

FATTY ACIDS AND EXECUTIVE FUNCTIONS: BEHAVIORAL PERFORMANCE AND  
CORTICAL ACTIVATION ACROSS THE LIFESPAN

Kelly Will Sheppard

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Approved by:

Carol L. Cheatham

J. Steven Reznick

Peter A. Ornstein

Barbara Davis Goldman

Joseph B. Hopfinger

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## ABSTRACT

Kelly Will Sheppard: Fatty Acids and Executive Functions: Behavioral Performance and Cortical Activation Across the Lifespan  
(Under the direction of Carol L. Cheatham)

An imbalance in the omega-6 to omega-3 fatty acid ratio may be a preventable contributor to cognitive deficits across the lifespan. Omega-6 and omega-3 fatty acids are integral to neuronal growth and communication in the hippocampus and frontal cortex, brain areas that subserve executive functions (EF). EF are higher order cognitive functions that control thoughts, behaviors, and emotions. The present study focused on how the balance of omega-6 and omega-3 fatty acids contributes to EF in children 7 to 12 years old and older adults 65 to 79 years old. One hundred fifty-two children were screened for their omega-6 and omega-3 fatty acid intake using three 24-hour diet recalls, and 78 children representing equal recruitment of nine fatty acid intake patterns completed standardized measures of memory, working memory, and planning and one novel planning task, the Electric Maze Task (EMT). Near-infrared spectroscopy (NIRS) data were also collected. Eighty-eight older adults recruited for a study of cognitive decline also completed standardized measures of memory, working memory, and visual processing.

The omega-6 to omega-3 ratio predicted performance on EF tasks among the children and older adults. The younger children (7- to 9-year-olds) and oldest adults (75- to 79-year-olds) benefitted from balanced ratios (e.g., low omega-3 and low omega-6). The older children (10- to 12-year-olds) and youngest adults (65- to 69-year-olds) benefitted from imbalanced ratios (e.g., high omega-3 and low omega-6). The ratio also predicted brain activity in the right and central prefrontal cortex associated with better performance on the EMT and planning problems. The balance of fatty acids likely supports the flexible use of prefrontal cortical resources necessary for complex EF. Different balances of omega-6 and omega-3 fatty acids are optimal at different points in development, and additional work with the omega-6 to omega-3 ratio will help elucidate the optimal diet for cognitive function across the lifespan.

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## LIST OF ABBREVIATIONS

ARA	Arachidonic acid
CANTAB	Cambridge Neuropsychological Test Assessment Battery
DCCS	Dimensional change card sort
dGLA	di-Hommo-gamma linoleic acid
DHA	Docosahexanoic acid
EF	Executive functions
EPA	Eicospentaenoic acid
LA	Linoleic acid
LCPUFA	Long-chain polyunsaturated fatty acids
LNA	Alpha-linolenic acid
LTP	Long-term potentiation
MWM	Morris Water Maze
PAL	Paired Associates Learning
RCTs	Randomized, controlled trials
RVP	Rapid Visual Processing
SOC	Stockings of Cambridge
SWM	Spatial Working Memory

## CHAPTER 1: INTRODUCTION

Fatty acids are important building blocks for neuronal membranes (Martinez & Mougan, 1998). The fatty acids incorporated into the membrane affect the neuron's structure and function (Schairer & Overath, 1969). Omega-6 and omega-3 fatty acids are the most abundant fatty acids in the brain (Fraser, Tayler, & Love, 2010; Patel & Clark, 1980), and are found particularly in the frontal cortex and hippocampus (Martinez, 1992). In these brain areas, the omega-6 and omega-3 fatty acids have been shown to affect neurotransmitter levels (Chalon, Vancassel, Zimmer, Guilloteau, & Durand, 2001; De La Presa Owens & Innis, 2000; Delion et al., 1997), receptor density and function (Davis et al., 2010; du Bois, Deng, Bell, & Huang, 2006; Zimmer et al., 2000), and neuronal growth (Auestad & Innis, 2000; Calderon & Kim, 2004). Despite a large literature on the role of fatty acids in neuronal structure and function, particularly in the frontal cortex and hippocampus, there hasn't been a consensus as to the importance of fatty acids in brain function or cognitive development. In fact, the Cochrane review on fatty acid supplementation of infants born at term concluded there wasn't enough evidence to state that fatty acids were beneficial to cognitive development (Simmer, Patole, & Rao, 2011).

The challenges of studying fatty acid supplementation are well-documented (for review: Cheatham & Colombo, 2006; Willatts & Forsyth, 2000). In particular, there is the need to use assessments of specific cognitive functions that are developmentally appropriate (Cheatham et al., 2006). The role that omega-6 and omega-3 fatty acids play in neuronal growth and communication in the hippocampus and frontal cortex indicate that they would be most important while the hippocampus and frontal cortex are developing and for the cognitive functions that are subserved by the hippocampus and frontal cortex. Executive functions (EF) are higher-order cognitive processes that control behavior, emotion, and cognition (Bull, Espy, & Wiebe, 2008; S. M. Carlson, 2005; Wiebe et al., 2011; Zelazo, Carter, Reznick, & Frye, 1997) that are often defined by their connection to the frontal lobes (Roberts &

Pennington, 1996). EF reliably activate the frontal cortex (Casey et al., 1995; Casey et al., 1997), giving the frontal cortex status as the ‘executive’. It coordinates input from many brain areas to formulate coherent responses in the face of complex cognitive, emotional, and behavioral needs. EF develop from early childhood into adulthood (Conklin, Luciana, Hooper, & Yarger, 2007; Pelphrey & Reznick, 2003), and EF such as working memory, inhibitory control, and planning are linked to theory of mind (S. M. Carlson & Moses, 2003; S. M. Carlson, Moses, & Breton, 2002; S. M. Carlson, Moses, & Claxton, 2004) and math and reading abilities (Bull, Espy, & Senn, 2004; Bull et al., 2008). There are many specific tests of EF across development, and the role of fatty acids in the frontal cortex indicate that the omega-6 to omega-3 fatty acid ratio may support EF development.

The balance of omega-6 and omega-3 fatty acids is one challenge that is not as widely discussed in the literature. The omega-3 fatty acids have been the main focus of investigations, and yet omega-6 fatty acids are not only also prevalent in the brain, they also play integral and complementary roles to omega-3 fatty acids (S. E. Carlson, 2001; S. E. Carlson, Werkman, Peeples, Cooke, & Tolley, 1993; Connor, Tenorio, Clandinin, & Sauve, 2012; Richards, Bliss, & Richards, 2003). Supplementation with fatty acids should support the brain’s need for both omega-6 and omega-3 fatty acids. Moreover, an imbalance of these two families of fatty acids may prevent the beneficial effects of supplementation. The omega-6 to omega-3 fatty acid ratio provides a measure of the balance of fatty acids.

The present investigation is focused on the role of the balance of omega-6 and omega-3 fatty acids, as measured by the omega-6 to omega-3 fatty acid ratio, in EF in children and older adults. EF may be particularly susceptible to imbalances in omega-6 and omega-3 fatty acids. In children, EF are developing, and fatty acids are important for the changes occurring in the frontal cortex and with connections between brain areas. In older adults, EF are declining, and fatty acids are important for maintaining brain functions that tend to decline with age. First, I will review the evidence of the importance of both omega-6 and omega-3 fatty acids, their competition for biochemical resources, and the gaps in the literature that inform the current investigation of the omega-6 to omega-3 ratio and EF. Second, I will discuss the unique demands of EF and their development that offer clues as to why the

balance of fatty acids may be important for EF and how future research can approach the study of fatty acids and EF.

### **The Omega-6 to Omega-3 Fatty Acid Ratio**

The omega-6 to omega-3 fatty acid ratio is a measure of the balance of fatty acids. Fatty acids can be consumed in the diet and are found mostly in oils, pork, grains, nuts, and fish (Blasbalg, Hibbeln, Ramsden, Majchrzak, & Rawlings, 2011). Linoleic (LA, omega-6) and alpha-linolenic (LNA, omega-3) acids are the only fatty acids that must be consumed in the diet (Lee, East, & Froud, 1986). Long-chain polyunsaturated fatty acids (LCPUFA), such as docosahexaenoic acid (DHA, omega-3) and arachidonic acid (ARA, omega-6), can be synthesized from LA and LNA in the pathway shown in Figure 1. The omega-6 and omega-3 families utilize the same desaturase and elongase resources for production of fatty acids further down the pathway. The hypothesis in the field is that overconsumption of one family of fatty acids will deplete desaturase and elongase resources for metabolizing the other family of fatty acids. If this occurs, one fatty acid family would be overwhelmingly available for incorporation into neuronal membranes, whereas the other fatty acid family would be relatively scarce. The resulting imbalance could impede neuronal function, and therefore cognitive function, because both omega-6 and omega-3 fatty acids are needed for communication between neurons (Calderon & Kim, 2004; Chalon et al., 2001; De La Presa Owens & Innis, 2000; Richards et al., 2003; Zimmer et al., 2002).

Researchers have clearly demonstrated the negative effects of omega-3 fatty acid deficiency on cognitive function in rodents. Significant omega-3 fatty acid deficiency impairs Morris Water Maze (MWM) performance (T. Moriguchi, Greiner, & Salem, 2000; Salem et al., 2001), olfactory discrimination performance (Greiner, Moriguchi, Slotnick, Hutton, & Salem, 2001; Salem et al., 2001), and learning (Bourre et al., 1989; Catalan et al., 2002). The degradation in performance is often quite large, with rodents fed omega-3 deficient diets taking twice as long to learn to avoid a shock (Bourre et al., 1989) or failing to improve in their olfactory discrimination errors after many weeks of training (Salem et al., 2001). The evidence that supplementation can subsequently reverse these deficits is mixed, with studies finding that the ability to replete fatty acid levels depends on the area of the brain under study

(Carrie, Clement, de Javel, Frances, & Bourre, 2000; T. Moriguchi & Salem, 2003), and the ability to improve performance on cognitive tasks depends on the balance of fatty acids used in the diets. In general, these studies suffer from a confound in that by attempting to maintain similar amounts of total fatty acids in the diets, most deficient diets have an unbalanced omega-6 to omega-3 fatty acid ratio, and most supplemented or control diets have a more balanced omega-6 to omega-3 fatty acid ratio.

### **Competition for resources.**

The competition for desaturase and elongase resources has produced the hypothesis that consuming more of one family of fatty acids will deplete these resources such that there won't be enough desaturases and elongases to metabolize the other family of fatty acids. In both animals (Gibson, Neumann, Lien, Boyd, & Tu, 2013) and cells (Harnack, Andersen, & Somoza, 2009), the most DHA (an omega-3) is produced in the presence of omega-6 fatty acids, and the most ARA (an omega-6) is produced in the presence of omega-3 fatty acids. Holman (1964, in cells) and Bourre et al. (1989, in rats) demonstrated that increasing LNA decreases delta-6 desaturation of LA. Additionally, consumption of dihommo-gamma linolenic acid (dGLA, omega-6), ARA, DHA, or eicosapentaenoic acid (EPA, omega-3) decreases delta-6 desaturase activity. Bezard, Blond, Bernard, and Clouet (1994) suggested that the delta-6 desaturase enzyme is very sensitive to feedback from the presence of LA and LNA products. These results suggest that the field's hypothesis is accurate, but the actual relationship between fatty acid intake and desaturase and elongase activity is likely more complicated than "more of one, less of the other". Providing a balanced omega-6 to omega-3 ratio leads to similar levels of omega-6 and omega-3 fatty acids in the brain, regardless of the ultimate amount of either fatty acid family, whereas providing an imbalanced omega-6 to omega-3 ratio produces deficiencies in omega-3 fatty acids, regardless of the amount of specific fatty acids in the diet (Li et al., 2006). In humans, supplementation with DHA and ARA in infant formula was more likely to result in cognitive test scores that either matched the breast-fed reference or outperformed the DHA only group (Agostoni, Trojan, Bellù, Riva, & Giovannini, 1995; Birch et al., 2002; Scott et al., 1998; P. Willatts, Forsyth, Dimodugno, Varma, & Colvin, 1998). Thus, the

mixed findings in human work may be because supplementation studies have largely focused on omega-3 fatty acids instead of the omega-6 to omega-3 fatty acid ratio.

