provide the biological basis for impaired cognition in the iodine-deficient individual.

Neurobiology of Cognition

White matter development and cognition. Scientists once thought that the brain could not change or grow new cells past adolescence. This is now widely refuted as both neurogenesis and gliogenesis still occur in the adult brain, albeit in specialised regions (Gage, 2002). White matter in the brain is comprised of myelinated axons (Bear et al., 2007). Myelin is a fatty tissue produced by oligodendrocytes in the mammalian central nervous system (Bauman & Pham-Dinh, 2001), and functions to increase conduction of electrical impulses between brain regions (Filley, 2010; Gur et al., 1999). Myelin is important for a diverse array of functions within the nervous system, and is also thought to be the only structure in the brain that can also truly repair itself in the adult central nervous system (Calza, Fernandez, & Giardino, 2010).

White matter begins to rapidly develop at birth and continues this trajectory into adolescence (Baumann & Pham-Dinh, 2001). Myelination and white matter volume continues to increase after adolescence and into adulthood

IODINE AND COGNITION IN YOUNG ADULTS

(e.g., Bartzokis, Beckson, Lu, Nuechterlein, Edwards, & Mintz, 2001; Bartzokis et al., 2010; Ge, Grossman, Babb, Rabin, Mannon, & Kolson, 2002), reaching a plateau at approximately 40 years of age (Courchesne et al., 2000). In older adults, white matter is degraded and undergoes a reduction in volume (Guttman et al., 1998), however this decrease does not begin until around the sixth decade of life (Bartzokis et al., 2001). Ge et al. (2002) assessed white and gray matter maturation in adults to investigate the effect of age and sex on brain volume. Fifty-four participants, aged between 20 and 86 years underwent magnetic resonance imaging (MRI), in order to calculate the percentages of white and gray matter in the brain. It was demonstrated that on a global level, white matter volume increased slightly between 20 to 40 years, after which it levels off and then subsequently declines in volume. A different pattern was shown for gray matter volume, which declines in a linear fashion after adolescence (Ge et al., 2002). These patterns of gray and white matter change are particularly robust and have been demonstrated in many neuroimaging studies (e.g., Barzokis et al., 2001; Courchesne et al., 2000; Ge et al., 2002; Giedd et al., 1999).

Myelin allows neurons to transmit signals more quickly (Bear et al., 2007). This may translate into improvements in problem solving (Nagy, Westerberg, & Klingberg, 2004), processing speed, and working memory (Edin, Macoveanu, Olesen, Tegner, & Klingberg, 2007). Age-related changes in fluid intelligence and short-term memory have been associated with processing speed, suggesting that processing speed appears to be a meaningful measure of cognitive capacity (Krail & Salthouse, 1994). Neuroimaging studies are able to map white matter tracts and activity at the time of cognitive task performance. It has been shown that increases in white matter are associated with increased

IODINE AND COGNITION IN YOUNG ADULTS

cognitive performance (e.g., Bava, Thayer, Jacobus, Ward, Jernigan, & Tapert, 2010; Olesen, Nagy, Westerberg, & Klingberg, 2003; Nagy et al., 2004; Zahr, Rohlfsing, Pfefferbaum, & Sullivan, 2009).

In one longitudinal study, diffuse tensor imaging (DTI) was used to measure white matter changes in individuals after 16 months (Bava et al., 2010). Twenty-two participants (15 males and 7 females) were recruited from high schools, with a mean age of 17.8 years. Behavioural and neuropsychological tests were administered at both the beginning of the study and at follow-up, where participants were on average 19.2 years of age. Participants were measured on working memory, executive function, learning and recall. The study investigated the pattern of white matter maturation over this time period as well as the association with cognitive performance. The authors observed correlations for maturation of different brain regions and performance in specific cognitive tests, namely those that reflected working memory and perceptual reasoning (Bava et al., 2010).

Likewise, Olesen et al. (2003) used fMRI to demonstrate a link between working memory performance and white matter development in children and adolescents. Images from a small number of specific brain regions in 23 participants were analysed. Participants were aged from 7.8 to 18.5 years. Axonal thickness was used to indicate myelination, and was found to increase with age-related white matter development and working memory (Olesen et al., 2003). Together, these studies demonstrate the relation between white matter development and working memory for individuals under 20 years of age.

There is a general lack of studies examining cognition and white matter maturation in neurologically healthy, young adults. One exception is a study

IODINE AND COGNITION IN YOUNG ADULTS

that used DTI and MRI to show that in adults aged 20 to 80 years, cognitive performance was positively correlated with white matter structure (Bendlin et al., 2010). Participants included neurologically healthy individuals, who 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 (Bendlin et al., 2010).

Neurotransmitter development and cognition. Neurotransmitters are chemicals, which signal between neurons. They are released at synapses between axon terminals and responding cells, and act on receptors in the postsynaptic cell membrane. The rate and magnitude of neurotransmission can alter the speed at which signals are relayed throughout the nervous system (Bear et al., 2007). Prior to and after birth, neurotransmitters and their receptors are involved in critical periods of development and are important for brain development (Herlenius & Lagercrantz, 2004). However, neurotransmission may be altered in both adults and children (Seedat et al., 2002). Many different neurotransmitter systems are found within the central nervous system and these may be involved in cell proliferation, migration, growth, or differentiation (Nguyen et al., 2001); however, the full extent of their purpose is unknown. Neurotransmitter systems also change in function, and mature over the lifetime of an individual (Dratman & Gordon, 1996), specifically increasing or decreasing due to demands from development or environmental factors (Herlenius & Lagercrantz, 2004). As many systems have been postulated to be

IODINE AND COGNITION IN YOUNG ADULTS

involved in cognition, it is likely that multiple and complex pathways are used (Silva, Elgersma, & Costa, 2000).

The connection between neurotransmission and cognition has been well documented. Norepinephrine, dopamine, serotonin, acetylcholine, and glutamate are just some of the neurotransmitters that have been shown to affect brain development, learning, and cognitive ability (Herlenius & Lagercrantz, 2004). For example, dopamine is a neurotransmitter that has been implicated in cognition, particularly for functions that stem from the prefrontal cortex such as working memory, reward processing, and reinforcement learning (Li, Lindenberger, & Bäckman, 2010). An optimal level of dopamine signalling has been shown to be associated with optimal cognitive functioning, so that cognitive performance appears as an inverted-U function. Too little or excessive neurotransmitter levels are associated with impaired cognitive performance (Li et al., 2010). Both non-human primate studies, as well as neuroimaging studies in humans have demonstrated the effects of dopamine receptors on cognition (McNab et al., 2009; Sawaguchi & Goldman-Rakic, 1991; Wang, Vijayraghavan, & Goldman-Rakic, 2004; Williams & Goldman-Rakic, 1995). There is little research into the changes of dopamine signalling across the lifespan and how this affects cognition (Li et al., 2010), but differences between young and older adults indicate that the more efficient transmission of dopamine in young adults is associated with improved cognitive performance (Bäckman et al., 2011). It is unlikely that dopamine is responsible for this effect on cognition alone; instead interactions with other neurotransmitters, such as N-methyl-D-aspartate (NMDA), are important (Li et al., 2010).

IODINE AND COGNITION IN YOUNG ADULTS

Neurotransmission also plays an important function in synaptic plasticity. Synaptic plasticity is the ability of the synapse to alter the transmission between neurons through changing the numbers of receptors or the numbers of neurotransmitters released, and may be fundamental to cognition (Drever, Riedel, & Platt, 2011). Plasticity, along with neurotransmission, may also be altered across the lifespan of an organism (Li, Brehmer, Shing, Werkle-Bergner, & Lindenberger, 2006). Synaptic plasticity may be altered for both short-term and long-term periods. Short-term plasticity may appear as paired pulse facilitation, where previous synaptic transmission enhances the following transmission, and lasts for a matter of seconds (Sui, Wang, & Li, 2006). Long-term plasticity is developed with long-term potentiation or depression (Drever et al., 2011), and these alter synaptic transmission for a much longer period of time (from minutes to hours). Both paired pulse facilitation and long-term potentiation are thought to be of importance for memory formation and cognitive function (Sui et al., 2006). NMDA has been implicated as one of the neurotransmitter systems essential for synaptic plasticity. Superior performance on the water-maze task and the T-maze spatial working memory task is associated with increased synaptic plasticity, and has been shown in mice that over-express NDMA receptors (Cao et al., 2007; Tang et al., 1999).

Iodine and cognition. As described above, neurotransmission and white matter maturation continue throughout adulthood and this is often associated with improved cognitive functioning. These systems will be influenced by genetic and environmental components, including nutrition (Buccafusco & Terry, 2000). Changes in iodine (and therefore TH) may be accompanied by changes in cognitive ability. The relation between TH and cognition is poorly

IODINE AND COGNITION IN YOUNG ADULTS

understood (Erlanger, Kutner, & Jacobs, 1999), but the effects appear to be variable and multifunctional. TH may act directly on the central nervous system, and have effects on myelination, cell migration and differentiation, dendritic structure, and synaptogenesis (Thompson & Potter, 2000), as well as influencing synaptic plasticity (Koibuchi, 2008).

Myelin and iodine. Myelin production may be influenced by the environment, genes, and nutrition (Fields, 2008). Iodine (and TH) have been well established as critical for myelin development (Bernal, 1999; Zoeller & Rovert, 2004) although the exact mechanism for this relation is unknown (Thompson & Potter, 2000). Cognitive processes such as processing speed are thought to be sensitive to changes in nutrition, especially hypothyroidism (Zimmermann, Connolly, Bozo, Bridon, Rohner, & Grimci, 2006). However, there is little research into the effects of iodine deficiency, specifically on white matter and cognition. There appears to be several ways in which TH may affect myelin production, as TH are essential for oligodendrocyte differentiation (Bernal, 1999), and are also involved in regulation of myelin forming genes (Thompson, 1999). TH bind to specific nuclear receptors (TR), which allow for transcription of relevant genetic material (Magner, 1990). However, whether TH influence gene transcription for genes controlling myelin production or whether TH directly acts on oligodendrocytes is unknown (Thompson & Potter, 2000).

In animal studies, TH have been shown to be essential for the development of oligodendrocytes. Induced hyperthyroidism in newborn rats increases the number of oligodendrocytes present in the optic nerve. Also, oligodendrocyte progenitor cells cultured from rats do not develop into oligodendrocytes in the absence of TH (Barres, Lazar, & Raff, 1994). Myelin

IODINE AND COGNITION IN YOUNG ADULTS

production may still be influenced by TH in adulthood, by controlling oligodendrocyte differentiation (Fernandez, Pirondi, Manservigi, Gardino, & Calza, 2004). In a study by Fernandez et al. (2004), adult rats were induced to develop either hypo- or hyperthyroidism. The result of this manipulation showed that TH were important for the regulation of oligodendrocyte progenitor cells, including the maturation of the cells into myelinating oligodendrocytes in the adult CNS (Fernandez et al., 2004).

Neurotransmission and iodine. TH are often found in synaptic terminals in the brain (Dratman & Gordon, 1996) and have also been associated with changes in neurotransmitters in the brain, including functioning as neuromodulators in the CNS (Martinez, Santos, & Colino, 2002). It has also been suggested that TH may act as neurotransmitters themselves (Yen, 2001). Several animal studies have shown an association between iodine deficiency, cognitive impairment and deficits in synaptic plasticity (Fernandez-Lamo, Montero-Pedrazuela, Delgado-Garcia, Guadano-Ferraz, & Gruart, 2009; Gilbert & Sui, 2006; Opazo et al., 2008). Adult rats fed on a low iodine diet have been shown to have altered dopamine receptors (Overstreet, Crocker, Lawson, McIntosh, & Crocker, 1984). Rats with congenital iodine deficiency often show a dose-dependent relation with cognitive problems, and also impairment in synaptic transmission and plasticity (Gilbert & Sui, 2006). Iodine deficiency has also been shown to reduce the expression and maintenance of long-term potentiation. Using developmentally iodine-deficient rats, there was a significant effect of deficiency on long-term synaptic plasticity (Liu, Dong, Wang, Xi, & Chen, 2010). Rat studies of offspring with congenital iodine deficiency display impairment in long-term potentiation induction. This often

IODINE AND COGNITION IN YOUNG ADULTS

correlates with poor performance on cognitive (such as spatial memory) tasks, and this is thought to be analogous to humans (Opazo et al., 2008). Rats with adult-onset hypothyroidism also show deficits in learning processes and synaptic changes (Fernandez-Lamo et al., 2009). Short-term plasticity is decreased in animals that are hypothyroid (Vara, Martinez, Santos, & Colino, 2002). Vara et al. (2002) compared rats that were hypothyroid and euthyroid (normal thyroid function), and found that paired pulse facilitation was reduced in the hypothyroid rats.

Iodine Deficiency and Cognition

As described above, TH and therefore iodine have an important relation with brain structures such as myelin and neurotransmitters, which are linked to cognitive function. However it is important to note that the actual neural basis for cognition in normal development is not well known (Casey, Giedd, & Thomas, 2000) The iodine-deficient brain (especially during prenatal and neonatal development) appears to have a vast range of impaired brain processes, yet the behavioural effects of iodine deficiency on cognition are important too. Generally, the more severe the iodine deficiency, the more severe the effects on cognitive function will be. Iodine deficiency has effects on cognitive ability for all ages, and leads to a 10-15 point IQ loss globally, at population level (Delange, 2001). This statement has been contested, as the evidence initially for iodine and cognitive ability was mixed. It was suggested that only severe iodine deficiency resulted in cognitive impairment, and that there was no continuum of intellectual impairment with the severity of iodine deficiency. This was suggested in a study by Bleichrodt et al. (1980) of Indonesian children living in an iodine-deficient area, who did not have cretinism. Children were tested with

IODINE AND COGNITION IN YOUNG ADULTS

an extensive battery of cognitive and perceptual-motor tasks. It was concluded that although iodine deficiency is associated with some central nervous system abnormalities (such as psychomotor impairment), intellectual disability was not a result of iodine deficiency.

However, the notion that milder iodine deficiency does not cause cognitive impairment is inconsistent with studies comparing different levels of iodine deficiency. The children in 10 iodine-deficient villages in Uttar Pradesh, India were tested on learning and motivation to achieve (Tiwari, Godbole, Chattopadhyay, Mandal, & Mithal, 1996). Villages were all situated approximately six kilometres from the town of Padrauna and were similar with regard to measures of socioeconomic status and cultural indices. Analysis of urinary iodine, serum TSH, and serum Tg, determined whether participants were mildly or severely iodine-deficient. The 100 participants, aged 8 to 18 years, were tested on pictorial learning, achievement motivation scales, verbal learning and the human stylus maze. Significant differences emerged between severely and mildly deficient groups for maze learning, pictorial learning and motivation. The authors concluded that severely iodine-deficient children were significantly slower at learning tasks. Practice effects were found to be greater for mildly deficient children, indicating that deficiency reduces speed of learning. The authors did state that this may not be a purely neurological effect, but also that the environment in rural India may not be conducive for the psychological stimulation needed for development, especially as motivation was also lower in severely iodine-deficient children. Improving TH levels potentially improves performance as other symptoms of hypothyroidism include apathy, lethargy and sleepiness (Amarra, Bongga, Penano-Ho, Cruz, Solis, & Barrios,

IODINE AND COGNITION IN YOUNG ADULTS

2007). Motivation and learning ability may also explain the differences between iodine-deficient and iodine-sufficient populations rather than purely neuronal system changes (Tiwari et al., 1996).