The omega-6 and omega-3 fatty acids don't just use the same resources; each family is optimally metabolized in the presence of the other family. In rodents, Gibson et al (2013) found that the amount of DHA in plasma was related to both dietary LNA intake and the omega-6 to omega-3 ratio. The level of DHA in plasma peaked when LNA was 1% of fats in the diet by weight for rats fed low omega-6 to omega-3 ratios (0.5-0.8). At high ratios (7.4-11.3), the level of DHA in plasma peaked when LNA was 0.3% of the diet. Regardless of ratio, once LNA made up 2% or more of the diet, the relationship between LNA in the diet and DHA in plasma became negative, indicating that high levels of consumption of LNA actually decreased the amount of DHA produced (Gibson et al., 2013). The fatty acid metabolic pathway responds to the overall concentrations of both families of fatty acids, which is evidence that living organisms attempt to produce an optimal balance of fatty acids for daily function and do not simply require a set amount of either family of fatty acids.

The competition for resources and balance of omega-6 and omega-3 fatty acids matters because there is evidence that the consumption of omega-6 and omega-3 fatty acids is becoming increasingly unbalanced (Blasbalg et al., 2011). Kris-Etherton and Hill (2008) indicated that the Institute of Medicine recommends that LNA make up 0.6%-1.2% of fat intake. However, they have found that consumption of omega-3 fatty acids is subject to an "all-or-none" phenomenon. Some people consume fish, and tend to have adequate omega-3, while others consume no fish at all, and are likely well below recommended intakes. Blasbalg et al. (2011) found similar imbalances using economic disappearance data of food commodities. They concluded that Americans have been increasing their LA intake (i.e., pork and soybeans) while largely keeping LNA intake steady (i.e., fish and flaxseed), leading to an overall imbalance in fatty acid concentrations.

### **Omega-6 and omega-3 fatty acids in the brain.**

Both omega-6 and omega-3 fatty acids are involved in complementary functions supporting neuronal growth and communication. Researchers have demonstrated that fatty acid status affects neuron

size in the hippocampus (Ahmad, Moriguchi, & Salem, 2002; Ahmad, Murthy, Moriguchi, Salem, & Greiner, 2002) and neurite growth and amount of dendritic branching in the hippocampus (Ahmad, Murthy, et al., 2002; Calderon & Kim, 2004; Darios & Davletov, 2006; Ikemoto, Kobayashi, Watanabe, & Okuyama, 1997). Omega-6 and omega-3 fatty acids also affect ion currents (Fang, Zhou, Gao, Gu, & Mei, 2011; Kovalchuk, Miller, Sarantis, & Attwell, 1994; Lynch & Voss, 1994; Schweitzer, Madamba, & Siggins, 1990), complex protein kinase C signaling (Katsuki & Okuda, 1995; Schaechter & Benowitz, 1993; Schweitzer, Madamba, Champagnat, & Siggins, 1993; Seung Kim, Weeber, Sweatt, Stoli, & Marangell, 2001; Shinomura, Asaoka, Oka, Yoshida, & Nishizuka, 1991), and neurotransmitter activity (Chalon et al., 1998; De La Presa Owens & Innis, 2000; Delion et al., 1997; Delion et al., 1994; Zimmer et al., 2000; Zimmer et al., 2002). Both omega-6 and omega-3 fatty acids are integral to neuronal communication, and as such neither should be ignored in studies of fatty acids and brain or cognitive function.

The overall picture of the relationship between omega-3 and omega-6 fatty acids in the brain has yet to be fully understood. In an interesting investigation, Innis and de la Presa Owens (2001) found that supplementing rats with fish oil (high in omega-3 fatty acids) was negatively correlated with dopamine and serotonin levels in the rat brain. Dopamine and serotonin are two highly prevalent monoamine neurotransmitters in the frontal cortex, and alterations in these monoamines has been shown to affect EF (Maiti, Gregg, & McDonald, 2016; Puig & Miller, 2015; for review: Robbins & Roberts, 2007).

Interestingly, serotonin levels were highest in the brains of rats in high omega-6 group, followed by the brains of rats in the high omega-3, and the lowest serotonin levels were found in the brains of rats in the medium omega-6 group. The groups who consumed the two unbalanced ratios (371.5 and 0.12) had the highest levels of serotonin despite one being very high in omega-6 and one being very high in omega-3. This indicates that the balance of fatty acids is playing an important role in the ultimate outcome in the brain, and simply the amounts of omega-6 or omega-3 can't be the sole focus of research.

There is a clear role for fatty acids in neuronal growth, a process that would be particularly important during periods of considerable brain growth like the first two years of life and the adolescent

years. There is also a clear role for fatty acids in monoamine neurotransmitter regulation and function (see also for cholinergic pathways important to the hippocampus: Aid et al., 2003; Jones, Arai, & Rapoport, 1997), which can in turn affect cognitive functions related to monoamine function. It is therefore not surprising that some have found that omega-3 deficiency is linked to depression (McNamara, Jandacek, et al., 2010), schizophrenia (Liu, Jandacek, Rider, Tso, & McNamara, 2009), and affective disorders (McNamara, 2010). The omega-6 and omega-3 fatty acids play different but complementary roles in these processes by promoting growth and inhibiting growth (omega-6 and omega-3), altering LTP (omega-6 and omega-3), and affecting monoamine function (omega-6 and omega-3). In the quest to understand how fatty acids can affect cognitive function and brain health, the focus must include a consideration of the balance of omega-6 and omega-3 fatty acids in the brain.

### **Omega-6 and omega-3 fatty acids and cognitive functions.**

The jump from evidence of the importance of fatty acids in the brain to the importance of fatty acids to behavior and cognitive function has not been straightforward. Animal work has produced important results by focusing on specific measures of cognitive functions, like working memory, but the animal work largely uses severe deficiency models that can't be replicated with human populations. The animal work also varies widely in the underlying balance of fatty acids, making it difficult to conclude that differences in cognitive performance are solely due to omega-3 fatty acid deficiency. Work with humans has produced mixed results in part because of the use of many global measures of cognitive function and the focus on omega-3 fatty acids to the exclusion of understanding the importance of the ratio. Instead of summarizing the findings that describe the negative elements of omega-3 deficiency, I am going to highlight findings from researchers who have focused on the ratio and examine studies from the lens of how the ratio may be affecting results.

### **Animal work.**

Many studies of omega-3 deficiency in rodent populations could be viewed through the lens of the omega-6 to omega-3 fatty acid ratio. Ikemoto et al (2001) discussed how differences in the balance of omega-6 and omega-3 fatty acids used in studies may explain why some researchers can replete levels of



DHA after periods of deficiency and other studies can't. It may also explain why some researchers find effects and others do not find any effects. Catalan et al (2002) did not find that rats fed an omega-3 deficient diet performed worse on an olfactory discrimination task as others have (Greiner et al., 2001; Salem et al., 2001). The ratio used in the deficient diet in Catalan et al (2002) was lower than in many other studies, and this lower dietary ratio resulted in lower ratios in the brain (ratio of 7 vs 9-10). Catalan et al (2002) did find that the omega-3 deficient group performed worse on a difficult 20-item olfactory learning task, indicating that the lower ratio was still not optimal for difficult tasks requiring higher-level cognitive abilities but was low enough to allow similar performance on simpler tasks.

When attempting to replete levels of omega-3 fatty acids in the brain, Ikemoto et al (2001) found that a group supplemented with a combination of monounsaturated fatty acids, omega-3 fatty acids, and omega-6 fatty acids was able to replete levels of DHA faster than the group supplemented with just omega-3 fatty acids. The group provided with the mixture of fatty acids also improved in their performance on a learning task whereas the DHA-only supplemented group did not. Carrie et al (2000) also found they were able to replete DHA levels in the brain using supplementation that included omega-6 fatty acids. Unfortunately, the balance of fatty acids used in studies varies so widely, as do the specific fatty acids used to reach the desired balance, that it is difficult to directly compare many results. Investigations designed to examine differences in the ratio and balance of fatty acids are necessary to untangle the many possible explanations for cognitive performance.

One such investigation produced interesting results. Wainwright, Jalali, Mutsaers, Bell and Cvitkovic (1999) found that pups provided a very low ratio (0.32) diet had impaired performance on a battery of developmental tests compared to pups provided a "normal" ratio (4.0). The low ratio group performed similarly to the large litter group who were malnourished from sharing the same amount of food among more pups. The pups in the low ratio group also had slowed physical growth similar to the malnourished group. The researchers' focus on the ratio provides important information. As suggested by biochemical investigations, it is possible to add too much omega-3 fatty acids and lower the ratio too far (Gibson et al., 2013; Wainwright, 1992) such that it becomes detrimental to cognitive and physical

development. There is an optimal balance of fatty acids that needs to be struck, and more research of this nature is needed to fully understand optimal fatty acid levels.

### **Human work.**

Research on fatty acids and cognitive function in humans have used a supplementation model in which participants are provided either with a control supplement (such as corn oil) or a supplement rich in omega-3 fatty acids (such as fish oil). The problems of assessing human LCPUFA supplementation studies are well documented (for review: Cheatham & Colombo, 2006; Willatts & Forsyth, 2000). Here, I will focus on the issue of the omega-6 to omega-3 ratio and the developing human brain. Currently, it is not clear how much DHA or ARA is optimal for developing infants, children, or adults. As a result, it is not clear what the correct balance or ratio of omega-6 to omega-3 fatty acids is for the developing brain.

The majority of randomized clinical trials (RCT) of fatty acid supplementation have focused on the prenatal period and the first two years of life. The studies vary widely in treatment diets, timing, and assessment. In general, the treatment diets consist of some combination of an LA and LNA group without any ARA or DHA, a DHA and/or a DHA+ARA group, and a breast-fed reference group. The start of supplementation ranged from a few days after birth to a full month after birth for infant supplementation, and from 17 weeks gestation to 28 weeks gestation for maternal supplementation. Cessation of supplementation was commonly 3-4 months after the baby's birth, but sometimes extended a full year, in both infant and maternal supplementation studies. One study ended maternal supplementation when the baby was born (Dunstan, Simmer, Dixon, & Prescott, 2008). Studies assessed infants as early as the second day of life (Helland et al., 2001) and followed children up to 7 or 8 years old (Bakker et al., 2003; Cheatham, Nerhammer, Asserhoj, Michaelsen, & Lauritzen, 2011; Helland et al., 2008).

The results of the RCTs vary about as widely as the methods. Frequently, there aren't any differences between any of the formula groups. One trend that emerges from the literature is studies that include a DHA + ARA group are more likely to find differences at all. Scott et al (1998) found the DHA + ARA group was statistically the same at the breast-fed reference, and both had statistically significantly higher scores than the DHA only group on the Vocabulary Comprehension and Vocabulary Production

subscales of the MacArthur Communicative Development Index (CDI) at 14 months. Willatts and Forsyth (2000) reviewed 12 RCTs of PUFA supplementation that reveal a pattern of better results for infants supplemented with DHA + ARA. Eight of the studies in Willatts and Forsyth (2000) include a group supplemented with DHA + ARA, and 6 of those include results in which the DHA + ARA group did better than a DHA only group (e.g., Birch et al., 2002; Scott et al., 1998) or a control group (e.g., Agostoni, Trojan, Bellu, Riva, & Giovannini, 1995; Willatts, Forsyth, DiModugno, Varma, & Colvin, 1998).

Both the commencement of supplementation and the length of supplementation are relevant for whether or not any significant effects are found between diets. It is better to start earlier and supplement longer. Birch et al. (2002) did not start supplementation until infants were 6 weeks old. Despite supplementing through the first year, and including DHA and ARA in similar quantities to other studies, they did not find any differences between groups on measures of stereoacuity or forced choice preferential looking. The same researchers found differences in visual acuity (Birch, Hoffman, Uauy, Birch, & Prestidge, 1998) and Bayley Scales of Infant Development (BSID) scores (Birch, Garfield, Hoffman, Uauy, & Birch, 2000) when supplementation began within the first week after birth, even though supplementation only lasted for 4 months.

Only a handful of studies have investigated fatty acid levels and cognitive performance in children beyond 2 years old. None of them included measures of EF, and findings are appropriately mixed with one finding no effect (Ghys, Bakker, Hornstra, & van den Hout, 2002) on scores on the Kaufman Assessment Battery for Children (K-ABC), which is a global development scale, and another finding higher mental processing composite scores for children whose mothers consumed cod liver oil during pregnancy (Helland, Smith, Saarem, Saugstad, & Drevon, 2003). The importance of the preschool years is clearly emphasized in the EF literature (S. M. Carlson et al., 2002; Zelazo, 2004), and yet specific tests of EF in this age range are lacking in studies of fatty acid supplementation. The few findings that exist from early childhood demonstrate that early supplementation has long-lasting effects. Helland et al (2003) was the only group to test cognitive function after precise supplementation during pregnancy. Despite no

additional supplementation, they found a significant effect using a global development scale. By this age, it is important that researchers take advantage of the extensive number of tests of specific functions available. The limited findings with global development scales in infancy provide an indication of what could be teased apart with studies of specific functions that are developing during the preschool years.

By middle childhood, most neural substrates of the brain are in place and fine-tuning occurs for many years. There are even more tests of EF available by this age. However, most still follow the infant literature and use global development scales. Bakker et al. (2003) followed-up with 327 children from the older cohort that was followed in Ghys et al. (2002). Seven-year-old children were tested using the K-ABC, and again, neither plasma at age 7 nor umbilical cord DHA or ARA predicted the Mental Processing Composite or any subscale scores of the K-ABC. Helland et al. (2008) continued their follow-up of children who participated in their RCT to seven years old. This time, however, they did not find any differences in any K-ABC scores between the cod liver oil and corn oil group. However, maternal DHA and total omega-3 at birth were significantly, positively correlated with sequential processing scores on the K-ABC at seven years old, and the omega-6 to omega-3 ratio was significantly, negatively correlated with sequential processing scores on the K-ABC.

In one investigation that used a specific measure of EF after supplementation in infancy, Cheatham et al. (2011) reported that children supplemented from birth to 4 months old had blood levels of DHA that were correlated with performance on a test of inhibitory control, the day-night Stroop task. McNamara et al. (2010b) supplemented typically-developing boys 8 to 10 years old with DHA and found that the groups given DHA had increases in activation in the right dorsolateral prefrontal cortex (DLPFC), an area of the brain reliably activated during EF tasks, during a sustained attention task. Sheppard and Cheatham (2013) specifically examined the dietary ratio of 7- to 9-year-olds and performance on a battery of tests of EF. They found an interaction such that children who consumed low levels of omega-3 fatty acids performed best when consuming a low ratio, but children consuming high levels of omega-3 fatty acids performed best when consuming a high ratio. This finding is preliminary, but is in line with biochemical investigations that indicate it is possible to lower the ratio too far (Gibson et al., 2013; Huang

et al., 1992), and would help explain why there aren't always significant findings in human omega-3 fatty acid supplementation work. Imbalanced omega-6 and omega-3 fatty acid intake could perturb the balance of fatty acids needed for optimal cognitive function.

Research on fatty acids and cognitive function to date highlights a distinct need for a focus on the balance of omega-6 and omega-3 fatty acids. In animals, the imbalanced diets created by deficiency models in rodents may explain the observed deficits in cognitive functions. In humans, the lack of focus on the balance of fatty acids may mask important findings about the role of omega-6 and omega-3 fatty acids in cognitive function. Additionally, human work needs to use specific tests of cognitive functions subserved by the brain areas of interest. In this case, EF are likely affected by imbalances in omega-6 and omega-3 fatty acid consumption because they are subserved by the hippocampus and frontal cortex and require flexible use of many cortical resources. Understanding the unique nature of EF will help in understanding how fatty acids can support optimal EF development. The present study will focus on these gaps by focusing on the balance of omega-6 and omega-3 fatty acids, by focusing on specific EF tasks, and by focusing on age ranges during which EF are developing and declining.

### **Executive Functions and the Omega-6 to Omega-3 Fatty Acid Ratio**

Executive functions (EF) are higher-order cognitive functions that regulate emotion, behavior, and cognition. Approaches to studying EF have focused on goal-directed behaviors (Garon, Bryson, & Smith, 2008; Hughes & Ensor, 2005; Zelazo et al., 1997) and regulatory processes that control automatic responses (S. M. Carlson et al., 2002; Miyake & Friedman, 2012; Wiebe et al., 2011; Zelazo & Frye, 1998). Ultimately, EF are responsible for allowing people to make a coherent response in the face of a complex problem. EF include functions such as working memory, inhibitory control, set-shifting, sustained attention, and planning. They develop over a long time with most investigations of EF starting with children no younger than 2 years old and spanning well into adulthood (Conklin et al., 2007; Luciana & Nelson, 1998). The frontal cortex is considered the seat of EF because most EF tasks reliably activate the frontal cortex (Baddeley, 1996; Pennington & Ozonoff, 1996; Roberts & Pennington, 1996; Welsh & Pennington, 1988).

The frontal cortex is one of the main areas to accrete large amounts of omega-6 and omega-3 fatty acids (Martinez & Mougan, 1998), and the frontal cortex is sensitive to alterations in the balance of omega-6 and omega-3 fatty acids (Jumpsen, Lien, Goh, & Clandinin, 1997a, 1997b) with researchers finding that it is difficult to replete the frontal cortex after deficiency (Carrie et al., 2000). The omega-6 and omega-3 fatty acids are integral to neuronal growth and communication in the frontal cortex (Chalon et al., 2001; De La Presa Owens & Innis, 2000; Delion et al., 1997; Delion et al., 1994; Zimmer et al., 2000). Investigations with animals have demonstrated clear effects of omega-3 deficiency on MWM performance, a test of working memory (T. Moriguchi et al., 2000; T. Moriguchi & Salem, 2003; Salem et al., 2001). The limited work done in humans with omega-6 and omega-3 fatty acids and EF has shown promising early results (Cheatham et al., 2011; McNamara, Able, et al., 2010b; Sheppard & Cheatham, 2013).

The ratio is likely particularly important to the frontal cortex because of the unique demands of EF. The need to coordinate between many brain areas and to coordinate both incoming information and outgoing information to produce a coherent response would likely be susceptible to imbalances in fatty acids because of the integral nature of both omega-6 and omega-3 fatty acids to neuronal growth and communication. The frontal cortex is usually the focus of neuroimaging investigations of EF, but EF are actually subserved by additional functional cortical networks that incorporate areas outside the frontal cortex. There are different networks related to different elements of EF, such as trial-by-trial updating and sustained maintenance of overall goal-directed behaviors in adults (Dosenbach et al., 2007), and those networks undergo a process of segregation (decreases in short-range connections) and integration (increases in long-range connections) across development (Fair et al., 2007). Therefore, whereas the needs of the frontal cortex are important, understanding the fatty acid requirements of different structures within the EF networks and how those structures communicate is necessary. It is useful to approach EF in terms of the role of the frontal cortex (Roberts & Pennington, 1996; Welsh, Pennington, & Groisser, 1991) and from the lens of the inherent qualities of the functions that fall under the umbrella term ‘executive functions’ (Zelazo, 2004; Zelazo & Frye, 1998). Then, a few individual EF, specifically

inhibitory control, working memory, and planning, will be discussed in terms of the role the balance of fatty acids could play in their development.

### **What is the executive?**

In models of executive functions in adults, an executive component is seen as the seat of control of other functions (Baddeley, 1992, 1996). The executive parses input from multiple areas and develops a coherent response. The requirements of producing a coherent response include things like representing rules and rule structures (Crone, Donohue, Honomichl, Wendelken, & Bunge, 2006; Zelazo & Frye, 1998), inhibiting distracting or incorrect information (Kirkham, Cruess, & Diamond, 1997; Schroeter, Zysset, Wahl, & von Cramon, 2004), updating information while completing a task (Tsujii, Yamamoto, Masuda, & Watanabe, 2009), and finally, providing a correct response or series of responses to the situation.

The picture of EF in children is less clear. In some models, EF are considered to consist of three factors in children (Garon et al., 2008; Miyake et al., 2000) generally comprising working memory, inhibitory control, and set-shifting, whereas other models have still found EF to be a single factor in young children (Wiebe et al., 2011). Developmentally, EF are seen as becoming increasingly differentiated both in terms of behavioral function and cortical activation. The question remains as to how we develop from infants who perseverate in searching in the wrong location even while watching the object being hidden (the classic A-not-B error) to adults who can develop complex plans for long-term goals and reliably carry out those plans, and even update and alter those plans as needed. Interestingly, older adults exhibit declines in EF capacity commensurate with declines in differentiation in behavioral function and cortical activation (Baltes & Lindenberger, 1997; Carp, Park, Polk, & Park, 2011; S.-C. Li, Lindenberger, & Sikstrom, 2001).

Research on EF development has focused on where children differ from adults – what errors they make in tasks that require an executive. Considerable research has come out of the A-not-B error and the dimensional change card sort (DCCS) and developmental changes in performance across time (Diamond, 1985; Espy, Kaufmann, McDiarmid, & Glisky, 1999; L. B. Smith, Thelen, Titzer, & McLin, 1999;

Zelazo, Frye, & Rapus, 1996). As Smith et al. (1999) explain, the errors made in these tasks can be seen as a problem with action, a problem with inhibition, or a problem with working memory. The A-not-B task and DCCS task differ most in terms of complexity. They require similar functions and produce similar errors, and investigations of these errors across development have produced similar explanations.

The first consideration is the coordination of knowledge and action. Children and infants can correctly indicate where an object belongs in a sorting task through words or eye gaze (Zelazo, 2004; Zelazo, Reznick, & Pinon, 1995), and only fail at search tasks when asked to execute that search (Zelazo, Reznick, & Spinazzola, 1998). Even 8-month-old infants will often look at location B, but subsequently search at location A (Diamond, 1985; Diamond & Doar, 1989; L. B. Smith et al., 1999) (Diamond, 1985; Diamond & Doar, 1989; L. B. Smith et al., 1999). In the brain, the prefrontal cortex and cerebellum are developing connections throughout the first two years of life, and those connections are thought to support knowledge of the correct sorting or reaching behavior to guide actual actions (Diamond, 2000).

Another explanation for the A-not-B and DCCS task errors relates to inhibition. Young children struggle to inhibit a prepotent response because of an underdeveloped executive that could help them ignore rules and places that are no longer relevant. There is evidence that the influence of many aspects of the A-not-B set-up produce less perseveration to search in the incorrect location (such as different colors for A and B, Butterworth, Jarrett, & Hicks, 1982) or more perseveration (such as longer delays before a search is allowed, Diamond, 1985). Kirkham et al. (1997) demonstrated that several manipulations of the DCCS task could allow children as young as 2 to successfully switch rules, an age group previously thought to reliably fail, and make it difficult for 4-year-olds to successfully switch rules, an age group previously thought to reliably succeed. These manipulations include turning over the most recently sorted card so that incorrect sorting by the previous rule is not reinforced by seeing the card (easier), and placing the card in an envelope before sorting it so the card's picture has to be held in mind throughout the action of sorting (more difficult).

A third explanation for these errors relates to task representation and rule hierarchies. The cognitive control and complexity theory (Zelazo & Frye, 1998) was developed to describe errors made on



the DCCS, but it brings up an important issue with the A-not-B task as well. In the DCCS, the rules for success are hierarchical in nature. First, there are two games, and the correct rule must be followed. Then, there are the rules of the game being played that involve physically placing the card in one box or another. An inability to represent rules hierarchically would result in failure on the DCCS. Zelazo and colleagues have demonstrated that children as young as 2 can represent four separate rules quite easily such that the number of rules involved is not the issue (Zelazo & Frye, 1998; Zelazo et al., 1996). The issue can be discussed more broadly as an inability to represent the entirety of the task. This inability to represent the whole task has been described as not having enough “psychological distance” from the problem to fully represent the rule structure (Zelazo & Frye, 1998). The same issue could be applied to the A-not-B task in that infants are not able to fully represent the task. They perseverate because previous action sequences that involved only half the task (i.e., just one location) overwhelm an underdeveloped executive and prevent switching search locations.

Ultimately, the decision-action sequences in these tasks are handled as networks. An executive is needed to take all of the input required even for a simple A-not-B task and produce a coherent response, in this case reaching to the correct location. An explanation of the A-not-B and DCCS errors must incorporate all the elements of the problem to fully explain results. L. B. Smith et al. (1999) and Thelen, Schoner, Scheier, and Smith (2001) describe a general theory that encompasses not only the need to organize understanding of the correct sorting or reaching behavior and the action itself, but also the need to maintain that coordination across the entirety of the action despite conflicting prepotent responses. Morton and Munakata (2002) describe a neural network theory in which errors on a variety of tasks can be explained by immature functional connectivity that does not allow new information held in “active memory” to override latent biases from previous searches or tasks. In both the theoretical approach and cortical modeling approach, there is an inherent development of the connectivity between distant brain areas and an implied differentiation of function that allows specificity in the use of rules and actions to correctly respond to task demands.