Many studies have used different cognitive measures, yet overall there is a large effect of iodine deficiency on IQ (Bleichrodt & Born, 1994). A meta-analysis of cross-sectional studies conducted in children living in iodine-deficient regions, found a 13.5-point IQ difference between iodine-deficient and iodine-sufficient groups (Bleichrodt & Born, 1994). Another meta-analysis in China found that severe iodine deficiency produced profound intellectual deficits, with approximately 12.5-point IQ losses compared to children in an iodine-sufficient environment, which may partially be recovered with iodine supplementation in pregnancy. If supplementation was inadequate however, no improvement in cognitive scores was observed (Qian et al., 2005).

Nevertheless, these studies have several limitations. Many are observational and contain other confounding variables that may explain the effects of iodine deficiency. These include differences in socioeconomic status, area remoteness, infrastructure, school and healthcare facilities, as well as maternal nutrition and environmental stimulation (Melse-Boonstra & Jaiswal, 2010). There were also large levels of variation between studies in terms of outcomes (Bleichrodt, Shrestha, West, Haulvast, van der Vijer, & Born, 1996). Another limitation is that measures used to evaluate iodine status have been challenged, as many methods of evaluating iodine status may be used between studies (van den Briel, West, Hautvast, Vulsma, de Vijlder, & Ategbo, 2001). A study of iodine deficiency in schoolchildren in Benin, assessed the validity of the tools used to measure iodine levels (van den Briel et al., 2001). While

IODINE AND COGNITION IN YOUNG ADULTS

initially a randomised controlled trial, introduction of iodised salt during the intervention period caused an abrupt change in the study design. At baseline, thyroid volume, TT4 (total thyroxine), UIC, serum Tg and TSH were measured. Despite participants being moderately to severely deficient as measured by UIC, mean serum TSH and TT4 were in the normal range. All the indicators showed an improvement from baseline to the end of the study; however serum Tg and UIC were labelled as the most appropriate indicators as these had the closest association with iodine level changes. This may be due to the types of iodine changes that these tools measure, with UIC and serum Tg being more sensitive to changes in thyroid stimulation. Such findings demonstrate how different variables, such as the method used to measure iodine status, may contribute to the disparity in the results between studies. To properly evaluate the effects of iodine on cognition, randomised controlled trials must be used.

Iodine supplementation

Studies of iodine supplementation and cognition have generally been carried out with children. In a study of children in Bolivia, it was found that improving iodine status can reverse the adverse effects of iodine deficiency. While scores on the cognitive tests showed no overall difference between treatment groups, when controlling for goitre reduction, a positive effect was found for supplementation on school performance and cognitive ability (Bautista, Barker, Dunn, Sanchez, & Kaiser, 1982). A similar result was found for children given a single iodised oil supplement in Benin, West Africa (van den Briel, West, Bleichrodt, van de Vijer, Ategbo, & Hauvast, 2000). Although no association was initially found between supplementation and cognitive scores, when the children were classified after treatment into ‘improved’ and

IODINE AND COGNITION IN YOUNG ADULTS

‘unchanged’ iodine status groups, effects on cognition were observed. The group similarities in iodine status may have been related to numerous factors, including the addition of iodised salt into the community during the study period. The authors attributed the positive results to a developmental “catch up” for the cognitive ability improvement, particularly in abstract reasoning, although a general change in the state of apathy may have also resulted in improved scores.

Another study that did not find an association between improved iodine and cognitive status was carried out by Isa, Alias, Kadir, and Ali (2000). Sixty school children from remote areas of peninsular Malaysia were given a single dose of iodised oil, and compared with 105 control children who received no supplement. Iodine status was assessed through serum T4 and TSH, as well as urinary iodine levels. Follow-ups occurred at 6 and 12 months after the initial baseline testing. Both treatment and control groups had a significant increase in serum T4 and urinary iodine levels, but only the treatment group showed a decrease in serum TSH. While both groups improved their performance in the Test of Non-verbal Intelligence-Second Edition (TONI-2), the control group showed the superior improvement during the follow up at six months. However it is important to note that the two groups - treatment and control - were recruited from separate villages within the area of Perak, Malaysia, leading to the possibility that environmental or genetic differences between the two areas may have contributed to the differences in performance of the cognitive scores (Isa et al., 2000).

Huda, Grantham-McGregor, and Tomkins (2001) also found that supplementation of iodine-deficient children did not improve intelligence

IODINE AND COGNITION IN YOUNG ADULTS

scores, but did play a role in psychomotor skills. Children, who were living in a severely iodine-deficient population (as measured by goitre prevalence) in Bangladesh, were randomly assigned to receive a single dose of iodised oil or a placebo (poppy seed oil). At study enrolment and 4 months later, several different cognitive and motor tasks were measured. The test scores of both groups improved, yet there were no significant differences between treatment and placebo groups. The serum Tg levels did not change across the treatment period, suggesting that in this sample the treatment did not produce an adequate improvement in iodine status. The authors interpreted these findings as a display of thyroid adaptation to very low levels of iodine intake. Baseline levels for UIC showed moderate deficiency; however TSH and serum Tg levels were in the normal range, even with the high goitre prevalence. This led the authors to conclude that no cognitive performance increase was observed because there was no mental impairment (due to the efficiency of the thyroid to produce adequate amounts of TH). This is inconsistent with previous evidence in animal studies that shows that the brain cannot compensate for low TH levels in development (Sharlin et al., 2010).

Thus, there are several studies that have suggested iodine supplementation does not always increase cognitive performance. Yet, there have also been some positive findings. For instance, a randomised controlled trial for moderately iodine-deficient, Albanian children, demonstrated that iodine supplementation improves iodine status and subsequently cognitive test scores (Zimmermann et al., 2006). Ten- to 12-year-old children were given a single dose of iodised oil or a placebo. Iodine status was assessed using UIC, thyroid size, TSH and TT4 levels. After 24 weeks, there was a significant

IODINE AND COGNITION IN YOUNG ADULTS

improvement in various tests tapping abstract reasoning or fluid IQ. These cognitive improvements were associated with improved iodine status in the treatment group, whereas there were no changes from baseline to study termination for the placebo group. Furthermore, this study found that psychomotor ability was also enhanced by iodine supplementation, providing the strongest support for the effect of supplementation on moderate iodine deficiency in children.

The majority of research into iodine status and cognition has been in areas of severe or moderate deficiency, in populations of low socioeconomic status and low education levels. However it has been suggested that even mild deficiency may cause intellectual impairment (Zimmermann, 2009). In New Zealand, mild iodine deficiency has been documented in two studies. First, 300 school children aged 8 to 10 years were assessed in Wellington and Dunedin, between 1996 and 1998 (Skeaff et al., 2002). Thyroid volume and UIC were measured and it was concluded that this sample was mildly iodine-deficient. This result was later confirmed in a nationally representative survey of children aged 5 to 14 years, indicating that mild iodine deficiency is present in New Zealand school children (Parnell et al., 2003). It is important for the cognitive effects of mild iodine deficiency to be assessed in these populations as well as those with more severe deficiencies, as it will aid knowledge into the continuum of developmental effects that iodine deficiency has on cognitive function.

Second, Gordon et al. (2009) carried out a study investigating iodine supplementation effects on cognition in mildly iodine-deficient school children. Participants were 184 children aged 10 to 13 years living in Dunedin. The cognitive testing was comprised of four subtests from the Wechsler Intelligence

IODINE AND COGNITION IN YOUNG ADULTS

Scale for Children (WISC-IV), including Picture Concepts, Letter-Number Sequencing, Matrix Reasoning and Symbol Search. These tests assess perceptual reasoning, working memory and processing speed. Matrix Reasoning was used as a perceptual reasoning task, and such tasks are “recognized as good measures of fluid reasoning and reliable estimates of general intellectual ability” (Williams, Weiss, & Rolfhus, 2003, p. 4). Picture Concepts, another core perceptual reasoning task in the WISC-IV is thought to “measure fluid reasoning and abstract categorical reasoning ability” (Williams et al., 2003, p. 4). Letter-Number Sequencing, a test of working memory, “involves sequencing, mental manipulation, attention, short-term auditory memory, visual-spatial imaging, and processing speed” (Williams et al., 2003, p. 5). Symbol Search, a subtest of processing speed, may also measure “auditory comprehension, perceptual organisation, fluid intelligence, and planning and learning ability” (Wechsler, 2008).

Participants took daily iodine supplements over a 28-week period. Cognitive testing was carried out on enrolment and 28 weeks later, as was testing of UIC, TT4 and serum Tg samples. It was found that the participants were mildly iodine-deficient. After supplementation there was a significant improvement in serum Tg, indicating an adequate iodine status for the treatment group, while the placebo group was still considered iodine-deficient. Associated with the improvement in iodine status, was an increase in two of the four cognitive test scores relative to the placebo group. Both Picture Concepts and Matrix Reasoning produced significant differences between treatment groups. While Letter-Number Sequencing and Symbol Search were positively associated with iodine status, the scores did not reach significance. As a

IODINE AND COGNITION IN YOUNG ADULTS

randomised, placebo-controlled, double-blind trial, this study showed that in mildly iodine-deficient schoolchildren, improving iodine status is associated with increased cognitive performance, specifically perceptual reasoning ability or fluid IQ.

There is evidence that changes in brain structures (including myelin) are associated with cognitive functions, such as processing speed and working memory (Bendlin et al., 2010). These brain structures and cognitive functions are plastic and changing constantly, even after childhood (Bartzokis et al., 2001). While the most critical period for iodine and thyroid hormones for brain development is from the second trimester to the third year after birth (Qian et al., 2005), brain development and TH effects still occur into adulthood (Yen, 2001). White matter and neurotransmission continue developing in structure and function into adulthood. As these systems change across the lifespan, and as iodine deficiency has been shown to impair cognitive function in adults, it is important to investigate a wider range of ages with respect to cognition, not just childhood.

The Present Study

The evidence presented above demonstrates that even mild iodine deficiency can hinder cognitive performance. While previous research of cross-sectional studies has found mixed results, these studies often had design flaws or confounding variables. Randomised, placebo-controlled, double-blind trials demonstrate the effect of iodine deficiency on cognitive measures. However, the majority of research in this area has been conducted with children. While such studies are of interest, as the majority of learning and brain development occurs in childhood, brain development still continues into adulthood and its relation to

IODINE AND COGNITION IN YOUNG ADULTS

iodine deficiency should also be assessed (Durstun & Casey, 2006). White matter development increases throughout life and peaks at approximately 40 years of age (Bartzokis et al., 2010). Neurotransmission is also present and changing in adult brains (Dratman & Gordon, 1996). Iodine is associated with both changes in neurotransmitters and white brain matter (Bernal, 1999; Dratman & Gordon, 1996), so it is possible that iodine may still influence these brain systems in adulthood. Understanding the progression of a biological system such as iodine on brain functioning is important for determining interventions and effective treatments (Durstun & Casey, 2006).

In sum, as iodine deficiency is associated with mental impairment in all age groups, it is important to know whether supplementation can improve functioning in adult populations. This presents a very important public health question, and one that has not been addressed in mildly deficient young adults. The next step, then, is to assess the effects of iodine supplementation in mildly deficient young adults, the aim of the present study. Thus, the design of the present experiment was similar to that of Gordon et al. (2009), using a randomised, placebo-controlled, double-blind trial, with the exception that participants were between the ages of 18 and 30 years of age. Iodine status was assessed primarily though using serum Tg (collected through a finger-prick blood sample) and UIC.

Cognitive tests assessed working memory, processing speed and perceptual reasoning, using the Wechsler Adult Intelligence Scale (WAIS-IV). Matrix Reasoning, Coding, Symbol Search, Letter-Number Sequencing, Block Design, Backwards Digit Span and Visual Puzzles were selected as subtests. These were considered to be the most appropriate as they measure cognitive

IODINE AND COGNITION IN YOUNG ADULTS

skills such as processing speed and fluid IQ, and have been improved by iodine supplementation in previous studies of children, such as the trials by Gordon et al. (2009) and Zimmermann et al. (2006). The cognitive tests and biochemical samples were compared at baseline and at 32 weeks, for treatment and placebo groups. It was hypothesised that iodine supplementation in the treatment group would improve iodine status of mildly iodine-deficient young adults, and that this would be associated with positive increases in cognitive scores, compared to a placebo group.

Method

Participants

Participants were young adults recruited through the University of Otago. Recruitment of participants was through poster advertisement (see Appendix A), email to students, or through undergraduate psychology courses (in exchange for the opportunity to gain extra course credit). To be eligible for the study, participants had to be: between the ages of 18 to 30 years, consuming no more than two slices of bread per day, not taking an iodine-containing supplement, having no self-reported thyroid disease, not dyslexic, not pregnant or planning a pregnancy, and residing in the Dunedin area during the study time frame. The initial aim was to test 220 participants, with a projected attrition rate of 10%, giving a final sample of 198, which has been shown to have sufficient power to detect a 0.2 standard deviation difference in cognitive test scores (Gordon et al., 2009). Initially, 205 participants were recruited, with 69 males and 136 females (mean age of 21.36 years); however at study completion 172 participants had completed both required testing sessions. There were 61 males and 111 females (mean age of 21.28 years) for the final participant sample. Reasons for participant withdrawal included: lost to follow-up, not taking iodine or placebo supplements for the specified time period, having to take other iodine-containing supplements, and being out of the Dunedin area during the study time frame. Participants received a movie voucher and \$10 at the first testing session, and a further \$40 as compensation for completing the final session. All participants provided informed consent prior to commencing the study. The study was approved by the Human Ethics committee at the

IODINE AND COGNITION IN YOUNG ADULTS

University of Otago. The average duration of study enrolment was 33 (29.43 to 41.43) weeks.

Materials

Cognitive Assessment. The Wechsler Adult Intelligence Scale (WAIS-IV), Australian and New Zealand language adaption (Wechsler, 2008) was used to assess cognitive ability in participants. The WAIS-IV is designed to assess functioning in certain cognitive domains including verbal comprehension, perceptual reasoning, working memory, and processing speed. The WAIS-IV was chosen as it has been demonstrated to be a valid measure of these cognitive domains (Wechsler, 2008), and the equivalent scale for children (WISC-IV) has been used in studies of cognitive function and iodine deficiency (Gordon et al., 2009; Zimmermann et al., 2006). The cognitive tests were administered by two experimenters, both of whom had been trained by an experienced administrator of the WAIS-IV in the University of Otago Psychology department. Participants were asked to complete seven WAIS-IV subtests in each of the two testing sessions. The subtests were chosen because they are purported to measure fluid IQ, processing speed and working memory (Wechsler, 2008), all of which should benefit from enhancements in myelination or neurotransmitters in the iodine supplemented group (Fields, 2008; Gur et al., 1999; Herrera-Guzmán, Gudayol-Ferré, Herrera-Guzmán, Guàrdia-Olmos, Hinojosa-Calvo, & Herrera-Abarca, 2009).

The subtests included: Block Design, Digit Span Backwards, Matrix Reasoning, Symbol Search, Visual Puzzles, Coding, and Letter-Number Sequencing. All subtests have acceptable internal consistency (range of .81-.90, calculated using Fisher's z -transformations). Convergent and discriminative

IODINE AND COGNITION IN YOUNG ADULTS

validity of the constructs tested by the WAIS-IV, have been shown through correlations with scores on other cognitive assessments such as the WAIS-III, WISC-IV, Wechsler Memory Scale-Third Edition, Wechsler Individual Achievement Scale-Second Edition, and the Delis-Kaplan Executive Function System (Wechsler, 2008). The subtests are briefly described below.

Block Design. Block Design (BD) is a core subtest of perceptual reasoning, but also involves the use of “nonverbal concept formation and reasoning, broad visual intelligence, fluid intelligence, visual perception and organisation, simultaneous processing, visual-motor coordination, learning and the ability to separate figure-ground in visual stimuli” (Wechsler, 2008, p. 13). For the BD subtest, participants arrange four red-and-white blocks into designs as presented by a model picture, within a time limit of 60 seconds for each model. After six trials, the number of blocks increased to nine. This continued for four trials with a time limit of 120 seconds, which together made the task more difficult.

Digit Span Backwards. Digit Span Backwards (DSB) is a variation of the Digit Span subtest. As well as working memory, DSB assesses “working memory, transformation of information, mental manipulation, and visuospatial imaging” (Wechsler, 2008, p. 15). During the DSB subtest, participants were read lists of numbers, which they repeated in reverse order. An example of this would be “2-5-3”, which would be correctly repeated by the participant as “3-5-2”. Each item contained two trials. The items increased in length, with one additional digit in each new item. This subtest was discontinued if the participant scored zero on all trials of a item.

IODINE AND COGNITION IN YOUNG ADULTS

Matrix Reasoning. Matrix Reasoning (MR) is a perceptual reasoning subtest. MR is thought to measure “fluid intelligence, broad visual intelligence, classification and spatial ability, knowledge of part-whole relationships, simultaneous processing, and perceptual organisation” (Wechsler, 2008, p. 13). For the MR subtest, participants were given an incomplete series or matrix. The correct item must be selected from five options, in order to complete the pattern presented in the matrix or series.

Symbol Search. Symbol Search (SS) measures processing speed, as well as “short-term visual memory, visual-motor coordination, cognitive flexibility, visual discrimination, psychomotor speed, speed of mental operation, attention, and concentration” (Wechsler, 2008, p. 16). For the SS subtest, participants were presented with a row including two symbols (search group) and a target set of six symbols. Matches between symbols in the search and target groups were indicated by crossing out the matching target symbol. If no search symbol was present in the target group, then a ‘NO’ box was crossed out. The subtest consisted of 60 items and was discontinued after 120 seconds.

Visual Puzzles. Visual Puzzles (VP) is a relatively new subtest of perceptual reasoning in the WAIS-IV. It measures “nonverbal reasoning and the ability to analyze and synthesize abstract visual stimuli” (Wechsler, 2008, p.14) but is also similar to tests that measure fluid intelligence (Wechsler, 2008). Participants were instructed to select three pictures from six options, which together would make up a model picture. Each of the 26 items had a 30-second time limit, excluding items 20 to 26 which have a 45 second time limit (this last time limit addition is not typically used in the WAIS-IV but was added by the experimenters due to excessive testing times for some participants).

IODINE AND COGNITION IN YOUNG ADULTS

Coding. Coding (CD) is a core measure of processing speed in which participants complete as many items as possible in 120 seconds. “Short-term visual memory, learning ability, psychomotor speed, visual perception, visual-motor coordination, visual scanning ability, cognitive flexibility, attention, concentration, and motivation” may also be assessed in CD (Wechsler, 2008, p. 16). In the CD subtest, participants were presented with a model key. The key includes the numbers 1 to 9, each with a symbol that is unique to that number. Participants drew the correct symbols that matched the numbers presented in the test items.

Letter-Number Sequencing. Letter Number Sequencing (LNS) is a supplemental test of working memory. LNS may also assess “sequential processing, mental manipulation, attention, concentration, memory span, and short-term auditory memory” (Wechsler, 2008, p. 16). In the LNS subtest, participants were read sets of number and letter combinations that they had to repeat, starting numbers first (in ascending order), then letters (in alphabetical order). For example, “3-B-2” had to be repeated as “2-3-B”. There was a total of 10 possible items, each with 3 trials. Items increased in length over time until a maximum of eight letters and numbers. The subtest was discontinued if all three trials in an item were incorrect.

Biochemical Measures. Participants provided a urine sample and a non-fasting finger prick blood sample in order to collect 1ml of blood for the determination of serum Tg. Finger pricks were taken using a disposable Tenderlett lancet and the blood collected in a 1.5mL Eppendorf tube. Blood samples were left to clot for approximately 30 minutes, and then centrifuged at 7600 revolutions per minute, for 10 minutes. The separated serum was then

IODINE AND COGNITION IN YOUNG ADULTS

removed using a disposable Pasteur pipette and put into another Eppendorf tube that was frozen at -80°C . Urine was collected in small containers and then transferred into 5mL plastic sealable testtubes, which were frozen at -20°C . Urine samples were analysed for UIC by a single laboratory technician at the University of Otago Nutrition department. Tg, Total T4 (TT4), and the free T4 index (FTI) were analysed by Endolab in Christchurch Health Laboratories (Christchurch, NZ).

Supplements. Supplements were provided by Blackmores (Warriewood, Australia). Each supplement tablet contained 150 μg of iodine, corresponding to the daily recommended dose of iodine for adults (World Health Organisation, 2007). The placebo tablets were identical in size and colour; however they contained $<0.1 \mu\text{g}$ of iodine. Both sets of tablets weighed an average of 192.5mg. The iodine content of a random sample of 10 placebo and 10 iodine supplements were independently analysed by R J Hill Laboratories (Hamilton, NZ). The iodine tablets were confirmed to contain an average of 137 μg (133-139 μg) of iodine, while the placebo tablets contained an average of under 0.039 μg iodine. The placebo and iodine-containing supplements were labelled Q and T in order to blind the experimenters to the treatment group. Each bottle of supplements, contained approximately 110 pills, and new bottles were sent by post to participants every 13 weeks. Old bottles were sent back from participants.

Questionnaire. Participants completed a questionnaire at both Baseline and Time 32 weeks (at the first and final testing session respectively). Each questionnaire included contact information and demographic measures and a short form health survey (SF-36) section. Information on age, ethnicity,

IODINE AND COGNITION IN YOUNG ADULTS

household income, supplementation and medication use, medical conditions and specialty diets, were gathered in the demographics section (see Appendix B). This was followed by the SF-36 questionnaire that measured perceived health status (as measured by limitations of activities, general health, pain, physical and emotional health problems, as well as social activity). An example of an item (on general health) is, “During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?” Participants responded on a 5-point scale with options ranging from “All of the time” to “None of the time” (see Appendix C).

Procedure

The study was a randomised, placebo-controlled, double-blind trial. The independent variable was between-subjects (group: iodine versus placebo). The dependent variable was the cognitive scores for each participant, both at study enrolment and after 32 weeks of supplementation. Upon enquiry, participants were given an information sheet on the experiment and exclusion criteria, and provided consent prior to the commencement of the study trial. At study enrolment, participants were randomly and equally assigned to either group Q or group T. This ensured that both experimenters and participants were not aware of which group contained iodine and which was placebo. There were two testing sessions for each participant.

At the beginning of the testing session, participants were seated at a table, in a small, quiet and well lit room. After reading the information sheet (see Appendix D) and providing consent (see Appendix E), the participants were given the cognitive tests. Experimenters followed a specific introduction

IODINE AND COGNITION IN YOUNG ADULTS

verbatim for the cognitive tests (see Appendix F). All participants were given the seven cognitive tests in the following order (as per WAIS-IV instructions): Block Design, Digit Span Backwards, Matrix Reasoning, Symbol Search, Visual Puzzles, Coding and Letter-Number Sequencing. After the cognitive testing was completed, the participants provided urine and finger prick blood samples, and were instructed to complete the questionnaire. The entire process took approximately 60 minutes per participant. Finally, a bottle of supplements was provided and the participants instructed to take one a day, until the final testing session. The duration of the study was 32 weeks, over which participants were told they would be mailed two replacement bottles of supplements. Participants were then thanked and reimbursed. The second testing session followed the exact protocol as the first session, with the exception that participants were not required to complete the consent form again, and were asked to bring in any remaining bottles of tablets they may have had to the final session.

IODINE AND COGNITION IN YOUNG ADULTS

Results

Initially, for each variable, outliers were identified as over three *SDs* from the mean, and were reduced to the largest value within three *SDs* and then adding 1 to retain each outlier's ordinal position (Tabachnick & Fidell, 2001). Two outliers in the UIC samples were identified at baseline, and four UIC outliers at 32 weeks. For Tg data, four outliers were identified at both baseline and 32 weeks. For FTI, three outliers were identified at baseline and one at 32 weeks. TT4 data showed two outliers at baseline and three at 32 weeks. The cognitive scores and biochemical data were checked with Kolmogorov-Smirnov tests for normality. Many of the cognitive tests showed significant deviations from normality, as did the measures of iodine. Likewise, regression residuals showed significant non-normal distribution. For these reasons, non-parametric tests were used to examine the data. An alpha level of .05 was used to evaluate all statistical tests. Due to the non-normal distribution of the biochemical data, medians were used as the measure of central tendency.

Participant Demographics

Scores from the participant questionnaires were calculated for both baseline and 32 weeks. Only a small percentage of data was missing at baseline (1-5% missing for the different variables) and 99% of participants provided full data at 32 weeks. Age, sex, ethnicity, income, supplement and medication use, health, and diet information were recorded. Age, sex, ethnicity, and income were measured only at baseline, and are reported separately for iodine and placebo groups in Table 1. Comparisons between iodine and placebo groups were made for each demographic variable using Mann-Whitney U tests (see

IODINE AND COGNITION IN YOUNG ADULTS

Table 2). There were no significant differences between the iodine and placebo groups for any of these measures.

Supplement and medication use, as well as self-reported health and special diet use, were measured at both baseline and 32 weeks. The frequencies of participants in each category were calculated for both iodine and placebo groups, as shown in Table 3. For each variable, Wilcoxon Signed-Rank Tests were used to analyse the difference between baseline and 32 weeks, for the participants who remained in the study. These tests showed that there were almost no significant differences in each of the variables between baseline and 32 weeks (see Table 3), for either treatment group. However, self-reported health did change (i.e., it got worse) from baseline to 32 weeks for the iodine group but not placebo group.

Mann-Whitney U tests were conducted to examine whether there were significant differences between iodine and placebo groups for any of the demographic measures. No significant differences were found, indicating that the distribution of the sample was similar across treatment groups (see Table 2). Participants who withdrew from the study, showed no major differences between iodine and placebo groups. The iodine group had a 16% withdrawal rate ($n = 16$), and the placebo group had a 17% withdrawal rate ($n = 17$).

IODINE AND COGNITION IN YOUNG ADULTS

Table 1.

Baseline Frequencies for Participant Demographic Information for Iodine and Placebo Groups

Demographic Variable	Variable Categories	Iodine <i>n</i> = 102		Placebo <i>n</i> = 103	
		<i>n</i>	%	<i>n</i>	%
Sex	Male	34	33.3	35	34.0
	Female	68	66.7	68	66.0
Ethnicity	European/Pakeha	67	65.7	66	64.7
	Maori	9	8.8	4	3.9
	Pacific Island	2	2.0	3	2.9
	Other	24	23.5	29	28.4
Income	Under 20,000	49	48.0	53	52.0
	20,000-50,000	15	14.7	17	16.7
	Over 50,000	13	12.7	11	10.8
	No answer	25	24.5	22	20.6

Note. All variables were recorded at baseline only.

IODINE AND COGNITION IN YOUNG ADULTS

Table 2.

Mann-Whitney U Scores^a Comparing Participants in the Iodine Group to Those in the Placebo Group at Baseline and 32 Weeks

Demographics	Baseline		32 Weeks	
	<i>z</i>	<i>p</i>	<i>z</i>	<i>p</i>
Age	-.76	.45	-.84	.40
Sex	-.10	.92	-.80	.43
Ethnicity	-.38	.70	-.94	.35
Income	-.66	.51	-.29	.78
Supplements	-.38	.70	-.66	.51
Medication	-.18	.86	.00	1.00
Health	-.76	.45	-1.01	.31
Special Diet	-1.71	.09	-1.38	.17

Note. ^a Significance tests are 2-tailed.

IODINE AND COGNITION IN YOUNG ADULTS

Table 3.

Participant Health and Diet Information at Baseline and 32 Weeks for Iodine and Placebo Groups

Demographic Variable Variable Categories		Iodine					Placebo				
		Baseline		32Weeks			Baseline		32 Weeks		
		<i>n</i> = 102		<i>n</i> = 86			<i>n</i> = 103		<i>n</i> = 86		
		<i>n</i>	%	<i>n</i>	%	<i>p</i> ^{<i>a</i>}	<i>n</i>	%	<i>n</i>	%	<i>p</i> ^{<i>a</i>}
Regular Supplement use		27	27.0	25	29.1	.53	30	29.4	29	33.7	.37
Regular Medication use		37	37.0	31	36.0	.44	39	38.2	31	36.0	.76
Self- Reported Health	Excellent	46	45.5	32	37.2	.02	52	51.0	40	46.5	.07
	Good	54	53.5	53	61.6		49	48.0	43	50.0	
	Poor	1	1.0	2	1.2		1	1.0	3	3.5	
Diet:	No Special	79	77.5	68	79.1	.89	87	86.1	73	85.9	.29
	Vegetarian	10	9.8	7	8.1		9	8.9	10	11.8	
	Vegan	0	0.0	1	1.2		0	0.0	0	0.0	
	Other	13	12.7	10	11.6		5	5.0	2	2.4	

Note. The percentages may not add to 100 due to rounding. ^a Wilcoxon Signed-Rank was used to compare variables between baseline and 32 weeks.

IODINE AND COGNITION IN YOUNG ADULTS

SF-36

At both baseline and 32 weeks, 99% of participants completed the SF-36 questionnaire. Participants' scores for each category of the SF-36 were calculated by averaging across the questions corresponding to that category. The overall scores for each category were then calculated and the median scores are shown in Table 4. Mann-Whitney U tests indicated no significant differences between treatment groups for any of the SF-36 categories, and Wilcoxon Signed-Rank tests showed no significant differences between baseline and 32 weeks for most SF-36 categories (see Table 4). However, energy scores in the placebo group showed a significant increase at 32 weeks compared to baseline. In addition, social functioning in the iodine group showed a significant decrease from baseline to 32 weeks.

IODINE AND COGNITION IN YOUNG ADULTS

Table 4.