Children have also been shown to have reduced cognitive capacity and speed of processing compared to adults. These issues are largely discussed in the working memory literature, and are often studied using span tasks (Conway, 1996; Just & Carpenter, 1992; Luciana & Nelson, 1998) and search tasks (Luciana, Conklin, Hooper, & Yarger, 2005). Researchers have noted the importance of capacity in performance on span and search tasks (Conway, 1996; Just & Carpenter, 1992), and others have demonstrated the importance of the structure of the task, such as differences between backward and forward span tasks and the nature of the stimuli (boxes in space compared to words) (Conklin et al., 2007; Gathercole, Pickering, Ambridge, & Wearing, 2004).

In the case of capacity and speed of processing, older children show alterations in both functional connectivity and the ability to use neural resources. Tsujii, Yamamoto, Masuda, and Watanabe (2009) demonstrated that there is increased lateralization of the frontal cortex during a spatial working memory task from 5 to 7 years of age. Younger children had no lateralization whereas older children exhibited greater activity in the right frontal cortex during the task. The increase in lateralization from 5 to 7 years was accompanied by a decrease in reaction time. The more lateralization that occurred within an individual child, the faster they were able to respond. Older children who have lateralization similar to adults still have capacity problems. On verbal and spatial working memory tasks, children 7 to 12 years old did not evidence an increase in activation of working memory with increasing problem difficulty, whereas adults did call upon more working memory resources (Thomason et al., 2009). Therefore, whereas brain development across early childhood is marked by alterations in connectivity and functional activation (Barnea-Goraly et al., 2005; Paus et al., 1999; Perone, Simmering, & Spencer, 2011; Sowell, Trauner, Gamst, & Jernigan, 2002; Toga, Thompson, & Sowell, 2006), later childhood and adolescence is also a period of developing the ability to utilize those neural circuits and resources in the pursuit of goals (Hwang, Velanova, & Luna, 2010; for review: Tsujimoto, 2008).

The executive is the organizer of information from brain areas required for control of behavior, emotion, and cognition, and the increases in coordination and efficiency required to develop mature EF are going to be constrained by the brain's structural and functional development. Neuronal structure and

function are directly related to the availability of nutrients needed to produce neurons, neurotransmitters, and receptors. Broad changes across development include increases in gray matter until age 4 when it begins to decline and increases in white matter steadily into adulthood (Barkovich, Kjos, Jackson, & Norman, 1988; Pfefferbaum et al., 1994; Sowell et al., 2002; Toga et al., 2006). Later, changes in gray matter development differ between brain areas. Peaks in gray matter occur around adolescence and differ between the frontal, parietal, temporal, and occipital lobes (Giedd et al., 1999). Finally, older adults experience consistent declines in gray matter in the prefrontal cortex and hippocampus connected to declines in cognitive capacities (Sander, Lindenberger, & Werkle-Bergner, 2012; Zimmerman et al., 2006). The changes in white and gray matter are related to changes in the composition of the lipid bilayer and increased myelination that changes the overall balance of cholesterol, proteins, and fats in the brain (Barkovich et al., 1988). When studying fatty acids, it is important to understand how the brain is developing during a given period and what the optimal balance of nutrients may be to support structure and function (for review: Wainwright, 2007). The present study will focus on EF and the fatty acids that support the frontal cortex and hippocampus that subserve EF. Though there isn't much direct evidence of the role of fatty acids in EF, there are indications of what could be expected from the literature on inhibitory control, working memory, and planning.

### **Inhibitory control and fatty acids.**

Inhibitory control is a widely studied element of EF. In many respects, it holds a place at the core of higher-order thinking. Carlson, Moses, and Breton define inhibitory control as the ability to “suppress inappropriate but prepotent responses of various kinds”. It represents the ability to take the large amounts of information we get on a daily basis and select the relevant pieces for use while inhibiting irrelevant or distracting information. Further, inhibitory control is the ability to inhibit previously relevant information when new information becomes available or when task demands change. Research has indicated that inhibitory control undergoes considerable development in early childhood, with particularly rapid improvement from 2 to 5 years old (S. M. Carlson et al., 2004; Diamond, Kirkham, & Amso, 2002; Zelazo & Reznick, 1991).

The tasks used to assess inhibitory control, such as Go/No-go, Stroop, and the DCCS, share in common the need to distinguish between stimuli and apply task rules to determine the correct response. In the case of the simpler Go/No-go tasks, there is a single dimension on which two stimuli differ (such as a red and blue fish). The participant must remember to which dimension they must respond (Go stimulus) and inhibit that response when the other stimulus (No-Go stimulus) appears. Stroop tasks tend to test naturally prepotent responses, such as saying the color words presented (e.g., red, blue) instead of saying the color of the text in which the words appear. Hierarchical rule tasks, like the DCCS, add other dimensions to the stimuli and nested rules that have to be inhibited.

Inhibitory control tasks reliably activate the frontal cortex, and the development of inhibitory control is related to changes in the use of neural resources as the complexity of the inhibitory control requirements increases. Children will become proficient at simpler inhibitory control tasks, like Go/No-Go, before more complex tasks, like the DCCS. Hierarchical rules represent a more complex stimulus to inhibit. Rubia et al. (2006) found that adults performed better than adolescents and had different cortical activation than adolescents on three different inhibitory control tasks. Adults had greater anterior cingulate gyrus activation across all tasks (area of the brain involved in attentional control), but they only had different dorsolateral PFC activation (area of the brain reliably activated during working memory tasks) during the more complex inhibitory control tasks compared to adolescents. Brain activation clearly distinguishes between children who have developed the ability to control inhibition and those who have not. Even 3-year-olds who do not perseverate on a DCCS task show adult-like brain activation (Y. Moriguchi & Hiraki, 2009). Older adults experience declines in performance on more difficult tasks first, and typically recruit more executive resources for increasingly simpler tasks as they age (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Mattay et al., 2006; Schneider-Garces et al., 2010).

As discussed above, mature inhibitory control not only means knowing the correct response but carrying out the correct action in accordance with the correct response. Inhibitory control requires efficient coordination of a frontal network and connections to cerebellar areas for motor responses (Diamond, 2000; Rubia et al., 2006). Stevens, Skudlarski, Pearlson, and Calhoun (2009) found that

adolescents exhibited decreases in the coupling of bilateral frontopolar prefrontal, parietal, and caudate activation during a Go/No-go response inhibition task while also exhibiting increasing white matter connections with temporal and anterior cingulate areas into adulthood. This activation pattern was coupled with improved performance and reduced reaction time, which indicates that these patterns are more mature cortical network patterns. Rule-switching, such as that required by the DCCS, in adults involves coordination of the ventrolateral prefrontal cortex (VLPFC) and the pre-supplementary motor areas (pre-SMA). The VLPFC is postulated to be responsible for representing the rules involved in the task, and the pre-SMA area is responsible for inhibiting the irrelevant rules. Children reach adult levels of activation of the pre-SMA by adolescence, but even adolescents show different activation of the VLPFC compared to adults (Crone et al., 2006). The present study will investigate brain activity using near-infrared spectroscopy (NIRS) to investigate the use of prefrontal resources in children 7 to 12 years old.

Thus far, there haven't been any investigations of how fatty acids may support the development of inhibitory control, but some initial hypotheses can be gleaned from the literature. The frontostriatal network frequently discussed with inhibitory control is generally considered to include the prefrontal cortex, anterior cingulate cortex, striatum, and cerebellar areas. All of these areas are affected by omega-3 fatty acid deficiency and changes in the omega-6 to omega-3 fatty acid ratio (Delion et al., 1994; Jumpsen et al., 1997a, 1997b; Levant, Ozias, & Carlson, 2007). However, each brain area tends to respond differently. In the face of omega-3 deficiency, the frontal cortex tends to deplete of omega-3 fatty acids and only increase levels of omega-6 fatty acids somewhat, whereas the striatum and cerebellum tend to accumulate more omega-6 fatty acids and do not lose as much DHA (Favreliere, Barrier, Durand, Chalon, & Tallineau, 1998; Levant et al., 2007). The best accretion of ARA and DHA in the frontal cortex and cerebellum occurs in ratios close to 4:1 and not diets focused on one or the other fatty acid family (Jumpsen et al., 1997a, 1997b). These alterations in the fatty acid composition of membranes affects dopamine receptor density in the frontal cortex (Delion et al., 1994) and serotonin receptor density in the frontal cortex and anterior cingulate cortex (du Bois et al., 2006), which affects communication within the frontostriatal network as monoamine neurotransmitters are highly prevalent in these brain areas.

Disruption to dopamine and serotonin receptors have been shown to disrupt EF task performance in animals (Maiti et al., 2016; Puig & Miller, 2015). The full picture of neurotransmitter function that supports EF is of course complex, but these monoamines have been consistently implicated (Robbins & Roberts, 2007) such that the role of fatty acids in monoamine receptors and neurotransmission is likely an important element of their role in EF.

The present study will use a novel task, the Electric Maze Task (EMT) to investigate the contribution of the balance of fatty acids to inhibitory control. Specifically, the inhibitory control requirements of the EMT will be manipulated to determine if a specific balance of fatty acids best supports inhibitory control performance. The collection of behavioral performance data and brain activity data will hopefully begin to piece together a picture of how fatty acids best support brain function and inhibitory control performance in middle childhood. Based on the limited evidence, an interaction between the ratio and omega-3 intake will likely best support inhibitory control performance. The brain areas subserving mature inhibitory control respond very differently to changes in the balance of omega-6 and omega-3 fatty acids. Maintaining a balance that does not promote one family over another (low consumption of both omega-3 and omega-6 or high consumption of both omega-3 and omega-6) will likely best support the frontal, striatal, and cerebellar resources involved in inhibitory control. In older adults, there haven't been any investigations of the omega-6 to omega-3 ratio and cognitive function. Based on the evidence from changes in older adult brain function, the ratio is likely to support performance of more complex EF tasks in young older adults (65- to 69-year-olds) and simpler EF tasks in the oldest older adults (75- to 79-year-olds).

### **Working memory and fatty acids.**

Working memory is typically defined as a system for temporarily holding information and using it for complex cognitive tasks (Baddeley, 1992). Baddeley and Hitch's widely accepted tri-partite model of adult working memory is composed of the central executive and two subsystems. The central executive and subsystems of the tri-partite model of working memory develop at different rates and in different ways (for review: Gathercole, 1998). The central executive coordinates the activity of the two

subsystems, the phonological loop and visuospatial sketchpad, which are directly responsible for the information being stored and processed (for review: Baddeley, 1992). Similar to inhibitory control, mature working memory can't be achieved until the frontal areas are connected to response elements (visual, motor, or verbal). Researchers have described working memory in terms of both capacity and flexibility (Baddeley, 1996; Conway, 1996).

Investigations into the development of working memory highlight increases in the roles of distinct brain areas and increased connectivity between frontal, parietal, temporal, and occipital areas. In infancy, working memory is often studied using a delayed response (DR) task. Success on this task varies with the type of stimulus, delay, and response modality (for review: Pelphrey & Reznick, 2003). Infants who are successful at this task across longer delays show increased activity in frontal regions (Bell & Fox, 1992). Success on this task across development involves increasing specificity in the brain areas involved. Successful infants had greater electroencephalography (EEG) coherence across the whole brain, whereas children 4.5 years old who were successful had increased coherence only between medial frontal and posterior temporal areas and medial frontal and occipital areas (Bell & Wolfe, 2007). EEG coherence is thought to be indicative of the connections between brain areas, and greater coherence likely indicates more connectivity and organization between brain areas (Thatcher, Krause, & Hrybyk, 1986).

The development of mature working memory continues through adulthood, and cross-sectional and longitudinal studies of changes in working memory have demonstrated increasing differentiation in behavioral performance and cortical activation. In general, improvements in speed and accuracy proceed linearly across childhood and adolescence (Conklin et al., 2007; Gathercole et al., 2004; Luciana et al., 2005; Luciana & Nelson, 1998). However, investigations that use a variety of types of tasks often find that patterns of performance begin to diverge. Gathercole et al. (2004) found that performance on phonological and visuospatial tasks was highly correlated among 4- and 5-year-olds, but those correlations decreased over time until there were clearly distinct domains with phonological working memory tasks correlated with one another and distinct from visuospatial working memory tasks. Across middle childhood and adolescence, there are increases in activity in frontal, parietal, and temporal areas

that correspond to increases in accuracy and speed of processing (Blain-Briere, Bouchard, Bigras, & Cadoret, 2013; Klingberg, Forssberg, & Westerberg, 2002; Nelson et al., 2000). There is also evidence of a lateralization across development that is related to improved performance (Tsujii et al., 2009) and that it reflects the type of stimulus being held in memory and manipulated (spatial vs object number) (E. E. Smith et al., 1995). The development of working memory involves a process of differentiation (behaviorally and in use of cortical resources) and increased involvement of the frontal cortex.