Median and Mean (Standard Deviation) Scores on the Eight Categories of the SF-36 at Baseline and 32 Weeks for the Iodine and Placebo Groups

Category of SF-36	Time	Iodine		P^a	Placebo		P^a	P^b
		<i>Mdn</i>	<i>M (SD)</i>		<i>Mdn</i>	<i>M (SD)</i>		
Physical Functioning	Baseline	100	96.09(9.95)	.53	100	96.47(7.23)	.57	.48
	32Weeks	100	97.38(5.73)		100	94.88(14.82)		.54
Role Limitations: Physical Functioning	Baseline	100	90.93(23.54)	.16	100	92.89(21.22)	.30	.66
	32Weeks	100	85.17(33.73)		100	90.88(23.10)		.51
Role Limitations: Emotional Functioning	Baseline	100	85.29(29.13)	.44	100	85.15(27.27)	.30	.64
	32Weeks	100	84.88(29.66)		100	80.56(34.79)		.62
Energy	Baseline	65	61.17(16.59)	.23	60	60.83(15.84)	.01	.74
	32Weeks	65	63.84(14.59)		65	63.41(16.15)		.98
Emotional Wellbeing	Baseline	80	76.35(12.70)	.78	76	73.65(13.87)	.09	.17
	32Weeks	80	77.91(10.78)		80	75.54(13.66)		.41
Social Functioning	Baseline	100	89.71(14.86)	.04	100	87.62(17.72)	.39	.56
	32Weeks	100	87.41(16.67)		87.5	85.15(18.85)		.47
Pain	Baseline	90	84.48(17.96)	.19	90	83.38(17.80)	.58	.62
	32Weeks	90	82.85(18.94)		90	82.03(18.93)		.70
General Health	Baseline	77.5	75.00(17.56)	.61	80	76.84(16.84)	.31	.47
	32Weeks	80	76.02(16.92)		80	75.47(18.67)		.83

Note. ^a Wilcoxon Signed-Rank Tests were used to compare baseline and 32 week scores, ^b Mann-Whitney U Tests were used to compare iodine and placebo groups. Mdn = Median.

IODINE AND COGNITION IN YOUNG ADULTS

Biochemical Samples

Urinary iodine concentration (UIC), thyroglobulin (Tg), total thyroxine (TT4) and free thyroxine index (FTI) were analysed to calculate change in iodine status over the study period. Medians and interquartile ranges were calculated for each treatment group and are presented in Table 5. The median UICs at baseline were between 50 and 99 $\mu\text{g/L}$, and 40% were under 50 $\mu\text{g/L}$, indicating that the sample was mildly iodine-deficient. A Mann-Whitney U test showed UIC levels were not significantly different between the treatment groups at baseline (see Table 5). In accordance with WHO (2007) ranges for iodine status, the UIC data was reclassified into quartiles reflecting the iodine status (<20 $\mu\text{g/L}$, severe deficient; 20-40 $\mu\text{g/L}$, moderate deficiency; 50-99 $\mu\text{g/L}$, mild deficiency; 100-299 $\mu\text{g/L}$, iodine sufficient; and >300 $\mu\text{g/L}$, excessive iodine; see Figure 1). At 32 weeks, the placebo group showed an increase in median UIC of 12.5 $\mu\text{g/L}$ from baseline, but was still in the range of mild iodine deficiency. The iodine group showed an increase in median UIC of 50.5 $\mu\text{g/L}$ between baseline and 32 weeks, and only 11.7% of the sample was < 50 $\mu\text{g/L}$, putting the treatment group in the range of iodine sufficiency. Wilcoxon Signed-Rank tests showed that there were significant increases in UIC levels for the iodine group over time, compared to the placebo group (see Table 5). Mann-Whitney U tests also showed that 32-week measures for iodine were significantly improved compared to placebo.

The same analyses conducted for UIC were then used to examine the remaining biochemical measures. Tg showed a similar pattern of no significant difference between groups at baseline, but a significant decrease (indicating more iodine) in the iodine supplement group at 32 weeks. The median Tg at

IODINE AND COGNITION IN YOUNG ADULTS

baseline indicated that the sample was mildly iodine-deficient, but very close to iodine sufficiency. At 32 weeks, both samples could be considered iodine sufficient, however the iodine group showed a greater drop in Tg levels, indicating better iodine status relative to placebo group. As for UIC, Tg scores were reclassified into quartiles concentration (<10 $\mu\text{g/L}$, iodine-sufficient; 10-19 $\mu\text{g/L}$, mild deficiency; 20-39 $\mu\text{g/L}$, moderate deficiency; and >40 $\mu\text{g/L}$, severe deficiency), as shown in Figure 2. TT4 did not differ between treatment groups at baseline, and showed a significant increase in the iodine group over time. Yet, when TT4 was adjusted to form the free thyroxine index (FTI), the FTI in the two treatment groups was not significantly different at either time point. As the FTI was within the normal reference range, and did not change from baseline to 32 weeks in the iodine or placebo groups, further analyses concentrated on the Tg and UIC data.

IODINE AND COGNITION IN YOUNG ADULTS

Table 5.

Median (Mdn) and Mean (Standard Deviation) for Biochemical Measures at Baseline and 32 Weeks for the Iodine and Placebo Groups

Biochemical Measure		Iodine		p^a	Placebo		p^a	p^b
		Mdn	M (SD)		Mdn	M (SD)		
UIC μg/L	Baseline	64.50	74.21 (54.31)		66.00	75.35 (55.37)		.90
	32 Weeks	115.00	246.52 (255.96)	<.001	78.50	92.52 (66.82)	.12	<.001
Tg μg/L	Baseline	9.95	12.96 (8.86)		10.20	12.38 (9.49)		.48
	32 Weeks	8.10	10.71 (8.37)	.02	9.35	12.88 (10.41)	.86	.13
TT4 nmol/L	Baseline	96.00	100.62 (20.07)		98.00	99.45 (17.07)		.78
	32 Weeks	102.00	105.21 (20.74)	.001	97.00	102.31 (25.32)	.16	.17
FTI	Baseline	96.50	98.10 (15.97)		97.00	96.73 (15.12)		.97
	32 Weeks	98.00	99.99 (15.90)	.27	98.00	98.95 (19.09)	.07	.85

Note. ^a Comparison between baseline and 32 weeks made using Wilcoxon Signed-Rank tests. ^b Comparisons between iodine and placebo groups made using Mann-Whitney U tests.

IODINE AND COGNITION IN YOUNG ADULTS

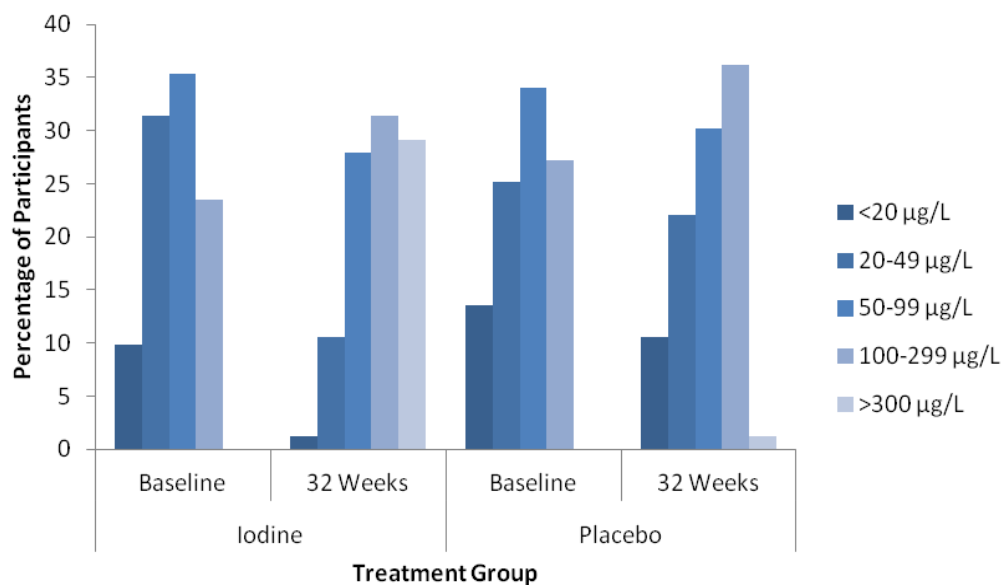


Figure 1. Categorisation of urinary iodine concentration (severe: <20 µg/L, moderate: 20-49 µg/L, mild: 50-99 µg/L, sufficient: 100-299 µg/L, and excessive: >300 µg/L) (UIC) for iodine and placebo groups at baseline and 32 weeks.

IODINE AND COGNITION IN YOUNG ADULTS

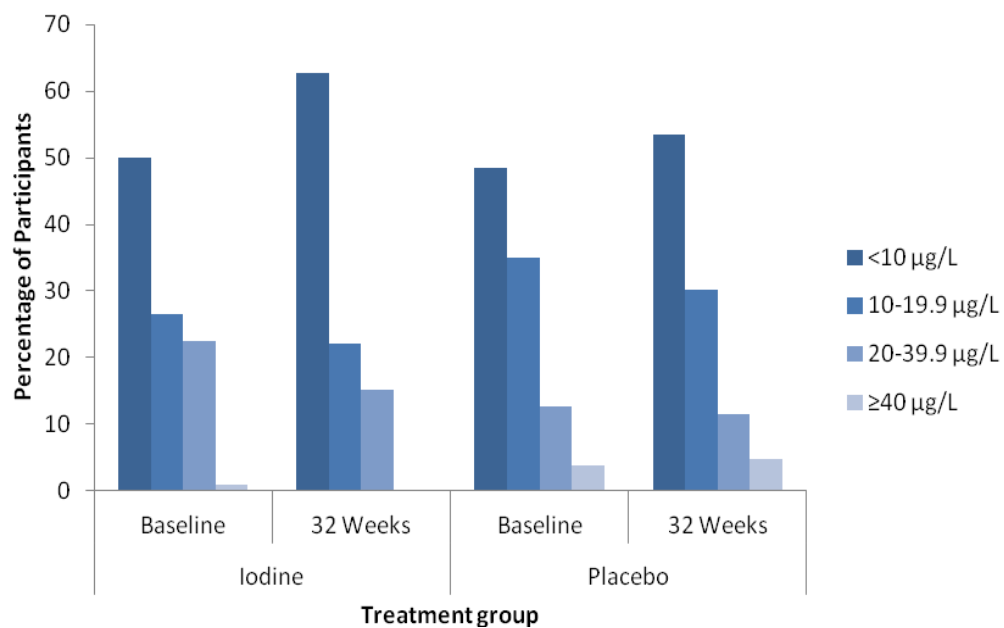


Figure 2. Categorisation of thyroglobulin concentration (sufficient: <10 µg/L, mild: 10-19 µg/L, moderate: 20-39 µg/L, and severe: >40 µg/L) (Tg) for iodine and placebo groups at baseline and 32 weeks.

IODINE AND COGNITION IN YOUNG ADULTS

Difference scores were used to capture change over time and compare the placebo to the iodine group. Differences were calculated by subtracting baseline scores from 32-week scores, and the placebo and iodine groups were then compared using Mann-Whitney U tests. UIC difference scores were significantly larger for the iodine relative to the placebo group (Iodine $M = 157.30$, $SD = 208.63$, Placebo $M = 15.63$, $SD = 82.22$, $z = -4.66$, $p < .001$). Tg difference scores were also significantly larger for the iodine compared to the placebo group (Iodine $M = -1.81$, $SD = 5.88$, Placebo $M = 0.05$, $SD = 4.58$, $z = -3.14$, $p = .002$).

Compliance

Compliance was assessed in two ways. First, the number of supplements returned to the Think2 project by participants was examined. For each participant the remaining number of tablets was subtracted from the total number of tablets, and then divided by the duration of the trial. Across both treatment groups, participants who returned all three bottles of supplements were estimated to have a mean compliance rate of 78% (i.e., for participants who returned all bottles of supplements, the number of supplements taken was approximately 78%). Yet when accounting for all participants enrolled at 32 weeks of study (participants who did not return all bottles of tablets, $n = 89$), estimated overall compliance over both groups went down to 48%.

Second, difference measures in biochemical data were calculated to assess changes in participants' iodine status. As the median UIC increase in the control group was 12.5 $\mu\text{g/L}$, this value was used as the cut-off for compliance in the iodine group. That is, all participants in the iodine group whose increase in UIC was not greater than 12.5 $\mu\text{g/L}$ were deemed to be non-compliant. Using

IODINE AND COGNITION IN YOUNG ADULTS

this measure, a quarter of participants in the iodine supplement group showed no improvement in iodine status, above that of the placebo group. The same method was then used for Tg and placebo data. Once again, Tg levels decrease with improved iodine status. In the present study, Tg levels decreased by a median of 0.1 in the placebo group over time, and just under a third of the treatment group did not show a comparable decrease in Tg. These results are shown in Table 6. Below, data are analysed for all participants, and then only for compliant participants.

IODINE AND COGNITION IN YOUNG ADULTS

Table 6.

Frequency of Compliance in the Iodine Group as Determined by the Difference in Iodine Status over 32 Weeks

Difference Scores	Iodine		Placebo	
	<i>n</i>	%	<i>n</i>	%
UIC				
<12.5 µg/L	22	25.6	43	50
≥12.5 µg/L	64	74.4	43	50
Tg				
>-0.1 µg/L	26	30.2	46	53.5
≤-0.1 µg/L	60	69.8	40	46.5

Note. <12.5 µg/L and >-0.1 µg/L indicate non-compliance.

Cognitive Scores

The cognitive scores for each treatment group were calculated for both baseline and 32 weeks, and descriptive statistics are presented in Table 7. Wilcoxon Signed-Rank tests were used to compare cognitive scores over time in each treatment group. In both the placebo and iodine groups, all cognitive scores showed a statistically significant increase with time, except Matrix Reasoning and Letter-Number Sequencing (see Table 8). In contrast, there were no differences in cognitive scores for the iodine versus the placebo groups, at either time point (see Table 8, Mann-Whitney U tests).

IODINE AND COGNITION IN YOUNG ADULTS

Table 7.

Median and Mean (Standard Deviation) of Cognitive Test Scores at Baseline and 32 Weeks for the Placebo and Iodine Groups

Cognitive Subtest	Test time	Iodine (n=86)		Placebo (n=86)	
		<i>M (SD)</i>	<i>Mdn</i>	<i>M (SD)</i>	<i>Mdn</i>
BD	-Baseline	50.51 (10.56)	53	49.50 (12.33)	52
	-32 weeks	54.97 (8.48)	57	53.37 (10.89)	57
DSB	-Baseline	9.33 (2.20)	9	8.92 (1.99)	9
	-32 weeks	9.97 (2.40)	10	9.40 (2.17)	9
MR	-Baseline	20.29 (3.50)	21	20.10 (3.57)	20
	-32 weeks	20.85 (3.43)	22	20.59 (3.27)	21
SS	-Baseline	36.31 (6.11)	37	37.50 (6.88)	37
	-32 weeks	39.97 (6.76)	40	41.23 (8.25)	41
VP	-Baseline	18.09 (3.99)	19	17.98 (4.35)	19
	-32 weeks	19.43 (3.57)	20	18.95 (3.89)	20
CD	-Baseline	81.22 (12.20)	83	82.76 (16.15)	81
	-32 weeks	86.01 (12.87)	88	87.60 (17.41)	88.5
LNS	-Baseline	21.28 (3.07)	21	20.69 (2.53)	21
	-32 weeks	21.50 (2.91)	21.5	20.77 (3.22)	21

Note. BD = Block Design, DSB = Digit Span Backwards, MR = Matrix Reasoning, SS = Symbol Search, VP = Visual Puzzles, CD = Coding, LNS = Letter-Number Sequencing.

IODINE AND COGNITION IN YOUNG ADULTS

Table 8.

Cognitive scores at Baseline and 32 Weeks for Iodine and Placebo Groups

Cognitive Subtest	Test Time (Weeks)	Iodine	Placebo	Mann-Whitney U	p^b
		p^a	p^a		
BD	Baseline			-.02	.99
	32 weeks	<.001	<.001	-.39	.70
DSB	Baseline			-1.08	.28
	32 weeks	.02	.01	-1.57	.12
MR	Baseline			-1.26	.21
	32 weeks	.37	.12	-.78	.43
SS	Baseline			-.98	.33
	32 weeks	<.001	<.001	-1.38	.17
VP	Baseline			-.19	.85
	32 weeks	.006	<.001	-.55	.58
CD	Baseline			-.56	.58
	32 weeks	<.001	<.001	-.85	.40
LNS	Baseline			-1.24	.22
	32 weeks	.95	.38	-1.48	.14

Note. ^a Wilcoxon Signed-Rank tests were used to compare cognitive scores within each treatment group between baseline and 32 weeks. ^b Mann-Whitney U Tests were used to compare the iodine and placebo groups within each time point.

Difference scores for cognitive measures were then calculated by subtracting 32-week scores from baseline scores, and Spearman's correlations between cognitive difference scores and the participant group (iodine versus placebo, see Table 9) were computed. If the iodine group (but not the placebo group) had experienced a gain in cognitive ability, then there should have been correlations between the difference scores and the participant group. In fact, there were no significant correlations between the cognitive difference scores

IODINE AND COGNITION IN YOUNG ADULTS

and the participant group, indicating that increases in cognitive scores were not associated with participants being in the iodine versus the placebo group.

Given the low rate of compliance, the results for UIC and Tg were then re-analysed including only those who complied in taking iodine. In the iodine group, participants whose gain in UIC was $<12.5 \mu\text{g/L}$ were removed. Likewise, Tg data were subjected to the same method with participants whose mean Tg loss was >0.1 being removed from the iodine group.

IODINE AND COGNITION IN YOUNG ADULTS

Table 9.

Spearman's Correlations Between Cognitive Difference Scores and Intervention (n = 172)

	I	BD	DSB	MR	SS	VP	CD	LNS
I								
BD	.02							
DSB	.01	.01						
MR	.03	.01	-.09					
SS	-.01	-.02	.08	-.19*				
VP	.07	.09	.16*	.13	-.19*			
CD	-.00	-.05	-.13	-.05	.15*	-.06		
LNS	.04	-.02	.06	.03	-.00	-.04	.10	

Note. I = intervention: iodine versus placebo. * $p < .05$ (2-tailed)

Spearman's correlations were also used to analyse the difference scores for the biochemical (iodine) measures and cognitive scores for participants within the iodine group (see Table 10). In general, iodine difference scores did not correlate with cognitive difference scores. The exceptions were a negative correlation between Digit Span Backwards and UIC (in the direction *opposite* to that expected) and a negative correlation between Visual Puzzles and Tg (consistent with expectations). However, as these two correlations were in opposite directions to each other, and as the results for these measures were inconsistent with other correlations, this suggests that chance may have played a role in results.

IODINE AND COGNITION IN YOUNG ADULTS

Table 10.

Spearman's Correlations Between Iodine Difference Scores and Cognitive Difference Scores Within the Iodine Group

Cognitive Score	UIC Difference Score	Tg Difference Score
Difference	<i>n</i> = 64	<i>n</i> = 55
BD	.03	-.03
DSB	-.26*	.14
MR	.22	-.09
SS	-.17	.18
VP	-.03	-.28*
CD	.11	-.05
LNS	.02	-.12

Note. Difference scores calculated by subtracting 32-weeks scores from baseline. Only scores in which the iodine level increased above median placebo levels are included. * $p < .05$ (2-tailed).

Cognitive scores and biochemical measures were also analysed within time points. If iodine is related to participants' cognitive functioning, then there should have been a relation between iodine levels and cognitive performance at each time point. Baseline UIC and baseline cognitive scores were examined using Spearman's correlations (see Table 11). Cognitive scores and UIC at 32 weeks were also analysed using Spearman's correlations (see Table 12). At both baseline and 32 weeks, there were no significant positive associations between cognitive scores and iodine status as measured by UIC. There was however, one exception. Block Design showed a significant positive association with UIC scores at 32 weeks. However, at baseline there were no significant associations

IODINE AND COGNITION IN YOUNG ADULTS

found for Block Design and iodine, and the correlations went in the opposite direction to what was expected (i.e., with increasing iodine, cognitive scores decreased), suggesting the one significant result at 32 weeks was likely due to chance. Tg data were analysed in a similar way and showed a similar lack of relation to cognitive scores at both baseline (see Table 13) and 32 weeks (see Table 14). There was one significant positive correlation between Tg and Visual Puzzles at 32 weeks, yet this was in the opposite direction to that expected.

Compliance measured through supplements returned was also analysed, by selecting for participants who returned all three bottles. However, analyses using this measure yielded a similar pattern of results, with no significant associations found for iodine status (UIC or Tg) and cognition.

IODINE AND COGNITION IN YOUNG ADULTS

Table 11.

Spearman's Correlations Between Cognitive Scores and Urinary Iodine Concentration (UIC) at Baseline for the Iodine Group (n = 102)

	UIC	BD	DSB	MR	SS	VP	CD	LNS
UIC								
BD	-.00							
DSB	.01	.04						
MR	.01	.34**	.23*					
SS	-.02	.47**	.31**	.16				
VP	.01	.51**	.14	.29**	.19			
CD	-.16	.11	.21*	.20*	.34**	.08		
LNS	-.03	.06	.43**	.13	.37**	.09	.19	

Note. * $p < .05$ (2-tailed). ** $p < .01$ (2-tailed).

IODINE AND COGNITION IN YOUNG ADULTS

Table 12.

Spearman's Correlations Between Cognitive Scores and Urinary Iodine Concentration (UIC) at 32 Weeks Within the Iodine Group (n = 64)

	UIC	BD	DSB	MR	SS	VP	CD	LNS
UIC								
BD	.25*							
DSB	-.20	.05						
MR	-.07	.31*	.29*					
SS	-.07	.30*	.24	.17				
VP	.12	.65**	-.06	.27*	.22			
CD	-.07	.11	.24	.29*	.63**	.03		
LNS	.14	.35**	.36**	.37**	.20	.22	.32*	

Note. * $p < .05$ (2-tailed). ** $p < .01$ (2-tailed). Participants deemed non-compliant (difference of $<12.5 \mu\text{g/L}$) were excluded from the analysis

IODINE AND COGNITION IN YOUNG ADULTS

Table 13.

Spearman's Correlations Between Cognitive Scores and Thyroglobulin Concentration (Tg) at Baseline for the Iodine Group (n = 102)

	Tg	BD	DSB	MR	SS	VP	CD	LNS
Tg								
BD	.06							
DSB	.14	.04						
MR	-.15	.35**	.13					
SS	.15	.41**	.38**	.12				
VP	.09	.64**	.18	.35**	.23			
CD	-.12	.14	.22	.23	.24**	.15		
LNS	.05	.04	.36**	.19	.45**	.19	.26*	

Note. * $p < .05$ (2-tailed). ** $p < .01$ (2-tailed).

IODINE AND COGNITION IN YOUNG ADULTS

Table 14.

Spearman's Correlations Between Cognitive Scores and Thyroglobulin (Tg) at 32 Weeks in the Iodine Group (n = 55)

	Tg	BD	DSB	MR	SS	VP	CD	LNS
Tg								
BD	.03							
DSB	.11	.08						
MR	-.13	.37**	.34**					
SS	-.11	.29*	.39**	.20				
VP	.30*	.71**	-.02	.32*	.17			
CD	-.15	.20	.30*	.37**	.54**	.13		
LNS	.19	.42**	.30*	.33*	.40**	.28*	.36**	

Note. * $p < .05$ (2-tailed). ** $p < .01$ (2-tailed). Participants deemed non-compliant (difference of $>0.1 \mu\text{g/L}$) were excluded from the analysis.

Overall, there were no significant positive correlations, indicating that with increases in iodine status, there was no associated increase in cognitive scores in this sample.

Despite the non-normality of many variables, I then checked the findings described above using a mixed-design analysis of variance (ANOVA) with particular interest in interactions between changes in cognitive scores over time and intervention group. For each of the seven cognitive tests a 2 (Treatment group: Placebo, Iodine) x 2 (Time: Baseline, 32 weeks) mixed-design ANOVA was carried out, with the dependent variable the raw scores on the cognitive subtest. Treatment Group was the between-subjects factor and Time was the within-subjects factor. For all the cognitive tests, there were no significant

IODINE AND COGNITION IN YOUNG ADULTS

interactions between Time and Treatment Group. This result again suggests that iodine supplementation was not related to a rise in cognitive scores.

IODINE AND COGNITION IN YOUNG ADULTS

Discussion

The aim of the present study was to explore the association between iodine and cognition. Participants underwent two testing sessions, at baseline and after 32 weeks. At both times, participants gave biochemical samples, and completed seven cognitive tests. The tests were designed to measure cognitive domains such as processing speed, perceptual reasoning, and fluid intelligence (Wechsler, 2008). Urinary iodine concentration (UIC) and serum thyroglobulin (Tg), total thyroxine (TT4), and a free thyroxine index (FTI), were measured from urine and blood samples taken. This study examined whether iodine supplementation in mildly iodine-deficient young adults would improve cognitive scores compared to a placebo group. It was hypothesised that the treatment group, who had received a daily dose of 150 µg/L of iodine over 32 weeks, would show an improvement in cognitive scores above that of the placebo group. While the iodine status in the intervention group did increase over time, the results did not support the hypothesis, as the consistent finding was of no association between cognitive scores and intervention group, indicating that there were no differences in cognitive scores between participants who took iodine and those who took a placebo.

Biochemical Measures

The present study showed an association between iodine status and intervention group. The iodine supplements were effective at changing iodine status from iodine deficiency to iodine sufficiency, as it was predicted for the iodine group. This was indicated by two of the biochemical measures used in the study: UIC and Tg. TT4 also increased in the intervention group. However, after using FTI to adjust the thyroid hormone measure, the results indicated that

IODINE AND COGNITION IN YOUNG ADULTS

the difference between treatment groups across time was negligible. This is consistent with the literature on iodine supplementation, as thyroid hormones show little change with improved iodine status (World Health Organisation, 2007).

Overall, the biochemical results are consistent with other trials using iodine supplements. However, there are several points of interest. At baseline, UIC data clearly demonstrated mild iodine deficiency in the participants, while Tg levels showed borderline mild iodine deficiency. UIC is an indirect measure of thyroid function, instead measuring recent dietary iodine (Zimmermann, 2009). One disadvantage of UIC is that it varies considerably within an individual throughout the day, and may be influenced by food intake in the days prior to when the samples were taken (World Health Organisation, 2007). Due to the influence of diet, the UIC of an individual may appear to be in the range of iodine deficiency, when in fact the individual may be iodine-sufficient (Zimmermann, 2009). Some researchers have stated that over 10 urine samples may be needed across time for each individual, in order to gain an accurate measure of iodine status using UIC (König, Andersson, Hotz, Aeberli, & Zimmermann, 2011). For the surveillance and estimates of iodine status in a *population* (as opposed to an *individual*), UIC is a good measure, especially for adult samples (World Health Organisation, 1994). However, in the present study our interest was also in *individual* differences, and how iodine status in an individual related to cognitive performance. Tg was likely to be the more appropriate measure for the present study's purposes because it was less subject to small-scale variation due to dietary changes.

IODINE AND COGNITION IN YOUNG ADULTS

While Tg may be a more reliable measure of iodine status, and is deemed an appropriate indicator of thyroid function in adults (Andersson & Zimmermann, 2010), the range in which Tg improved in the present study was very narrow across the iodine group. This could be because Tg is less susceptible to change following iodine supplementation when given to adults compared to children (Zimmermann et al., 2006), or due to the inadequacies of the Tg measure (the cut-off point for iodine sufficiency in a group of adults is small: $<10 \mu\text{g/L}$; World Health Organisation, 1994). Alternatively, the compliance of the participants may be at fault. It is possible that the participants did not comply with the study criteria for most of the trial duration except for the period close to when the final testing session was to occur. This would have resulted in the larger difference between baseline and 32 weeks for UIC in the intervention groups, but a small difference in Tg. In addition, a large percentage of the participants in the iodine group (26 to 36%) seemed not to comply at all with the instructions to take the supplements daily; these participants showed no change (or reduced iodine status) in biochemical measures. Future studies could carry out more frequent biochemical tests to accurately monitor participant iodine status over time, or use a different participant group who might be more likely to comply. Alternatively, supplementation which does not require much compliance (such as a single dose of iodized oil), may be more appropriate for this age group.

Thyroid hormones were also assessed in the present study. When iodine intake is insufficient, circulating thyroid levels decrease. It is this drop in thyroid hormones that results in the disorders caused by iodine deficiency (Hetzel, 1983). However, tests of thyroid hormones are typically considered

IODINE AND COGNITION IN YOUNG ADULTS

unreliable and insensitive tests in mild iodine deficiency, and typically decrease but remain within normal ranges in mildly iodine-deficient samples, as was the case in this study (Zimmermann et al., 2008). For this reason, a free thyroxine index (FTI) was also calculated for participants. The FTI adjusts TT4 by accounting for unbound thyroxine binding globulins (TBG), which may be influenced by other hormones, such as those found in oral contraceptives (Schatz et al., 1968). FTI is considered a good indicator of thyroid function in clinical settings (Howorth & Ward, 1972). In the present study, TT4 had shown a significant increase over time in the iodine group, compared to the placebo group. Interestingly, the FTI showed no change from baseline to 32 weeks in the placebo and iodine groups, indicating that once T4 was adjusted for, no change was seen in iodine status over time for either treatment group using these measures. As similar studies of iodine supplementation generally find no change (or even a decrease) in TH, this result was not unusual.

Iodine and Cognition in Adults

Analyses comparing the two intervention groups, and within each group, were consistent in failing to find any relation between iodine and cognition scores. These findings cannot *prove* that iodine has no effect on cognition in mildly iodine-deficient adults. However, the lack of difference between groups (even when analyses were based only on participants who complied), and the lack of within-time point correlations between iodine and cognition, are consistent with the view that mild iodine deficiency might be unrelated to cognition in young adults.

Previous research has largely focused on the effects of iodine on child cognitive ability. Childhood is a crucial age to investigate for the effects of

IODINE AND COGNITION IN YOUNG ADULTS

micronutrient deficiencies on cognition as the brain is still developing at a rapid rate (Courchesne et al., 2000; Hayakawa, Konishi, Kuriyama, Konishi, & Matsuda, 1990), and iodine deficiency has been clearly linked to impaired cognitive function in infants and children (Bleichrodt et al., 1980; Gordon et al., 2009; Pharaoh & Connolly, 1987; Zimmermann et al., 2006). However, the literature on iodine deficiency in adulthood is less clear. Thyroid function has been examined relative to cognition in older adults and clinical populations (Andersen, 2001; Bauer, Goetz, Glenn, & Whybrow, 2008; Prinz et al., 1999), and adult-onset hypothyroidism has been shown to induce cognitive deficits such as impaired working memory (Samuels, Schuff, Carlson, Carello, & Janowsky, 2007). Cognition and thyroid function associations have also been found in older, male adults with normal thyroid function (Prinz et al., 1999).