In older adults, researchers have found support for decreased differentiation with age that is linked to worse working memory performance (Mattay et al., 2006; Schneider-Garces et al., 2010). Additionally, executive resources are recruited for simpler tasks as we age (Nagel et al., 2011; Nagel et al., 2009). Both “overactivation”, or increased activity in older adults compared to younger adults, and “underactivation”, or decreased activity in older adults compared to younger adults, is seen in working memory tasks. Generally, the prefrontal cortex is found to be overactive, and posterior areas of the brain are found to be underactive (Reuter-Lorenz & Park, 2010; Sander et al., 2012). These changes in the use of cortical resources to complete working memory tasks implies changes in the nutritional support the brain may need.

Similar to inhibitory control, there hasn't been significant research on fatty acids and working memory in humans. However, evidence still points to the important role of omega-6 and omega-3 fatty acids. First, the hippocampus, a brain area recruited during memory and spatial processing tasks, is another area of the brain to accumulate considerable omega-3 and omega-6 fatty acids (Martinez, 1992). The hippocampus is also sensitive to deficiency and imbalance of fatty acids (Jumpsen et al., 1997a, 1997b). Working memory tasks, particularly spatial tasks, recruit both the frontal cortex and hippocampus. This recruitment of two brain areas sensitive to alterations in fatty acid balance makes working memory a function of specific interest in understanding the role of fatty acids. Alterations in monoamine vesicles in the presynaptic terminal (Zimmer et al., 2000), neuron size and amount of dendritic branching (Ahmad, Murthy, et al., 2002), and basal acetylcholine activity and muscarinic receptor density (Aid et al., 2003) have been found in the hippocampus in response to omega-3



deficiency. All these alterations relate to the ability of the hippocampus to communicate with other brain areas. Interestingly, Ikemoto et al. (2001) found that simply adding DHA at levels similar to other studies did not replete omega-3 fatty acid levels in the brain or improve MWM performance in previously deficient rats. Instead, increasing the level of DHA and lowering omega-6 fatty acids to lower the ratio repleted brain levels of omega-3 fatty acids and improved performance on the MWM.

The working memory literature also highlights the role of differentiation in the development of mature EF. Over time, brain function becomes more distinct in response to specific stimuli and specific processing requirements, and with aging, brain structure and function reduce in differentiation. This process of integration and differentiation through the growth of neurons, synapses, and dendritic branching combined with synaptic pruning supports the growth of necessary connections and decrease in unused or excess connections. Typically, researchers have demonstrated that omega-3 fatty acids increase neuronal growth and dendritic branching, and omega-6 fatty acids decrease neuronal growth and dendritic branching in both the hippocampus and frontal cortex (Ahmad et al., 2004; Ahmad, Murthy, et al., 2002; Ikemoto et al., 1997). A balance between omega-6 and omega-3 fatty acids could therefore support a system that is changing neuronal connections and structure in support of newly developing functions. In children, it would be expected that balanced fatty acid ratios would support the process of differentiation associated with mature working memory. In older adults, it would be reasonable to hypothesize that balanced fatty acid ratios could support the maintenance of activation across the working memory network. Activation more similar to young adults (i.e., no overactivation of the prefrontal cortex or underactivation of posterior resources) could then support better working memory performance in older adults.

### **Planning and fatty acids.**

Planning is an executive function characterized by assessing a goal, determining how to reach the goal, executing the steps, and then evaluating errors and goal attainment (Lezak, 1982; Welsh & Pennington, 1988). Planning is an important part of life (Welsh & Pennington, 1988) that develops from early childhood through adulthood (Luciana, Collins, Olson, & Schissel, 2009; Welsh et al., 1991).

Currently, the Tower tasks are some of the most widely used tasks to assess planning. These tasks consist of two sets of discs arranged on 3 to 5 dowels. The goal is to make one set of discs match the other set of discs. To successfully match the sets of discs, participants must first work out a general plan for how to make them match, and then move the discs accordingly without deviating from the plan or forgetting the final goal. Mature planning is thought to be represented by the ability to solve the problems in the minimum number of moves required, which indicates creating an initial plan, not deviating from that plan despite potentially distracting stimuli, and being able to update the plan if needed.

Planning develops well into the adult years, and even studies with adults demonstrate considerable variability in performance (Luciana et al., 2009; Luciana & Nelson, 1998). Welsh and Pennington (1988) discuss research demonstrating that, in early childhood, children's plans are usually focused on one dimension of a problem. They are not able to step "outside" the problem and reflect on all the information pertinent to the problem (Kaller, Rahm, Spreer, Mader, & Unterrainer, 2008; Lezak, 1982; Welsh et al., 1991), which is an idea analogous to Zelazo's psychological distance (Zelazo & Frye, 1998). In particular, success on tasks that require moving away from the goal develops later. Welsh, Pennington, and Groisser (1991) investigated EF in children 3 to 12 years old and a group of adults. The researchers used 3-disk and 4-disk versions of a Tower of Hanoi task. Children reached adult performance on the 3-disk version by age 6, but did not reach adult performance by age 12 on the 4-disk version. They propose that the added complexity likely taxed the working memory necessary for efficient planning. Bull et al. (2004) also described the difference between tasks that can be solved using a perceptual strategy, one that does not require stepping outside the problem, and tasks that require stepping back to see all the requirements of the task. The 3-disk versions of Tower of Hanoi tasks typically provide perceptual support for each step, whereas the 4-disk problems frequently require the ability to create psychological distance.

Success on planning tasks typically reaches adult levels by adolescence and early adulthood (Luciana et al., 2009; Welsh, Satterlee-Cartmell, & Stine, 1999; Zook, Davalos, Delosh, & Davis, 2004). Mature planning requires other executive capacities, such as working memory and inhibitory control, to

be functional (Lezak, 1982; Welsh et al., 1991; Welsh et al., 1999). In young children, planning tasks do not show high correlations with other tasks (Welsh et al., 1991), and performance tends to lag behind other EF measures. By adolescence, however, performance on planning tasks tends to be predicted by performance on working memory and inhibitory control tasks, and planning improves with improving working memory and inhibitory control (Luciana et al., 2009; Welsh et al., 1999; Zook et al., 2004). Across development, the ability to step outside the problem is related to improvements in planning and to the development of underlying functions. Improved working memory and inhibitory control would allow someone to succeed at increasingly complex planning tasks and allow simpler planning tasks to become more automated.

The issue of psychological distance is important in discussions of the development of EF. Zelazo says that psychological distance is required for preschoolers to be successful on the DCCS. The DCCS can be seen as a simple planning problem, and young children who can't create the psychological distance necessary to order the two steps involved in the task (apply higher level rule followed by the lower level rule) fail at the task. Children as young as four can easily create plans for perceptually supported two-step planning problems (Luciana & Nelson, 1998) and reliably solve most DCCS tasks (Kirkham et al., 1997). However, there is still improvement through age 6 on 3-step planning problems that are perceptually supported but require holding more information in mind (Luciana & Nelson, 1998). It isn't until adolescence that general success can be seen on 4-step and 5-step planning problems requiring counterintuitive moves (psychological distance) and considerable working memory capacity (Luciana et al., 2009; Luciana & Nelson, 1998). The psychological distance has two components that are related to inhibitory control. The first is ordering steps, which requires inhibiting taking action on subsequent planned steps so that steps can be completed in the correct order. Success on the DCCS and 2- and 3-step planning problems requires this level of psychological distance. The next component involves the ability to make counterintuitive moves that appear to move one away from the solution but actually allow one to attain the goal. This level of psychological distance is often required for 4- and 5-step planning problems and develops much later. The present study will analyze data from the Cambridge Neuropsychological

Test Assessment Battery (CANTAB) Stockings of Cambridge (SOC, a Tower task analogue) task and the novel EMT task in order to distinguish between planning problems that require counterintuitive moves and those that do not.

Planning recruits similar cortical resources to working memory and inhibitory control. The dorsolateral and rostralateral PFC (Baker et al., 1996), inferior frontal gyrus (Fincham, Carter, van Veen, Stenger, & Anderson, 2002) and superior frontal areas (Morris, Ahmed, Syed, & Toone, 1993) are found to be activated during planning tasks. Two versions of the Tower tasks – one in which people complete the moves and another where they simply indicate the minimum number of moves required – are typically used in cortical imaging studies. These different methods for eliciting planning have different results. The inferior frontal gyrus (Fincham et al., 2002) and the right dorsolateral PFC (Newman, Carpenter, Varma, & Just, 2003) are often activated during completion of a move, and the bilateral dorsolateral PFC, anterior cingulate cortex, and rostralateral PFC are often activated when indicating the minimum number of moves required (Baker et al., 1996; Schall et al., 2003). Just like working memory and inhibitory control, response modality is relevant when assessing planning performance.

Many studies also find that planning activates different frontal areas based on the difficulty of the task (Baker et al., 1996; Fincham et al., 2002; Newman et al., 2003), which is interesting because the more difficult problems are also those most likely to require stepping “outside” the problem and making moves contrary to the goal in order to ultimately attain the goal. Unfortunately, researchers who have compared easy and difficult planning tasks have used subtle differences in the structure of their tasks. Knowing that differences in planning tasks lead to differences in performance (Bull et al., 2004), it is important that investigations using brain imaging use the same task design – or systematically alter the task design – in order to understand the brain areas that underlie planning and those that are related to task differences.

The contribution of fatty acids to planning development will be similar to the role of fatty acids in the development of inhibitory control and working memory, which set the groundwork for the development of planning. The appropriate balance of fatty acids during the development of inhibitory

control and working memory will likely set the stage for optimal planning development. Our investigation of EF and fatty acids found a relationship between the omega-6 to omega-3 ratio and planning performance (Sheppard & Cheatham, 2013). Using the SOC task, we found that the omega-6 to omega-3 fatty acid ratio predicted mean subsequent thinking time on the 5-step planning problems above and beyond omega-3 and omega-6 intake in children 7 to 9 years old. The mean subsequent thinking time measure is an indication of the amount of time needed to think through the problem after beginning to move pieces to solve the problem. This measure has the movement time removed through a yoked follow condition such that the “thinking time” is not confounded by differences in reaction time or movement time between children. Children who required more time either did not develop a plan, were unable to hold it in mind to complete it, or became distracted by perceptually supported but actually incorrect moves. Children with lower ratios required less time to solve the problems. Lower mean subsequent thinking times were correlated with performance, such as making fewer errors.

There was additionally an interaction between the ratio and omega-3 intake. Children who consumed a large amount of omega-3 fatty acids (defined as one standard deviation above the mean) had lower mean subsequent thinking times when they had a higher ratio. Children who consumed a small amount of omega-3 fatty acids (defined as one standard deviation below the mean) had lower mean subsequent thinking times when they consumed a lower ratio. This finding supports the notion that the balance of fatty acids is important when supporting cognitive function, but also that there could be multiple paths to balance fatty acid consumption. Those with limited access to sources of omega-3 fatty acids, such as fish, can attain balance through reducing omega-6 fatty acid intake. Those with higher intake of omega-3 fatty acids can attain balance through also consuming more omega-6 fatty acids. The hypothesis then becomes balanced intake supports optimal metabolism of each family of fatty acids that supports neuronal structure and function. Both inhibitory control and working memory are supported by balanced fatty acid intake, and planning appears to be no different. Going forward, using developmentally appropriate measures of EF from infancy to adulthood will help establish exactly what the appropriate ratio is depending on the brain development occurring at the time.