However, studies on iodine deficiency do not provide such a clear comparison. While iodine deficiency can result in hypothyroidism, it is not the sole cause of thyroid problems and comparisons between iodine deficiency and thyroid problems, such as hypothyroidism, should be made with caution. Most of the information on adult cognitive impairment with iodine deficiency has come from an anecdotal observation reported by Hetzel (1983) of apathetic adults in an iodine-deficient area. The results of the present study, which was a randomised, placebo-controlled trial, are consistent with the idea that improving iodine status has no impact on cognitive function in this age group.

Mild iodine deficiency, rather than more severe deficiency, may have contributed to this result. The literature on the effects of mild iodine deficiency is considerably lacking. For development *in utero*, there is uncertainty whether mild maternal iodine deficiency will have long-lasting consequences for the

IODINE AND COGNITION IN YOUNG ADULTS

fetus (Zimmermann, 2008). It may be that mild iodine deficiency has no impact on cognition at all, or that biological compensation mechanisms are used to counteract the effects of iodine deficiency. Huda and colleagues (2001) suggested that the thyroid gland may be able to adapt to the effects of iodine deficiency, becoming increasingly effective at trapping iodine. This would mean that no difference in cognitive function would be observed between iodine-sufficient and iodine-deficient samples. However, Gordon and colleagues (2009) did show improvement in two cognitive subtests through supplementation in children corrected for mild iodine deficiency.

One explanation for the discrepancy between studies is the difference in environment in which participants were recruited from. It may be argued that the environment, in which the present study's participants were living, is notably different from that of some previous studies. The present sample was recruited from the University of Otago, consisting mainly of undergraduate students. Other study populations have often been in areas of severe iodine deficiency, in countries that are economically less developed. Importantly, different populations are affected to different degrees by iodine deficiency (Laurberg et al., 2006). For example, other chemicals in the environment have been shown to inhibit iodine uptake. Certain foods which are more popular in certain areas, such as cassava, have also been associated with iodine deficiency and goitre (Gaitan & Dunn, 1992). Other 'protective' factors such as oral contraceptives and alcohol consumption (Laurberg et al., 2006), may be more available in some areas. Environmental enrichment has also been shown to influence myelination (Fields, 2005). Such enrichment may come from formal education. Previous studies have either not divulged the schooling of participant

IODINE AND COGNITION IN YOUNG ADULTS

families, or have shown that parents of schoolchildren tested often had little or no schooling themselves (Huda et al., 2001). This indicates that although the child participants are in school at the time of the studies, they may not receive many years of schooling. In the present study sample, it is possible that many years of formal education and living in an economically developed country, may have resulted in increased stimulation and enrichment, where participants were used to novelty and learning associated with cognitive testing. This may have influenced the study results as participants were able to compensate for the effects of mild iodine deficiency on the learning process, from years of experience with secondary and tertiary education.

Biological Basis of Iodine and Cognition

The present study consistently found no significant interaction between any of the cognitive tests and iodine status. When considering the results alongside the findings of the Gordon et al. (2009) study, it appears that iodine may have its effect through the development of white matter. Although little is known about the precise mechanism that links iodine deficiency and cognition, it has been proposed that it is based on iodine changing underlying neural processes such as neurotransmission and myelination (Dratman & Gordon, 1996; Thompson & Potter, 2000). Neurotransmission has been shown to respond rapidly (i.e., within minutes or hours; Walker & Kuhn, 2008) to stimulation from other chemical compounds, in both childhood and adulthood (Seedat et al., 2002). Thus, if iodine had its effect on cognition by facilitating neurotransmission, an improvement in cognition might have been expected in the present study. This was not the case, therefore, the present data do not

IODINE AND COGNITION IN YOUNG ADULTS

support the notion that iodine supplementation improves cognitive function through alterations in neurotransmitter levels.

A more conciliatory explanation for the differences between the present study and Gordon et al. (2009) is through myelination. Myelin (white matter) helps to increase conduction velocity and facilitate information processing. In disorders where myelin structure is impaired, cognitive function may also be impaired (Fields, 2008). Myelin increases from birth until middle age, only decreasing in the sixth decade of life (Bauman & Pham Dinh, 2001). However, the rate of myelin increase does change in the early years of life, with the most rapid myelin production occurring in the first two years (Hayakawa et al., 1990). The timing of myelination in neural pathways is also important. These critical periods occur in childhood and adolescence (Snook, Paulson, Roy, Phillips, & Beaulieu, 2005), but are especially vulnerable to insult in the younger years of life (Rice & Barone, 2000).

Thus, there is evidence that the timing and speed of myelin development is more critical in childhood than adulthood, whereas this is not necessarily the case with neurotransmitter changes. As a result, one can speculate that if iodine affects cognition through enhancing white matter, iodine supplementation might be more likely to assist children compared to adults. Consistent with this idea are the results of Gordon and colleagues (2009), who found iodine supplementation facilitated cognition in 9- to 11-year-old children (possibly because white matter is more susceptible to change in this age group). While this interpretation of findings seems plausible, it must remain speculative. In the first instance, it would benefit from a replication in a sample of adults in which

IODINE AND COGNITION IN YOUNG ADULTS

compliance was higher than in the present study (also, see below for ideas about neuroimaging evidence).

Furthermore, if the above reasoning is correct, it should be noted that iodine might have a facilitative effect on adult cognition over a longer time frame. While 32 weeks in the present study was longer than many other studies examining iodine supplementation that have found improvement in cognitive functioning, these studies were carried out with child participants, in which developmental and structural changes may occur more rapidly.

Implications

One of the important implications of the results of this project is the addition of information to the evidence base for iodine effects on cognition. Few studies have examined mildly iodine-deficient participants over 18 years of age. This specific area of investigation needs to be further developed in order to properly determine the mechanisms behind the association between iodine and cognition. Above, I speculated that the mechanism behind cognitive impairment in iodine deficiency might be through changes in myelin. In order to further investigate this idea, future studies could use neuroimaging methods to observe structural changes in white matter with iodine supplementation. Understanding the mechanisms behind the effects of iodine deficiency on cognition is important in order to understand the implications of iodine deficiency and to formulate more effective and efficient remediation strategies for at-risk populations.

Another implication of the present study is to simply show that despite the fact that bakery and bread products have been fortified for approximately two years in New Zealand, iodine deficiency is still prevalent in young adults.

IODINE AND COGNITION IN YOUNG ADULTS

The results are consistent with a previous study of school age children in the same area, which revealed mild iodine deficiency prior to the fortification of bread with iodised salt (Skeaff et al., 2002). Further monitoring of New Zealand's population for iodine deficiencies therefore seems important.

Strengths, Limitations, and Future Research

The major strength of the present study was the experimental design. This was a randomised, placebo-controlled trial. A randomised design is important in order to control for variables that may have spontaneously arisen due to the placement of participants into separate groups. Micronutrient deficiencies rarely occur in isolation, but often have interactions or co-occur with deficiencies in other micronutrients and vitamins (Grantham-McGregor & Ani, 1999). Aside from nutrition, other factors such as smoking and exercise have been demonstrated to interact with thyroid hormones (Grantham-McGregor & Ani, 1999; Vestergaard, 2002), and other chemical compounds may compete for iodine uptake (Meletis, 2011). However, due to the randomised-controlled design of the present study, the possible effects of iodine on cognitive function should have been isolated from any concurrent nutritional and environmental problems.

The use of both Tg and UIC measures was also a strength of the present study. These two measures are complimentary, reflecting both short-term changes (days: UIC) and intermediate changes (weeks to months: Tg; Zimmermann et al., 2008). Complimentary measures provide a more comprehensive gauge of the change in iodine status over time.

One of the main limitations identified in the present study was that a large percentage of the sample appeared to be non-compliant. In the intervention

IODINE AND COGNITION IN YOUNG ADULTS

group, approximately $\frac{1}{4}$ showed a reduction or no improvement in urinary iodine levels, and approximately $\frac{1}{3}$ of the participants in the iodine group showed no decrease in Tg, indicating that their iodine status had not improved. This indicates either that the participants were not compliant over this period, or that potential goitrogens (chemical compounds that may compete for iodine uptake) may have resulted in decreased iodine levels (Meletis, 2011).

It is difficult to tell from the biochemical measures and number of supplements returned, what the true rate of compliance was, and future studies would benefit from greater compliance. More frequent meetings with participants and increased emphasis on the importance of taking the supplements may have aided compliance. Another method would be to use other participant populations which may be more likely to comply with the study criteria (i.e., middle-aged samples might be more likely to comply than young adults). However, even when controlling for low or unchanged levels of UIC in the iodine intervention group, there was no significant difference for cognitive test scores over the intervention trial. Likewise, there were no within-time point correlations between iodine levels and cognition. These results are consistent with the idea that iodine would not have an effect on the cognition of adults with mild iodine deficiency even with full compliance.

Another potential limitation included the measurement of Tg. Tg is considered an appropriate indicator of iodine status in adults, yet it may also be influenced by the presence of Tg antibodies (TgAb). Individuals with TgAb will have a lower Tg level, wrongly appearing to have better iodine status (Demers & Spencer, 2002). In the present study TgAb were not analysed prior to the analysis of Tg. This was due to restrictions on financial resources, and because

IODINE AND COGNITION IN YOUNG ADULTS

research on this analysis is not clear as to the importance of the test, or prevalence of TgAb in the population (Demers & Spencer, 2002). The results for UIC in the present study did show mild iodine deficiency, however Tg levels were borderline. It could be anticipated that a small percentage of the sample may have produced Tg levels, which in reality should have been higher (i.e., lower iodine status), and that excluding participants with TgAb from analyses could have given a more accurate Tg measure. Future studies using Tg might include TgAb analyses in order to overcome this limitation.

Conclusion

In conclusion, evidence from previous research supports a link between iodine and cognition in children, yet there has been little research investigating this association in adults. Previous research indicates that severe and moderate iodine deficiencies are implicated in impaired cognitive function, and mild iodine deficiency has at least *some* bearing on cognitive ability. The present study found no association between cognitive scores and improvement in iodine status in mildly iodine-deficient young adults, although future research is needed to examine this relation further. The potential mechanisms behind the effects of iodine on the central nervous system include neurotransmission and myelination. I have speculated that the present results indicate that iodine might have its effects on cognition through changes in myelination, although again, future research is needed to examine this relation further. In addition, future studies should investigate whether more severe forms of iodine deficiency affect cognition in adults, and when in the lifespan mild iodine deficiency has a significant impact on cognitive development, an important issue if we wish to attain the goal of global iodine sufficiency.

References

- Ahmed, O. M., El-Gareib, A.W., El-bakry, A. M., El-Tawab, S. M. A., & Ahmed, R. G. (2008). Thyroid hormone states and brain development. *International Journal of Developmental Neuroscience*, 26, 147-209.
- Amarra, M. S., Bongga, D. C., Penano-Ho, L., Cruz, F. B., Solis, J. S., & Barrios, E. B. (2007). Effect of iodine status and other nutritional factors on psychomotor and cognitive performance of Filipino schoolchildren. *Food and Nutrition Bulletin*, 28, 47-54.
- Andersen, G. W. (2001). Thyroid hormones and the brain. *Frontiers in Neuroendocrinology*, 22, 1-17.
- Andersson, M., & Zimmermann, M. B. (2010). Influence of iodine deficiency and excess on thyroid function tests. In G. A. Brent (Ed.), *Thyroid Functioning Testing* (pp 45-69). New York: Springer.
- Bäckman, L., Karlsson, S., Fischer, H., Karlsson, P., Brehmer, Y., Rieckmann, A., . . . Nyberg, L. (2011). Dopamine D₁ receptors and age differences in brain activation during working memory. *Neurobiology of Aging*, 32, 1849-1856.
- Barres, B. A., Lazar, M. A., & Raff, M. C. (1994). A novel role for thyroid hormone, glucocorticoids and retinoic acid in timing oligodendrocyte development. *Development*, 120, 1097-1108.
- Bartzokis, G., Beckson, M., Lu, P. H., Nuechterlein, K. H., Edwards, N., & Mintz, J. (2001). Age-related changes in frontal and temporal lobe volumes in men. *Archives of General Psychiatry*, 58, 461-465.

IODINE AND COGNITION IN YOUNG ADULTS

Bartzokis, G., Lu, P. H., Tingus, K., Mendez, M. F., Richard, A., Peters, D. G., .

. . Mintz, J. (2010). Lifespan trajectory of myelin integrity and maximum motor speed. *Neurobiology of Aging*, 31, 1554-1562.

Bauer, M., Goetz, T., Glenn, T., & Whybrow, P. C. (2008). The thyroid-brain interaction in thyroid disorders and mood disorders. *Journal of Neuroendocrinology*, 20, 1101-1114.

Bauman, N., & Pham-Dinh, D. (2001). Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiological Reviews*, 81, 871-927.

Bautista, A., Barker, P. A., Dunn, J. T., Sanchez, M., & Kaiser, D. L. (1982). The effects of oral iodized oil on intelligence, thyroid status, and somatic growth in school-age children from an area of endemic goiter. *The American Journal of Clinical Nutrition*, 35, 127-134.

Bava, S., Thayer, R., Jacobus, J., Ward, M., Jernigan, T. L., & Tapert, S. F. (2010). Longitudinal characterization of white matter maturation during adolescence. *Brain Research*, 1327, 38-46.

Bear, M. F., Connors, B. W., & Paradiso, M. A. (2007). *Neuroscience: Exploring the Brain* (3rd Ed.). Philadelphia: Lippincott Williams and Wilkins.

Bendlin, B. B., Fitzgerald, M. E., Ries, M. L., Xu, G., Kastman, E. K., Thiel, B. W., . . . Johnson, S. C. (2010). White matter in aging and cognition: A cross-sectional study of microstructure in adults aged eighteen to eighty-three. *Developmental Neuropsychology*, 35, 257-277.

Bernal, J. (1999). Iodine and brain development. *BioFactors*, 10, 271-276.

IODINE AND COGNITION IN YOUNG ADULTS

- Bleichrodt, N., & Born, M. (1994). A metaanalysis of research on iodine and its relationship to cognitive development. In J.B. Stanbury (Ed.), *The Damaged Brain of Iodine Deficiency* (pp. 195-200). New York: Cognizant Communication Corp.
- Bleichrodt, N., Drenth, P. J. D., & Querido, A. (1980). Effects of iodine deficiency on mental and psychomotor abilities. *American Journal of Physical Anthropology*, 53, 55-67.
- Bleichrodt, N., Shrestha, R. M., West, C. E., Haulvast, J. G., van de Vijer, F., & Born, M. (1996). The benefits of adequate iodine intake. *Nutrition Reviews*, 54, 72-78.
- Buccafusco, J. J., & Terry, A. V. (2000). Multiple central nervous system targets for eliciting beneficial effects on memory and cognition. *The Journal of Pharmacology and Experimental Therapeutics*, 295, 438-446.
- Calza, L., Fernandez, M., & Giardino, L. (2010). Cellular approaches to central nervous system remyelination stimulation: Thyroid hormone to promote myelin repair via endogenous stem and precursor cells. *Journal of Molecular Endocrinology*, 44, 13-23.
- Cao, X., Cui, Z., Feng, R., Tang, Y. P., Qin, Z., Mei, B., & Tsien, J. Z. (2007). Maintenance of superior learning and memory function in NR2B transgenic mice during aging. *European Journal of Neuroscience*, 25, 1815-1822.
- Casey, B. J., Giedd, J. N., & Thomas, K. M. (2000). Structural and functional brain development and its relation to cognitive development. *Biological Psychology*, 54, 241-257.

IODINE AND COGNITION IN YOUNG ADULTS

Courchesne, E., Chisum, H. J., Townsend, J., Cowles, A., Covington, J., Egaas,

B., . . . Press, G. A. (2000). Normal brain development and aging:

Qualitative analysis at in vivo MR imaging in healthy volunteers.

Neuroradiology, 216, 672-682.

Delange, F. (2001). Iodine deficiency as a cause of brain damage. *Postgraduate*

Medical Journal, 77, 217-220.

Demers, L. M., & Spencer, C. A. (2003). Laboratory medicine practice

guidelines: Laboratory support for the diagnosis and monitoring of

thyroid disease. *Clinical Endocrinology*, 58, 138-140.

Dratman, M. B., & Gordon, J. T. (1996). Thyroid hormones as

neurotransmitters. *Thyroid*, 6, 639-647.

Drever, B. D., Riedel, G., & Platt, B. (2011). The cholinergic system and

hippocampal plasticity. *Behavioural Brain Research*, 221, 505-514.

Durstun, S., & Casey, B. J. (2006). What have we learned about cognitive

development from neuroimaging? *Neuropsychologica*, 44, 2149-2157.

Edin, F., Macoveanu, J., Olesen, P., Tegner, J., & Klingberg, T. (2007).

Stronger synaptic connectivity as a mechanism behind development of

working memory-related brain activity during childhood. *Journal of*

Cognitive Neuroscience, 19, 750-760.

Erlanger, D. M., Kutner, K. C., & Jacobs, A. R. (1999). Hormones and

cognition: Current concepts and issues in neuropsychology.

Neuropsychology Review, 9, 175-207.

Farsetti, A., Mitsuhashi, T., Desvergne, B., Robbins, J., & Nikodem, V. M.

(1991). Molecular basis of thyroid hormone regulation of myelin basic

IODINE AND COGNITION IN YOUNG ADULTS

- protein gene expression in rodent brain. *The Journal of Biological Chemistry*, 266, 23226-23232.
- Fernandez-Lamo, I., Montero-Pedrazuela, A., Delgado-Garcia, J. M., Guadano-Ferraz, A., & Gruart, A. (2009). Effects of thyroid replacement on associative learning and hippocampal synaptic plasticity in adult hypothyroid rats. *European Journal of Neuroscience*, 30, 679-692.
- Fernandez, M., Pirondi, S., Manservigi, M., Giardino, L., & Calza, L. (2004). Thyroid hormone participates in the regulation of neural stem cells and the oligodendrocytes precursor cells in the central nervous system of adult rat. *European Journal of Neuroscience*, 20, 2059-2070.
- Fields, R. D. (2005). Myelination: An overlooked mechanism of synaptic plasticity? *Neuroscientist*, 11, 528-531.
- Fields, R. D. (2008). White matter in learning, cognition and psychiatric disorders. *Trends in Neurosciences*, 31, 361-370.
- Filley, C. M. (2010). White matter: Organization and functional relevance. *Neuropsychological Review*, 20, 158-173.
- Gage, F. H. (2002). Neurogenesis in the adult brain. *The Journal of Neuroscience*, 22, 612-613.
- Gaitan, E., & Dunn, J. T. (1992). Epidemiology of iodine deficiency. *TEM*, 3, 170-175.
- Ge, Y., Grossman, R. I., Babb, J. S., Rabin, M. L., Mannon, L. J., & Kolson, D. L. (2002). Age-related total gray matter and white matter changes in normal adult brain. Part I: Volumetric MR imaging analysis. *American Journal of Neuroradiology*, 23, 1327-1333.

IODINE AND COGNITION IN YOUNG ADULTS

- Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., . . . Rapoport, J. L. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, 2, 861-863.
- Gilbert, M. E., & Sui, L. (2006). Dose-dependent reductions in spatial learning and synaptic function in the dentate gyrus of adult rats following developmental thyroid hormone insufficiency. *Brain Research*, 1069, 10-22.
- Gordon, R. C., Rose, M. C., Skeaff, S. A., Gray, A. R., Morgan, K., & Ruffman, T. (2009). Iodine supplementation improves cognition in mildly iodine-deficient children. *The American Journal of Clinical Nutrition*, 90, 1264-1271.
- Grantham-McGregor, S. M., & Ani, C. C. (1999). The role of micronutrients in psychomotor and cognitive development. *British Medical Bulletin*, 55, 511-527.
- Gur, R. C., Turetsky, B. I., Matsui, M., Yan, M., Bilker, W., Hughett, P., & Gur, R. E. (1999). Sex differences in brain gray and white matter in healthy young adults: Correlations with cognitive performance. *The Journal of Neuroscience*, 19, 4066-4072.
- Guttman, C. R. G., Jolesz, F. A., Kikinis, R., Killiany, R. J., Moss, M. B., Sandor, T., & Albert, M. S. (1998). White matter changes with normal aging. *Neurology*, 50, 972-978.
- Hayakawa, K., Konishi, Y., Kuriyama, M., Konishi, K., & Matsuda, T. (1990). Normal brain maturation in MRI. *European Journal of Radiology*, 12, 208-215.

IODINE AND COGNITION IN YOUNG ADULTS

- Herlenius, E., & Lagercrantz, H. (2004). Development of neurotransmitter systems during critical periods. *Experimental Neurology*, 190, 8-21.
- Herrera-Guzmán, I., Gudyol-Ferré, E., Herrera-Guzmán, D., Guàrdia-Olmos, J., Hinojosa-Calvo, E., & Herrera-Abarca, J. E. (2009). Effects of selective serotonin reuptake and dual serotonergic-noradrenergic reuptake treatments on memory and mental processing speed in patients with major depressive disorder. *Journal of Psychiatric Research*, 43, 855-863.
- Hetzel, B. S. (1983). Iodine deficiency disorders (IDD) and their eradication. *The Lancet*, 322, 1126-1129.
- Hollowell, J. C., & Hannon, W. H. (1997). Teratogen update: Iodine deficiency, a community teratogen. *Teratology*, 55, 389-405.
- Howorth, P. J. N., & Ward, R. L. (1972). The T₄-free thyroxine index as a test of thyroid function of first choice. *Journal of Clinical Pathology*, 25, 259-262.
- Huda, S. N., Grantham-McGregor, S. M., & Tomkins, A. (2001). Cognitive and motor functions of iodine-deficient but euthyroid children in Bangladesh do not benefit from iodized poppy seed oil. *The Journal of Nutrition*, 131, 72-77.
- Isa, Z., Alias, I. Z., Kadir, K. A., & Ali, O. (2000). Effect of iodized oil supplementation on thyroid hormone levels and mental performance among *Orang Asli* schoolchildren and pregnant mothers in an endemic goitre area in Peninsular Malaysia. *Asia Pacific Journal of Clinical Nutrition*, 9, 274-281.

IODINE AND COGNITION IN YOUNG ADULTS

- Koibuchi, N. (2008). Hormonal regulation of cerebellar development and plasticity. *Cerebellum*, 7, 1-3.
- König, F., Andersson, M., Hotz, K., Aeberli, I., & Zimmermann, M. B. (2011). Ten repeat collections for urinary iodine from spot samples or 24-hour samples are needed to reliably estimate individual iodine status in women. *The Journal of Nutrition*, 141, 2049-2054.
- Krail, R., & Salthouse, T.A. (1994). Processing speed as a mental capacity. *Acta Psychologica*, 86, 199-225.
- Laurberg, P., Jørgensen, T., Perrild, H., Ovesen, L., Knudsen, N., Pedersen, I. B., . . . Vejbjerg, P. (2006). The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *European Journal of Endocrinology*, 155, 219-228.
- Li, S. C., Brehmer, Y., Shing, Y. L., Werkle-Bergner, M., & Lindenberger, U. (2006). Neuromodulation of associative and organizational plasticity across the life span: Empirical evidence and neurocomputational modelling. *Neuroscience and Biobehavioural Reviews*, 30, 775-790.
- Li, S. C., Lindenberger, U., & Bäckman, L. (2010). Dopaminergic modulation of cognition across the life span. *Neuroscience and Behavioural Reviews*, 34, 625-630.
- Liu, W., Dong, J., Wang, Y., Xi, Q., & Chen, J. (2010). Developmental iodine deficiency and hypothyroidism impaired *in vivo* synaptic plasticity and altered PKC activity and GAP-43 expression in rat hippocampus. *Nutritional Neuroscience*, 13, 213-221.
- Loosen, P. (1992). Effects of thyroid hormones on central nervous system in aging. *Psychoneuroendocrinology*, 17, 355-374.

IODINE AND COGNITION IN YOUNG ADULTS

- Magner, J. A. (1990). Thyroid-stimulating hormone: Biosynthesis, cell biology, and bioactivity. *Endocrine Reviews*, 11, 354-385.
- Magner, J. A. (1997). Pituitary-thyroid relationships. In E. E. Bittar, & N. Bittar (Eds.), *Molecular and Cellular Endocrinology* (pp. 165-189). Connecticut: JAI Press Inc.
- Mano, M. T., Potter, B. J., Belling, G. B., Chavdej, J., & Hetzel, B. S. (1987). Fetal brain development in response to iodine deficiency in a primate model (*Callithrix jacchus jacchus*). *Journal of Neurological Sciences*, 79, 287-300.
- Mattson Porth, C., & Matfin, G. (2009). *Pathophysiology: Concepts of Altered Health States* (8th ed.). Philadelphia: Lippincott Williams & Wilkins.
- McElduff, A., & Beange, H. (2004). Iodine deficiency in Australia: Be alarmed. *Journal of Intellectual and Developmental Disability*, 29, 85-87.
- McNab, F., Varrone, A., Farde, L., Jucaite, A., Bystritsky, P., Fossberg, H., & Klingberg, T. (2009). Changes in cortical dopamine D1 receptor binding associated with cognitive training. *Science*, 323, 800-802.
- Meletis, C. D. (2011). Iodine: Health implications of deficiency. *Journal of Evidence-Based Complementary and Alternative Medicine*, 16, 1-5.
- Melse-Boonstra, A., & Jaiswal, N. (2010). Iodine deficiency in pregnancy, infancy and childhood and its consequences for brain development. *Best Practice and Research Clinical Endocrinology and Metabolism*, 24, 29-38.
- Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of Cognitive Neuroscience*, 16, 1227-1233.

IODINE AND COGNITION IN YOUNG ADULTS

- Nguyen, L., Rigo, J., Rocher, V., Belachew, S., Malgrange, B., Rogister, B., Leprince, P., & Moonen, G. (2001). Neurotransmitters as early signals for central nervous system development. *Cell and Tissue Research*, 305, 187-202.
- Olesen, P. J., Nagy, Z., Westerberg, H., & Klingberg, T. (2003). Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. *Cognitive Brain Research*, 18, 48-57.
- Opazo, M. C., Gianini, A., Pancetti, F., Azkcona, G., Alarcon, L., Lizana, R., . . . Riedel, C. A. (2008). Maternal hypothyroxinemia impairs spatial learning and synaptic nature and function in the offspring. *Endocrinology*, 149, 5097-5106.
- Overstreet, D. H., Crocker, A. D., Lawson, C. A., McIntosh, G. H., & Crocker, J. M. (1984). Alterations in the dopaminergic system and behaviour in rats reared on iodine-deficient diets. *Pharmacology Biochemistry and Behaviour*, 21, 561-565.
- Parnell, W., Scragg, P., Wilson, N., Schaaf, D., & Fitzgerald, E. (2003). *NZ food NZ children: Key results of the 2002 national children's nutrition survey*. Wellington: Ministry of Health.
- Patrick, L. (2008). Iodine: deficiency and therapeutic considerations. *Alternative Medicine Review*, 13, 116-127.
- Pharoah, P. O. D., & Connolly, K. J. (1987). A controlled trial of iodinated oil for the prevention of endemic cretinism: A long-term follow up. *International Journal of Epidemiology*, 16, 68-73.

IODINE AND COGNITION IN YOUNG ADULTS

Potter, B. J., Mano, M. T., Belling, G. B., Martin, D. M., Cragg, B. G.,

Chavadej, J., & Hetzel, B. S. (1984). Restoration of brain growth in fetal sheep after iodized oil administration to pregnant iodine-deficient ewes.

Journal of the Neurological Sciences, 66, 15-26.

Prinz, P. N., Scanlan, J. M., Vitaliano, P. P., Moe, K. E., Borson, S., Toivola,

B., . . . Reed, H. L. (1999). Thyroid hormones: Positive relationships with cognition in healthy, euthyroid older men. *Journal of Gerontology*,

54, 111-116.

Qian, M., Wang, D., Watkins, W.E., Gebiski, V., Qin Yan, Y., Li, M., & Pei

Chen, Z. (2005). The effects of iodine on intelligence in children: A metaanalysis of studies conducted in China. *Asia Pacific Journal of*

Clinical Nutrition, 14, 32-42.

Rice, D., & Barone, S. (2000). Critical periods of vulnerability for the

developing nervous system: Evidence from humans and animal models.

Environmental Health Perspectives, 108, 511-533.

Rivas, M., & Narajo, J. R. (2007). Thyroid hormones, learning and memory.

Genes, Brain and Behaviour, 6, 40-44.

Samuels, M. H., Schuff, K. G., Carlson, N. E., Carello, P., & Janowsky, J. S.

(2007). Health status, mood, and cognition in experimentally induced subclinical hypothyroidism. *The Journal of Clinical Endocrinology and*

Metabolism, 92, 2646-2661.

Sawaguchi, T., & Goldman-Rakic, P. S. (1991). D1 dopamine receptors in

prefrontal cortex: Involvement in working memory. *Science*, 251, 947-

950.

IODINE AND COGNITION IN YOUNG ADULTS

- Schatz, D. L., Palter, H. C., & Russell, C. S. (1968). Effects of oral contraceptives and pregnancy on thyroid function. *Canadian Medical Association Journal*, 99, 882-886.
- Seedat, S., Stein, D. J., Ziervogel, C., Middleton, T., Kaminer, D., Emsley, R., & Rossouw, W. (2002). Comparison of response to a selective serotonin reuptake inhibitor in children, adolescents, and adults with posttraumatic stress disorder. *Journal of Child and Adolescent Psychopharmacology*, 12, 37-46.
- Sharlin, D. S., Gilbert, M. E., Taylor, M. A., Ferguson, D. C., & Zoeller, R. T. (2010). The nature of the compensatory response to low thyroid hormone in the developing brain. *Journal of Neuroendocrinology*, 22, 153-165.
- Silva, A. J., Elgersma, Y., & Costa, R. M. (2000). Molecular and cellular mechanisms of cognitive function: Implications for psychiatric disorders. *Biological Psychiatry*, 47, 200-209.
- Skeaff, S., Thomson, C.D., & Gibson, R. S. (2002). Mild iodine deficiency in a sample of New Zealand schoolchildren. *European Journal of Clinical Nutrition*, 56, 1169-1175.
- Snook, L., Paulson, L. A., Roy, D., Phillips, L., & Beaulieu, C. (2005). Diffusion tensor imaging of neurodevelopment in children and young adults. *NeuroImage*, 26, 1164-1173.
- Sui, L., Wang, F., & Li, B. M. (2006). Adult-onset hypothyroidism impairs paired-pulse facilitation and long-term potentiation of the rat dorsal hippocampo-medial prefrontal cortex pathway in vivo. *Brain Research*, 1096, 53-60.