## The Present Study

The present study was designed to investigate the role of the omega-6 to omega-3 ratio in the support of EF. Very few researchers interested in cognitive function in humans have ever focused on the balance of omega-6 and omega-3 fatty acids even though there have been calls to use the omega-6 to omega-3 ratio (Kirby, Woodward, Jackson, Wang, & Crawford, 2010; McNamara, Able, et al., 2010a). The present study was designed to address several questions that follow from previous research. First, the role of the ratio as planning abilities are developing and declining was investigated using a cross-sectional design. Second, the role of the ratio in EF that underlie planning was investigated through a novel task that allows systematic control of inhibitory control and working memory demands. Finally, the link between the ratio, brain function, and cognitive function was investigated through the use of near-infrared spectroscopy (NIRS) data collected during task completion. The specific aims of the present study were:

**Specific Aim 1: to determine the relation between the omega-6 to omega-3 fatty acid ratio and planning performance across the lifespan.** The purpose of this aim is to replicate the previous study with 7- to 9-year-olds and to expand upon those findings by investigating the optimal ratio at different ages. It might be that balanced ratios are important across development or that optimal performance will be seen at different ratios across development.

**Specific Aim 2: to validate a novel electric maze task as an assessment of EF.** The purpose of this aim was to ensure that the novel EMT task assessed planning and that the working memory and inhibitory control manipulations were successful.

**Specific Aim 3: to determine the relation between the omega-6 to omega-3 ratio, cortical activation in the prefrontal cortex, and planning abilities.** The purpose of this aim was to examine the prefrontal resources used to complete standardized measures and the novel EMT task. Then, the goal is to examine the role of the ratio in prefrontal activation during EF tasks. The expectation is that lower ratios will support more efficient processing and better performance on EF tasks.

**Specific Aim 4: to determine whether altering the demands of specific elements of the planning task – working memory and inhibitory control – changes the relation between the omega-6 to omega-3 fatty acid ratio and performance.** The purpose of this aim was further determine that the working memory and inhibitory control manipulations through differences in brain activity stemming from the manipulations. The other purpose was to determine whether the ratio plays different roles supporting working memory compared to inhibitory control.

## CHAPTER 2: METHODS

### **Participants**

Seventy-eight children 7 to 12 years old and 88 adults 65 to 79 years old were recruited from the Charlotte, NC area. Children were excluded if they had any developmental delays, such as diagnoses of attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), or fetal alcohol spectrum disorder (FASD). Fifty-one percent of participants were female, and 92% identified as Caucasian, 4% identified as African-American, 1% identified as Asian, and 3% identified as mixed race. Nine percent of the sample identified themselves as Hispanic or Latino. Participants came from households with a diverse range of incomes (42% below \$90,000), and most mothers, 67%, had at least a college degree. Table 1a shows the descriptive statistics for the sample of children.

The adults included in these analyses were a subset of the participants in a larger study of nutrition and cognitive decline in 65- to 79-year-olds. Participants were recruited in age subgroups through a tertile split creating groups of evenly recruited 65- to 69-year-olds, 70- to 74-year-olds, and 75- to 79-year-olds. The subset included in the present study scored within the normal range on the Montreal Cognitive Assessment (MoCA), which was the screening instrument used to determine if the participant had mild cognitive impairment. Adults were excluded if they had any neurological conditions or took any psychoactive medications. Sixty percent of participants were female, and 97% identified as Caucasian, 2% identified as African-American, and 1% identified as American Indian/Alaska Native. No participants identified as Hispanic or Latino. Thirty-three percent of participants had some college, and 39% had at least a college degree. Table 1b shows the descriptive statistics for the sample of older adults.

## **Procedure**

### **7- to 12-year-olds.**

*Screening.* All children were screened for omega-6 and omega-3 fatty acid intake. We demonstrated in a previous study (Sheppard & Cheatham, 2013) that there were significant differences between children with low and high ratios relative to low and high intakes of omega-3 fatty acids. In order to recruit the best sample for our specific aims, participants were chosen who had low ratios and low, mean, or high omega-3 intake, mean ratios and low, mean, or high omega-3 intake, and high ratios and low, mean, or high omega-3 intake. Cutoffs were determined by calculating tertile splits from the previous sample and checked with the current sample once enough participants had been screened. The present sample consumed more omega-3 fatty acids on average while maintaining similar omega-6 fatty acids to the previous sample. This consumption pattern lowered ratios among screened participants, but low ratios were still the most difficult ratios to find. Using the current sample's cutoffs would only have lowered the low ratio tertile cutoff and made recruitment difficulties worse. This process ensured that we sampled as equally as possible across types of diets instead of basing results on a sample largely made up of one or two types of diets. Table 2 outlines the grouping strategy for participants and the final cell sizes for each diet type.

To determine diet, each participant was called three times to discuss what they had eaten the day prior to the phone call. These diet recalls occurred on two weekdays and one weekend day in order to obtain the best snapshot of the participant's typical week. The mean omega-6 to omega-3 fatty acid ratios were calculated for each day by summing all omega-6 fatty acids consumed that day and dividing that number by the sum of all omega-3 fatty acids consumed that same day. Dietary supplements were included in the diet recalls, and any omega-6 or omega-3 fatty acids obtained through supplements were included in the totals. The three omega-6 to omega-3 fatty acid ratios were then averaged to obtain a measure of the participant's typical consumption. The primary researcher, who collected cognitive performance data, remained blinded to fatty acid group status. Two other researchers computed the omega-3 intake and omega-6 to omega-3 ratios and informed the primary researcher if a participant could



be included. One hundred and fifty two children were screened in order to obtain the 78 in the final sample.

Twenty-four hour diet recalls are considered the most valid mechanism for determining a person's diet (Thompson et al., 2002). Diet recalls were conducted using the 4-pass methodology described below and originally published in the Journal of the American Dietetic Association (Baxter et al., 2009). This 24-hour technique was chosen because it is considered the best way to collect diet data from children. Additionally, all 7- to 12-year-olds had a parent present to help answer questions about the quantity of food consumed and how the food was cooked. Data collection was guided by and entered into the Nutrition Data System for Research (NDSR).

First pass - Quick list: "We'll be talking about what you ate or drank yesterday. After you got up yesterday morning, what was the first time you had something to eat or drink? What did you eat or drink at that time? Did you eat or drink anything else at that time? What was the next time yesterday that you had something to eat or drink? What did you eat or drink. . .?" The interviewer repeated this process to cover yesterday's intake in chronological order. Then, the child was asked "Can you remember any other times yesterday that you had something to eat or drink?"

Second pass - Review: The interviewer repeated back everything the child reported at each time, and asked "Can you think of anything else you ate at that time?" and "Can you think of anything else you drank at that time?" (The interviewer repeated this process for yesterday's intake in chronological order.)

Third pass - Details: The interviewer asked the child to name each eating occasion (response options: school breakfast, breakfast, school lunch, lunch, dinner, supper, snack), identify the location of each meal (response options: home, school, somewhere else), provide details about each item, indicate additions to items, and indicate amounts consumed for each item. The interviewer began with the earliest time yesterday morning and continued in chronological order to cover yesterday's intake.

Fourth pass - Final review: Each eating occasion was reviewed with the child for correctness. The interviewer began with the earliest time yesterday morning and repeated this process in chronological order to cover yesterday's intake. Then, the child was asked one final time "Can you remember any other times yesterday that you had something to eat or drink?"

**Behavioral testing.** Participants who fit into a diet group were called to be invited into the in-person part of the study, which consisted of one visit to the Cheatham Nutrition & Cognition Lab at the Nutrition Research Institute.

*The Electric Maze Task (EMT).* The EMT consisted of a black carpet of 6 x 8 gray squares (Figure 2). The researcher placed pegs in a box connected to the carpet that marked the correct path across the

platform. Any square that was not marked as correct emitted a beeping sound if touched. Participants made their way across the platform working out which squares were correct. Each time the participant stepped on an incorrect square (signaled by beeping), she or he was required to back out of the maze and start again. The starting and ending squares were marked with light blue outlines so that participants always knew the goal and where to start again if they had stepped on an incorrect square.

The mazes were designed to alter the working memory and inhibitory control demands of the EMT in two simple ways. For working memory, the number of steps required to solve the maze began at 6 and was increased to 8, thereby increasing how much information must be held in mind to successfully complete the maze. For inhibitory control, red and yellow stars and circles were placed on the maze squares (Figure 3). The colored shapes appeared randomly distributed, but were carefully placed to create mazes made of only one color (red or yellow) or only one shape (star or circle). Instructions similar to those used during the dimensional change card sort (DCCS) tasks were used. Children were told that they were playing either the color game or the shape game. In the color game, they were to only step on one color. The children then made their way across the platform stepping only on red or yellow shapes depending on the mazes they were randomized to complete. They completed both 6- and 8-step mazes with the color game rules. Then, they were told that they were switching to play the shape game. They made their way across the platform, now stepping only on stars or circles. In this way, children had to inhibit a previous set of rules in order to successfully complete all mazes, and the inhibitory control demands were held constant while the working memory demands were increased. Participants completed a total of 4 mazes, and the starting game (color or shape) and starting location (one of the two possible starting squares) were counterbalanced across participants for both age groups (7- to 9-year-olds and 10- to 12-year-olds).

**CANTAB.** The CANTAB system consists of standardized measures of cognitive function that have been computerized and a touch-screen instrument that automatically stores data as the participants go through the test battery. The CANTAB offers several benefits: many tests can be done in one place with minimal equipment, language ability does not skew results, and minimal reading and directions are

required. The tests chosen for this study were based on information from several studies testing executive function that included children 7 to 12 years old (Green et al., 2009; Luciana & Nelson, 2002). The spatial working memory and planning tests were repeated to replicate findings from the previous study (Sheppard & Cheatham, 2013).

*Motor Task (MOT):* This is a baseline test of motor function to ensure the participants were able to correctly press the screen and participate in the study. The participant saw a series of flashing Xs on the screen that they must touch accurately.

*Reaction Time (RTI):* This is a baseline test of reaction time. It familiarizes the participant with the press-pad and provides simple and choice reaction and movement times. The participants first held down the button on the press-pad. They then saw a yellow dot appear inside a circle. The participants released the button as quickly as possible and touched the spot where the yellow dot appeared. The second section had 5 circles on the screen, and the yellow dot appeared in any of the 5 circles. The participants had to release the button as quickly as possible and press the circle where they saw the yellow dot appear.

*Stockings of Cambridge (SOC):* This is a spatial planning task analogous to the Tower of London. The participant saw two sets of colored balls in “stockings” on the screen. The goal was to move the balls in the bottom set to look exactly like the balls displayed in the top set. There are rules that govern how the participant can move the balls. Participants were instructed to consider how to make the bottom screen look like the top screen before making any moves. The test started with patterns that only required 3 moves and then increased the number of required moves to 5.

*Spatial Working Memory (SWM):* This is a working memory and planning task that incorporates a heuristic strategy. The participant saw boxes on the screen – each of which contained a blue token. They had to find the blue tokens in the correct order. They also had to remember which boxes they had already searched that contained a blue token and which ones did not. The test started with 4 boxes and increased to 8 boxes.

*Paired Associates Learning (PAL):* This is a memory task requiring participants to identify where they have seen patterns on the screen. The participant was first shown a screen with 6 boxes. The boxes revealed patterns in random order. Participants had to remember the location of each pattern, and the number of patterns to remember increased from 2 to 8 with each successful trial.

**NIRS acquisition.** Near-infrared spectroscopy (NIRS) has been used to study prefrontal cortex activation in a variety of populations (Fekete, Beacher, Cha, Rubin, & Mujica-Parodi, 2014; Nakao et al., 2013; Suzuki et al., 2004). Briefly, NIRS takes advantage of the coupling of blood flow with neural activity as well as the differential light absorption properties of oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb). A light using two wavelengths in the spectral region of 600-940 is shown from each of the sources in a continuous wave. The light moves through the skin, skull, and 2 to 3 millimeters of cortex and is subsequently picked up by the detectors. Using wavelengths of

approximately 780 nm and 830 nm is considered optimal for measuring both oxy-Hb and deoxy-Hb. The light that is scattered and picked up by the detectors is dependent on the relative level of oxy-Hb and deoxy-Hb in the brain area through which the light moves. The alteration in the concentrations of oxy-Hb and deoxy-Hb are then time-locked to the specific task the participant is completing.

Previous applications of NIRS have demonstrated that it can detect differences in cortical activation related to task difficulty (Colier, Quaresima, Oeseburg, & Ferrari, 1999), can detect differences in task processing between children with and without developmental delay diagnoses (Kajjume, Aoyama-Setoyama, Saito-Hori, Ishikawa, & Kobayashi, 2013), and can detect differences over time in longitudinal investigations designed to identify children at risk for psychopathology (Fekete et al., 2014). NIRS is quickly becoming a preferred brain imaging technique for studies requiring significant movement and for children (who might find it challenging to remain still during testing) because movement does not compromise data collection. The early literature has suggested that NIRS will be an excellent brain imaging technique for studying EF and for nutritional investigations due to its ease of use with children and its ability to pick up on small changes in oxy-HB and deoxy-HB (for review: Jackson & Kennedy, 2013; Lloyd-Fox, Blasi, & Elwell, 2010).

Before cognitive testing, the participants were fitted for a portable 7.81 Hz NIRS device (NIRSport, NIRx Medical Technologies, LLC). NIRS data were recorded as the participants worked their way through the mazes and while completing the SOC and SWM CANTAB tasks. The NIRS system includes a cap placed on the participant's head and a backpack that holds the recording device. Cap size was chosen based on a measurement of head circumference from the brow ridge to 1 inch above the inion. To insure proper cap placement, the vertex of the head was marked midway between the nasion and inion and midway between the pre-auricular depressions. Electrolyte gel was placed on the 8 sources and 7 detectors fitted into the holes of the correctly-sized cap. The cap was then placed on the participant's head using the vertex mark as the guide. The locations of the sources and detectors (Figure 4a) were chosen based on the standard prefrontal map provided by NIRx. Each source-detector pair was 3 cm apart and created a banana-shaped channel of light that moved through the cortex to measure oxygenated and

deoxygenated hemoglobin levels (Figure 4b). The sources and detectors were then connected to the recording device in the backpack. A separate laptop communicated by way of a remote desktop connection with the recording device. All participants completed the tasks in the same order: MOT, SOC, the 4 mazes, SWM, RTI, and PAL. This order was chosen to insure that we obtained NIRS data from the most important tasks before the participant experienced any discomfort; if the participant wanted to remove the cap before the end of NIRS data collection, we were more likely to have data for the tasks of greatest interest.

***Covariates.*** In addition to the cognitive testing and blood samples, parents provided information on general family demographics including parental occupation and education, family income, and mode of infant feeding. Parents and children each completed a physical activity questionnaire to capture the child's regular physical activity. The Child Physical Activity Questionnaire (C-PAQ) asked the parents to estimate the total number of minutes the child spent in a list of activities common to children. These activities were then summed for vigorous activities (i.e., soccer), moderate activities (i.e., swimming for fun), light activity (i.e., walking), and sedentary time (i.e., doing homework). The Physical Activity Questionnaire for Children (PAQC, Kowalski, Crocker, & Faulkner, 1997) asked children to indicate how frequently they engaged in a list of activities and then, to estimate their perception of their overall level of activity over the past week. The frequency of activity was scored from 1 (none) to 5 (five or more times), and averages were calculated for the average activities and average daily level of activity. Parents also completed either the Temperament in Middle Childhood Questionnaire (TMCQ, 7- to 9-year-olds, Simonds & Rothbart, 2004, October) or the Early Adolescence Temperament Questionnaire (EATQ, 10- to 12-year-olds, Ellis & Rothbart, 2001) to assess temperament. The temperament questionnaire subscale scores were calculated according to the instructions to create three final subscales of negative reactivity, surgency, and effortful control.

#### **65- to 79-year-olds.**

***Screening.*** Adults were screened for cognitive impairment and nutritional status. The Montreal Cognitive Assessment (MoCA), Boston Naming Test, and Digit Span tasks were used as screening

instruments to determine cognitive impairment. Scores below 25 on the MoCA or a borderline score on the MoCA along with very low scores on the Boston Naming Test or Digit Span task indicated that the person likely had mild cognitive impairment. Participants with MoCA scores as low as 24 were included in the present analyses, and 22.73% of participants had a score of 24. In the larger study, if participants were categorized as having mild cognitive impairment, they were randomized to receive either a powdered blueberry supplement or a placebo for six months. For the present analyses, baseline scores were used to avoid any effect of the supplement.

***Diet Recalls.*** The NDSR 24-hour dietary record procedure was used to obtain three days of dietary intake from the older adults at their first session (before they received any supplement). The older adults were instructed to choose three days in the same week leading up to their first session to record their diet for 24 hours in their diet journal. The diet journal was then brought to the session and reviewed with a researcher using the 4-pass methodology. The three days chosen did not necessarily include one weekend day and two weekdays. However, as 83.12% of the adults were retired, the distinction between weekday and weekend was less relevant with the older adults.

***CANTAB.*** The older adults also completed a battery of computerized versions of standardized tests using the CANTAB system. CANTAB has been most widely used with older adults in an effort to develop tests to detect the progression of mild cognitive impairment and various forms of dementia, including Alzheimer's disease. The tests chosen for the larger study included those most sensitive to mild cognitive impairment. Participants were tested 3 times across the 6-month study, and only the first testing session, before any supplementation had occurred, was included in the present analyses. The tests included were the Motor Task, Reaction Time Task, Spatial Working Memory task, Paired Associates Learning task, and Rapid Visual Processing (RVP) task. RVP is a measure of sustained attention in which the participant must watch numbers appearing in the middle of the screen. Numbers from 1 to 9 appear randomly, and participants must press a button every time they see one of three sequences of numbers (2-4-6 or 4-6-8 or 3-5-7). Participants first learn the task with just one sequence (3-5-7) and are then tested

for 4 minutes with the three sequences. Latency and error measures were provided by the CANTAB software.

***Covariates.*** The older adults also completed questionnaires about their physical and psychological health, their physical activity, and a general demographic questionnaire. Their physical activity was measured using the Physical Activity Scale for the Elderly (PASE, Washburn, Smith, Jette, & Janney, 1993), which queries common physical activities among older adults in the past two weeks. Scoring of the PASE includes weighting of responses to items. The weighting was determined by typical energy expenditure for each activity. Activities such as heavy yard work (i.e., chopping wood) received larger weights than gardening, and running received a larger weight than walking. The total weighted activities were then summed for the physical activity score with higher scores indicating greater levels of activity. The PASE has been shown to be a reliable and valid physical activity questionnaire among older adults (Washburn et al., 1993).

## CHAPTER 3: RESULTS

### **Sample diet characteristics**

The 7- to 12-year-olds were recruited with specific dietary cutoffs initially determined by a previous sample (Sheppard & Cheatham, 2013). Table 3 shows the diet characteristics of the 7- to 12-year-olds. Even recruitment across ratio and omega-3 intake was not achieved. Recruitment of children who consumed a low ratio diet was challenging. Despite screening 152 children, only 78 (51.32%) could be included in diet groups. The low ratio diets were the most difficult to find. The smallest cells contain four participants (low ratio/mean omega-3 and low ratio/high omega-3), which is less than half of the original goal of nine participants per cell. The included participants did not differ from those not included on macronutrient intake (fat, carbohydrates, or protein). The 65- to 79-year-olds were not recruited for any specific fatty acid consumption patterns. Initially, the cutoffs used with the 7- to 12-year-olds were applied to the sample of 88 older adults. These cutoffs resulted in several cells without any participants and highly skewed overall cell sizes. In general, the adults consumed more omega-3 fatty acids and similar amounts of omega-6 fatty acids compared to the children, which resulted in lower ratios. When tertile cutoffs of omega-3 intake and the ratio were created based on the sample of older adults, a better overall balance in cells was achieved. However, when divided by age subgroups, the 70- to 74-year-olds still had no participants who consumed a low ratio/low omega-3 diet. Table 3 shows the diet characteristics and cutoffs for the 65- to 79-year-olds.

### **Data Reduction and Analyses**

All data were inspected for assumptions of the general linear model including normal distribution, linearity, and homoscedasticity of residuals. Variance inflation factors (VIF) were calculated for all regressions in order to determine if high correlations between omega-6 and omega-3 fatty acid consumption were problematic for model estimates, as was found in the previous study (Sheppard &



Cheatham, 2013). A VIF above 10 is considered problematic, and two age subgroups (10- to 12-year-olds and 65- to 69-year-olds) were found to have problems with VIF between omega-6 and omega-3 intake. VIF issues were handled by running models with omega-6 and omega-3 intake separately. Influence statistics, such as Cook's D, were also examined to insure that no individual observations unduly influenced results. Appropriate covariates were determined using one-way ANOVA testing, and education (maternal education for the child sample) and physical activity were included in all models. Statistical analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC) with the exception of the factor analysis conducted to validate the Electric Maze Task (Appendix 1), which was conducted with MPlus 7.11 (Muthen & Muthen, 1998-2012). NIRS data were analyzed with NIRx v2014.12 (NIRx Medical Technologies, LLC), and a detailed description of those analyses is included in the results for specific aims 3 and 4 that deal with the NIRS data.

### **Validating the Electric Maze Task (Specific Aim 2)**

The EMT was found to be a valid and reliable measure of planning in 7- to 12-year-olds. The full details of validating the EMT are shown in Appendix 1, and an overview of the analyses are presented here. Outcome measures from the mazes included errors made, duration spent on the correct path and in error zones on the maze, and latency to first and last errors made. All outcome measures were calculated automatically by Noldus Ethovision XT version 8.0. Average errors were calculated for 6-step mazes, 8-step mazes, mazes from the first condition, and mazes from the second condition. The errors made during the first condition were subtracted from the errors made during the second condition to produce a score reflecting the change in performance due to the rule switch. There were no significant differences in performance based on maze start location (1 or 2) or maze starting condition (color or shape).

Cronbach's alphas were calculated for the entire sample, each age group, and each maze manipulation (Table 4; 6-step, 8-step, first game, second game, and rule switch scores). The maze was a reliable task for the entire sample (Cronbach's  $\alpha = 0.92$ ), 7- to 9-year-olds (Cronbach's  $\alpha = 0.89$ ), and 10- to 12-year-olds (Cronbach's  $\alpha = 0.83$ ). A factor analysis revealed that the 6-step and 8-step mazes loaded onto separate factors,  $\chi^2(85) = 132.34$ ,  $p < 0.05$ , CFI = 0.94, TLI = 0.92, RMSEA = 0.09. The 6-step

mazes were reliable for the entire sample (Cronbach's  $\alpha = 0.89$ ), 7- to 9-year-olds (Cronbach's  $\alpha = 0.88$ ), and 10- to 12-year-olds (Cronbach's  $\alpha = 0.86$ ), and the 8-step mazes were reliable for the entire sample (Cronbach's  $\alpha = 0.88$ ), 7- to 9-year-olds (Cronbach's  $\alpha = 0.88$ ), and 10- to 12-year-olds (Cronbach's  $\alpha = 0.87$ ). A factor analysis also indicated that the 1<sup>st</sup> and 2<sup>nd</sup> conditions loaded onto separate factors, although not as strongly,  $\chi^2(98) = 188.52$ ,  $p < 0.05$ , CFI = 0.88, TLI = 0.86, RMSEA = 0.11. The first condition was reliable for the entire sample (Cronbach's  $\alpha = 0.89$ ), 7- to 9-year-olds (Cronbach's  $\alpha = 0.89$ ), and 10- to 12-year-olds (Cronbach's  $\alpha = 0.85$ ), and the second condition was reliable for the entire sample (Cronbach's  $\alpha = 0.87$ ), 7- to 9-year-olds (Cronbach's  $\alpha = 0.87$ ), and 10- to 12-year-olds (Cronbach's  $\alpha = 0.86$ ).

Independent samples t-tests were run to examine differences in maze performance between the two age groups. Older children performed better than younger children on both 6-step and 8-step mazes by making fewer total errors (6-step mazes,  $t(62.56) = 2.69$ ,  $p < 0.05^1$ , and 8-step mazes,  $t(53.06) = 3.71$ ,  $p < 0.05$ ) and having a shorter latency to last error (6-step mazes,  $t(45.61) = 2.76$ ,  $p < 0.05$ , and 8-step mazes,  $t(57.96) = 3.39$ ,  $p < 0.05$ ). The 8-step mazes increased the difficulty for the younger children as they also made more perseverative errors,  $t(56.29) = 2.65$ ,  $p < 0.05$ , than older children. The latency to last error measure is an indication of the errors made after the participant began attempting a solution. This is an indication of planning because participants who planned their routes would make errors early as they eliminated potential options, and they would use information about errors to update potential paths through the maze. Later errors are an indication of trial-and-error solution methods or an inability to fully use any plans made.