IODINE AND COGNITION IN YOUNG ADULTS

- Tabachnick, B. G., & Fidell, L. S. (2001). *Using Multivariate Statistics* (4th Ed.). New York: Allyn and Bacon.
- Tang, P., Shimizu, E., Dube, G. R., Rampon, C., Kerchner, G.A., Zhuo, M., Liu, G., & Tsien, J. Z. (1999). Genetic enhancement of learning and memory in mice. *Nature*, 401, 63-69.
- Thompson, C. C. (1999). Molecular mechanism of thyroid hormone action in neural development. *Developmental Neuropsychology*, 16, 365-367.
- Thompson, C. C., & Potter, G. B. (2000). Thyroid hormone action in neural development. *Cerebral Cortex*, 10, 939-945.
- Tiwari, B. D., Godbole, M. M., Chattopadhyay, N., Mandal, A., & Mithal, A. (1996). Learning disabilities and poor motivation to achieve due to prolonged iodine deficiency. *The American Journal of Clinical Nutrition*, 63, 782-786.
- Untoro, J., Timmer, A., & Schultink, W. (2010). The challenges of iodine supplementation: A public health programme perspective. *Best Practice & Clinical Endocrinology & Metabolism*, 24, 89-99.
- Van den Briel, T., West, C. E., Bleichrodt, N., van de Vijler, J. J. M., Ategbo, E. A., & Hautvast, J. G. A. J. (2000). Improved iodine status is associated with improved mental performance of schoolchildren in Benin. *The American Journal of Clinical Nutrition*, 72, 1179-1185.
- Van den Briel, T., West, C. E., Hautvast, J. G. A. J., Vulsma, T., de Vijler, J. J. M., & Ategbo, E. A. (2001). Serum thyroglobulin and urinary iodine concentration are the most appropriate indicators of iodine status and thyroid function under conditions of increasing iodine supply in schoolchildren in Benin. *The Journal of Nutrition*, 131, 2701-2706.

IODINE AND COGNITION IN YOUNG ADULTS

- Vara, H., Martinez, B., Santos, A., & Colino, A. (2002). Thyroid hormone regulates neurotransmitter release in neonatal rat hippocampus. *Neuroscience*, 110, 19-28.
- Vestergaard, P. (2002). Smoking and thyroid disorders- a meta-analysis. *European Journal of Endocrinology*, 146, 153-161.
- Walker, Q. D., & Kuhn, C. M. (2008). Cocaine increases stimulated dopamine release more in periadolescent than adult rats. *Neurotoxicology and Teratology*, 30, 412-418.
- Wang, M., Vijayraghavan, S., & Goldman-Rakic, P. S. (2004). Selective D2 receptor actions on the functional circuitry of working memory. *Science*, 303, 853-856.
- Wechsler, D. (2008). Wechsler Adult Intelligence Scale: Australian and New Zealand Language adaption (4th Ed.). In A. Madden (Ed.), *Technical and Interpretive Manual*. Australia: Pearson.
- Williams, G. V., & Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature*, 376, 572-575.
- Williams, P. E., Weiss, L. G., & Rolfus, E. (2003). WISC-IV Technical Report #1 *Theoretical Model and Test Blueprint*. San Antonio TX: The Psychological Corporation.
- World Health Organisation, United Nations Children's Fund, International Council for the Control of Iodine Deficiency Disorders (1994). *Indicators for Assessing Iodine Deficiency Disorders and their Control Programmes*. Geneva: WHO.
- World Health Organisation, United Nations Children's Fund, International Council for the Control of Iodine Deficiency Disorders (2007).

IODINE AND COGNITION IN YOUNG ADULTS

Assessment of Iodine Deficiency Disorders and Monitoring their Elimination (3rd Ed.). Geneva: WHO.

- Yen, P. M. (2001). Physiological and molecular basis of thyroid hormone action. *Physiological Reviews*, 81, 1097-1142.
- Zahr, N. M., Rohlfing, T., Pfefferbaum, A., & Sullivan, E. V. (2009). Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: A quantitative fiber tracking study. *NeuroImage*, 44, 1050-1062.
- Zimmermann, M. B. (2008). Iodine requirements and the risks and benefits of correcting iodine deficiency in populations. *Journal of Trace Elements in Medicine and Biology*, 22, 81-92.
- Zimmermann, M. B. (2009). Iodine deficiency. *Endocrine Reviews*, 30, 376-408.
- Zimmermann, M. B., Connolly, K., Bozo, M., Bridon, J., Rohner, F., & Grimci, L. (2006). Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: A randomized, controlled, double-blind study. *American Journal of Clinical Nutrition*, 83, 108-114.
- Zimmermann, M. B., Jooste, P.L., & Pandav, C.S. (2008). Iodine deficiency disorders. *Lancet*, 372, 1251-1262.
- Zoeller, R. T., & Rovett, J. (2004). Timing of thyroid hormone action in the developing brain: Clinical observations and experimental findings. *Journal of Neuroendocrinology*, 16, 809-818.

Appendix A

Poster Advertisement for Participant Recruitment

WANT TO **think** better?

In 2008 we found that giving Dunedin children extra iodine improved their ability to solve problems.

The human brain continues to develop throughout childhood, adolescence and into early adulthood.

We are doing another study to find out if similar results will occur in young adults. You will receive \$50 for participating.

If you're aged 18-30 years, eat no more than two servings of bread per day, do not take an iodine-containing supplement, and will be in Dunedin in October-November 2010 and July-August 2011, don't think twice.

Please contact:

Penelope or Kahla

Department of Human Nutrition / Psychology

Tel 021 129 7291 / 027 857 9448

Email think.project@otago.ac.nz



Appendix B

Questionnaire for Demographic Information

think2 project

Participant Questionnaire

Thank you for agreeing to participate in this study, and for taking the time to complete this questionnaire. **Answers will be kept strictly confidential**, and will help us better understand the effects of iodine supplementation on cognition in New Zealand adults.

Please complete the following questions to the best of your ability:

Name: _____

Address during semester: _____

Telephone Number: _____

Mobile Number: _____

Email Address: _____

Address outside of semester: _____
If different from above

Telephone Number outside of semester: _____
If different from above

In _____ (3 months from now), which address should your tablets be sent to?

☐ ₁ **During semester address** ☐ ₂ **Outside semester address** **Other:** _____

In _____ (6 months from now), which address should your tablets be sent to?

☐₁ During semester address ☐₂ Outside semester address Other _____
: _____

Please provide the name, relationship, address and phone number of three more contacts so we can remain in touch with you throughout the next 10 months.
(e.g. parents, grandparents, aunt, uncle, brother, sister)

Contact 1:

Name: _____
Relationship: _____
Address: _____
Phone number: _____

Contact 2:

Name: _____
Relationship: _____
Address: _____
Phone number: _____

Contact 3:

Name: _____
Relationship: _____
Address: _____
Phone number: _____

Date of birth: _____

Country of birth: _____

Ethnicity:☐₁ European/Pakeha☐₂ Maori☐₃ Pacific Island☐₄ Other, please state: _____**Total Household Income:**☐₁ < \$20,000☐₂ \$20,000- \$50,000☐₃ >\$50,000☐₄ Do not wish to answer**Do you take supplements of any sort including vitamin and mineral supplements?**☐₁ Yes (please specify below)☐₂ No

Type of Supplement	Brand name of supplement	How often is supplement taken?
e.g. Multivitamin	Horleys	Twice daily

Do you have any of the following medical conditions?☐₁ Dyslexia

Diagnosed by: _____

Date of
Diagnosis: _____☐₂ Thyroid Problems

Diagnosed by: _____

Date of
Diagnosis: _____☐₃ Hearing Problems

Diagnosed by: _____

Date of
Diagnosis: _____

**Please specify any other medical conditions you have:
(e.g. asthma, diabetes)**

Condition: _____
Approximate date of diagnosis: _____
Current treatment: _____

Condition: _____
Approximate date of diagnosis: _____
Current treatment: _____

Condition: _____
Approximate date of diagnosis: _____
Current treatment: _____

If you are female, are you pregnant or planning a pregnancy?

☐₁ Yes

☐₂ No

How do you describe your health?

☐₁ Excellent

☐₂ Good

☐₃ Poor

Are you currently taking Medication of any sort?

☐₁ Yes (please specify below)

☐₂ No

Type of Medication	What medication is for	How often do you take the medication?	Length of prescription
e.g. Ventolin	Asthma	Twice daily	Ongoing

Are you allergic to anything?
(e.g. disinfectant solutions, anaesthetic cream, plasters)

☐₁ Yes (please specify below)

☐₂ No

Are you currently on a special diet?

☐₁ No

☐₂ Vegetarian

☐₃ Vegan

☐₄ Other (please specify below)

Appendix C

Short-Form Health Questionnaire (SF-36)

SF-36 QUESTIONNAIRE

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

- ☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

Compared to one year ago, how would you rate your health in general now?

- ☐ Much better now than one year ago
☐ Somewhat better now than one year ago
☐ About the same
☐ Somewhat worse now than one year ago
☐ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

- ☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

- ☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Lifting or carrying groceries

- ☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing several flights of stairs

- ☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing one flight of stairs

- ☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bending, kneeling, or stooping

- ☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking more than a mile

- ☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking several blocks

- ☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking one block

- ☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bathing or dressing yourself

- ☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

☐ Yes

☐ No

Accomplished less than you would like

☐ Yes

☐ No

Were limited in the kind of work or other activities

☐ Yes

☐ No

Had difficulty performing the work or other activities (for example, it took extra effort)

☐ Yes

☐ No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

☐ Yes

☐ No

Accomplished less than you would like

☐ Yes

☐ No

Didn't do work or other activities as carefully as usual

☐ Yes

☐ No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

☐ Not at all

☐ Slightly

☐ Moderately

☐ Severe

☐ Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

☐ None

☐ Very Mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐ Not at all

☐ A little bit

☐ Moderately

☐ Quite a bit

☐ Extremely

ENERGY AND EMOTIONS:

These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you been a very nervous person?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you felt so down in the dumps that nothing could cheer you up?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you felt calm and peaceful?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Did you have a lot of energy?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you felt downhearted and blue?

- ☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Did you feel worn out?

- ☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Have you been a happy person?

- ☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Did you feel tired?

- ☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

SOCIAL ACTIVITIES:

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- ☐ All of the time
☐ Most of the time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

GENERAL HEALTH:

How true or false is each of the following statements for you?

I seem to get sick a little easier than other people

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

I am as healthy as anybody I know

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

I expect my health to get worse

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

My health is excellent

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

Appendix D

Information Sheet

think2 project

Iodine and Cognition in Young Adults

Thank you for showing an interest in this project. Please read this information sheet carefully before deciding whether or not to participate. If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you of any kind and we thank you for considering our request.

Why are we doing this project?

Iodine is a nutrient and like calcium and iron, is found in the foods we eat. Recently it has been reported that the level of iodine in the diets of New Zealanders has fallen. Iodine is needed by our bodies to make hormones for normal growth and it plays a role in the way the brain works and develops. We are doing this project to see if giving young adults extra iodine will improve their ability to think, reason and remember. We are interested in seeing if giving young adults more iodine will improve brain function.

Who can take part?

We are asking adults aged 18-30 years who will be living in Dunedin until the end of November to take part. Adults cannot take part in this study if they eat more than 2 servings of commercial bread products a day, regularly take dietary supplements containing iodine, have any form of thyroid disease, are pregnant, are dyslexic as this may interfere with the cognitive tests, or they are not willing to take a tablet that may contain iodine during the study.

What is involved?

Should you agree to take part in this project, you will be asked to take a tablet each day for 32 weeks that may or may not contain iodine. The amount of iodine in the tablets will be similar to the amount of iodine you would get from eating two portions of fish each day. The tablets are very small and contain no gluten, artificial additives or colourings. You will be placed in one of two groups; one group of participants will take tablets that contain a small amount of iodine and one group of participants will take tablets that contain no iodine. You will not be able to choose what group you are in, and the tablets will all look exactly the same. Tablets will be mailed to your home each month and you will be asked to return any unused tablets in a stamped envelope.

Taking part in this study also involves you:

- Providing a urine sample at the beginning and end of the study.
- Having a fingerprick blood sample taken at the beginning and end of the study.

- Undergoing a series of simple cognitive tests (eg solving picture puzzles) that should take approximately 60 minutes at the beginning and end of the study.

Is extra iodine safe?

Even if you have a diet that is high in iodine, it is very unlikely that the extra iodine in the tablet would cause you to get too much iodine, as the upper safety intake level is high (7 times the dose of the tablets).

Can I change my mind and withdraw from the project?

You may withdraw from participation in the project at any time and without any disadvantage of any kind.

What will happen to the results?

At the end of the study, any personal information will be destroyed. Other data collected will be securely stored for five years, and then destroyed. The results will be assigned a code – it will not be possible to identify you from the stored information in any way. All participants will receive a copy of the final project results within a year of completing the project.

What if I questions?

If you have any questions about our project, either now or in the future, please feel free to email think.project@otago.ac.nz or contact either:

Penelope Fitzgerald

Phone: 0211297291

Kahla Redman

Phone: 0278579448

Dr Sheila Skeaff

Phone: 479-7944

Department of Human Nutrition

Prof. Ted Ruffman

Phone: 479-7670

Department of Psychology University of Otago, Dunedin

This project has been reviewed and approved by the

University of Otago Human Ethics Committee. (Ref No: 10/026)



Appendix E**Consent Form****think2 project****Iodine and Cognition in Young Adults**

I have read the Information Sheet concerning this project and understand what it is about. All my questions have been answered to my satisfaction. I understand that I am free to request further information at any stage.

I know that:

1. my participation in the project is entirely voluntary;
2. I am free to withdraw from the project at any time without any disadvantage;
3. the personal information will be destroyed at the conclusion of the project but any raw data on which the results of the project depend will be retained in secure storage for five years, after which they will be destroyed.
4. the results of the project may be published but I will not be identified personally in any publication, results, or discussion to do with this study.

I agree to take part in this project.

.....
(Signature of participant)

.....
(Date)

This project has been reviewed and approved by the
University of Otago Human Ethics Committee (Ref no: 10/026).



Appendix F

Introductory Verbatim for Cognitive Testing

“Today we are going to be doing several cognitive tests. Some you will find easy, some you will find a bit harder. Most people don’t finish every item or get every one right, so just try your best.

When we come to each item, I will tell you the name and give you some instructions. I will be timing some of the tests. I won’t tell you which ones (but you will hear the timer).

If you want a break, feel free to take as many as you like, just not during a test. Before and after are fine though.

Do you have any questions?”