For the inhibitory control manipulation, older children made fewer total errors in the first condition,  $t(48) = 3.08$ ,  $p < 0.05$ , and the second condition,  $t(57.9) = 3.17$ ,  $p < 0.05$ , than younger children. Older children also made fewer perseverative errors,  $t(47.93) = 2.51$ ,  $p < 0.05$ , and had a shorter latency to last error,  $t(44.06) = 3.25$ ,  $p < 0.05$ , than younger children in the first condition. The inhibitory

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<sup>1</sup> The Satterthwaite-corrected degrees of freedom are reported when the Folded F test indicated there were significantly unequal variances between groups.

control manipulation may not have been fully successful as more children made no perseverative errors in the second condition, 52.78%, than the first condition, 51.39%, and there was no significant difference between the age groups in perseverative errors made in the second condition despite a significant difference between the age groups in the first condition. Table 5 shows all age group comparisons for maze performance.

Paired t-tests were also run for the sample as a whole and for each age group to determine if there were significant differences in performance created by each manipulation. For the working memory manipulation, all groups made significantly more errors on the 8-step mazes than on the 6-step mazes (entire sample:  $t(71) = 5.15, p < 0.0001$ ; 7- to 9-year-olds:  $t(35) = 4.08, p < 0.01$ ; 10- to 12-year-olds:  $t(35) = 3.21, p < 0.05$ ). All groups also had longer latency to last error on the 8-step mazes than on the 6-step mazes (entire sample:  $t(69) = 3.77, p < 0.01$ ; 7- to 9-year-olds:  $t(35) = 2.86, p < 0.01$ ; 10- to 12-year-olds:  $t(33) = 2.56, p < 0.05$ ). Table 6 shows all comparisons of maze performance after the working memory and inhibitory control manipulations.

Correlations were run between performance on the mazes and outcomes on the standardized measures, the PAL memory task, the SWM working memory task, and the SOC planning task (Table 7). Overall, the correlations between the standardized measures and maze performance indicate that the maze task can effectively elicit planning from 7- to 12-year-olds. The working memory and inhibitory control demands of the maze can also be effectively manipulated. Additional testing with more age groups and some new manipulations (i.e., 10-step mazes, 3 dimension rule switch) will be required to fully understand the maze. This initial analysis of the maze task indicates that the 6-step mazes were quite simple for 7- to 12-year-olds and may have been mostly solved using memory resources as indicated by correlations with the simpler PAL memory task. The 8-step mazes appear to have required planning skill as performance was correlated most with SOC and SWM measures. In particular, 8-step maze performance was correlated with performance on difficult SOC problems for younger children (5-move problems) and difficult SWM problems for older children (6-box and 8-box problems). There were indications that the rule switch did not successfully increase inhibitory control demands, and the

correlation pattern further supported this conclusion. The pattern of correlations did indicate more correlations between the SOC task and performance after the rule switch. The SOC task requires flexible use of working memory and inhibitory control abilities, and therefore increasing the inhibitory control requirements on the mazes would have been expected to correlate more with the SOC task than the other tasks. However, the correlations were in opposite directions for the 7- to 9-year-olds and 10- to 12-year-olds, making it difficult to conclude that a clear-cut manipulation of inhibitory control demands was accomplished.

### **Omega-6 to Omega-3 Ratio and Lifespan Cognitive Function (Specific Aim 1)**

Specific Aim 1 was designed to examine the omega-6 to omega-3 fatty acid ratio in executive functions across the lifespan in order to 1) replicate findings from a previous study with 7- to 9-year-olds (Sheppard & Cheatham, 2013) and 2) to investigate the optimal ratio at different ages as the brain changes with development. This aim was first explored across both older adults and children, and then the age groups were separated to determine if there were differences in the optimal ratio at different ages. The division of the ages into 7- to 9-year-olds and 10- to 12-year-olds in children and into 65- to 69-year-olds, 70- to 74-year-olds, and 75- to 79-year-olds in older adults has not been explicitly tested but is supported by previous literature in children (Conklin et al., 2007; Luciana et al., 2009; Luciana & Nelson, 2002) and older adults (Borella et al., 2014; H. Li et al., 2014; Pudas et al., 2013) demonstrating that individuals within these age groups perform similarly on EF tasks and that changes in brain function occur around these divisions. The data also support these divisions as age group (7- to 9-year-olds and 10- to 12-year-olds for children and 65- to 69-year-olds, 70- to 74-year-olds, and 75- to 79-year-olds for older adults) was consistently a predictor of cognitive performance on the CANTAB task and EMT. However, within each age group, age was not consistently a significant predictor of performance. Table 8 shows age group comparisons supporting the use of these age divisions.

A 2 (Age: 7-12 and 65-79) x 3 (Ratio group: high, mean, and low) multivariate analysis of covariance (MANCOVA) was conducted to determine the role of the ratio in performance on the Spatial Working Memory (SWM) and Paired Associates Learning (PAL) CANTAB tasks, which were the two

tasks used with both the older adult and child samples. Omega-3 fatty acids, omega-6 fatty acids, physical activity, and education (proxy for socioeconomic status) were included as covariates. Physical activity was measured with two different age-appropriate questionnaires (PASE and C-PAQ), and z-scores were created for each sample so that physical activity could be included in the model. For instance, a z-score of -1 indicated a participant who was one standard deviation below the mean activity level for their sample (older adult or child). The education included was years of maternal education for the children and individual years of education for the adults. There was no significant main effect of ratio group or significant age X ratio group interaction for any SWM or PAL tasks.

### **Fatty acid intake and older adults.**

The age groups were then divided to examine the role of the ratio and omega-3 intake in children and adults separately. Multivariate regressions were used to analyze the relation between the ratio and executive functions in older adults because balanced ratio and omega-3 groups could not be created. The ratio, omega-3 intake, and omega-6 intake were included in a multivariate regression predicting stages completed on the 1<sup>st</sup> try and total errors on the PAL task, total between errors and the mean time to first response on the SWM task, and A' and B'' on the Rapid Visual Processing (RVP) task. Education, age in months, and physical activity were included as covariates. Variance inflation factors indicated that there weren't any variance inflation issues with the model. The ratio, omega-3 intake, and omega-6 intake did not predict any cognitive outcomes for the sample as a whole.

Multivariate regressions were then run to determine if the ratio or fatty acid intake was a predictor for any specific age group (65- to 69-year-olds, 70- to 74-year-olds, and 75- to 79-year-olds). There was a variance inflation issue between omega-6 and omega-3 intake with 65- to 69-year-olds. Models including omega-3 and omega-6 fatty acid intake were run separately. In 75- to 79-year-olds, omega-3 and omega-6 intake predicted the total errors made ( $t(23) = -2.24, p < 0.05$  and  $t(23) = -2.07, p < 0.05$ , respectively) on the PAL task (Table 9), and the ratio predicted the mean time to first response on the 4-box SWM problems with omega-6 intake included,  $t(24) = -2.09, p < 0.05$ , and with omega-3 intake included,  $t(24) = -2.42, p < 0.05$  (Table 10). The time to first response is an indicator of time spent processing the box

array and considering how to find the tokens without making errors. Lower ratios predicted longer time to first response on the simplest SWM problems, and greater intake of omega-6 and omega-3 fatty acids predicted fewer total errors on the PAL task. Regressions were also run including interactions to determine if significant interactions would be found among older adults (as had been found in the previous study with children, Sheppard & Cheatham, 2013). The interaction between omega-3 intake and the ratio predicted mean time to first response on the 4-box problems in 75- to 79-year-olds,  $t(23) = -2.98$ ,  $p < 0.05$  (Table 11). The interaction between omega-3 intake and the ratio and omega-6 intake and the ratio predicted total between errors on the SWM task,  $t(30) = 2.74$ ,  $p < 0.05$  and  $t(30) = 2.56$ ,  $p < 0.05$ , respectively (Table 12), and the interaction between omega-6 intake and the ratio also predicted A' on the RVP task,  $t(30) = 2.49$ ,  $p < 0.05$  (Table 13), in 65- to 69-year-olds. A' is a measure of accuracy that takes into account false alarms.

Probing these interactions using Preacher's simple slopes tool (Preacher, Curran, & Bauer, 2006) demonstrated that 65- to 69-year-olds and 75- to 79-year-olds were quite different. The 75- to 79-year-olds processed the simplest SWM problems (4-box) faster when they had low omega-3 intake and a low ratio or high omega-3 intake and a high ratio (Figure 5). This result is similar to the findings with 7- to 9-year-olds in the previous study who processed the most difficult planning problems (5-move SOC) fastest with balanced ratios (low omega-3/low ratio or high omega-3/high ratio). In Figure 5, the high omega-3 intake slope was significant, indicating that those consuming high omega-3 diets performed significantly better with a higher ratio than those consuming a high omega-3 diet with a low ratio. The low omega-3 intake slope was not significant, indicating that those who consumed a low omega-3 diet did not perform significantly better with any particular ratio. Conversely, the 65- to 69-year-olds made fewer between errors across the SWM task when they consumed a high omega-3 diet and a low ratio or a low omega-3 diet and a high ratio (Figure 6). In this case, the high omega-3 intake and mean omega-3 intake slopes were significant, indicating that those who consumed a high omega-3 diet or a mean omega-3 diet performed significantly better with lower ratios compared to higher ratios.

### **Fatty acid intake and children.**

The analyses with the 7- to 12-year-olds followed the initial analysis plan. A 3 (Ratio group: high, mean, and low) X 3 (Omega-3 group: high, mean, and low) MANCOVA was run with the entire sample to determine the role of the ratio, omega-3 intake, and their interaction in executive functions in children. Age in months, maternal education, and physical activity were included as covariates. There was a main effect of ratio group on mean moves on the 5-move SOC problems,  $F(2,59) = 5.29, p < 0.05$  (Table 14). The low ratio group made significantly fewer moves to solve the 5-move SOC problems (Figure 7).

Next, 3 (Ratio group: high, mean, and low) X 3 (Omega-3 group: high, mean, and low) MANCOVAs were run separately for each age group (7- to 9-year-olds and 10- to 12-year-olds). Maternal education and physical activity were included as covariates. There was a significant main effect of ratio group,  $F(2,27) = 3.68, p < 0.05$ , and a significant interaction between the ratio and omega-3 intake,  $F(4,27) = 2.98, p < 0.05$ , on mean moves made on the 5-move SOC problems in 7- to 9-year-olds (Table 15 and Figure 8). As can be seen, the 7- to 9-year-olds who consumed balanced diets (low ratio/low omega-3 or high ratio/high omega-3) required fewer moves to solve the most difficult planning problems. The significant differences were for the low ratio group, in which the children who consumed a low quantity of omega-3 fatty acids required significantly fewer moves than those who consumed mean or high quantities of omega-3 fatty acids. There was also a significant ratio group X omega-3 intake group interaction predicting the mean moves on the 5-move SOC problems,  $F(4,20) = 3.66, p < 0.05$ , in 10- to 12-year-olds (Table 16). Specifically, the high ratio/high omega-3 group required significantly more moves to solve the 5-move SOC problems than the low ratio/high omega-3 group (Figure 8). This interaction was the opposite of the significant interaction found for 7- to 9-year-olds on the mean moves on the 5-move SOC problems.

The outcomes from the mazes were also included in the analyses of the role of the ratio in executive functions in 7- to 12-year-olds. The ratio, omega-3 intake, and the ratio X omega-3 intake interaction did not predict performance on the 6-step mazes or after the rule switch for the entire sample

or any age group. However, ratio group predicted the latency to last error on the 8-step mazes,  $F(2,23) = 5.69$ ,  $p < 0.05$ , in 7- to 9-year-olds. The ratio group and omega-3 group also predicted errors made on 8-step mazes,  $F(2,23) = 4.47$ ,  $p < 0.05$  and  $F(2,23) = 3.65$ ,  $p < 0.05$ , respectively, in 7- to 9-year-olds (Table 17). Specifically, the high ratio group made significantly more errors on 8-step mazes than the low and mean ratio groups. There was a trend for the low ratio group to have a significantly shorter latency to last error than the high ratio group as well. These results fit with the overall pattern of the 8-step mazes eliciting planning in the younger children and the ratio predicting planning performance.

### **Summary of omega-6 to omega-3 ratio and lifespan cognitive function.**

The results indicated that fatty acid intake and the balance of fatty acids are relevant to executive functions in older adults. There were no significant results for the older adults as a whole, but there were effects of the ratio, omega-3 intake, omega-6 intake, and their interactions for each age subgroup. These effects were in opposing direction for the youngest older adults (65- to 69-year-olds) and the oldest older adults (75- to 79-year-olds). These results indicate that different fatty acid intake supports optimal cognitive function across the age range (65-79). In general, the 65- to 69-year-olds performed better with lower intake of both omega-6 and omega-3 fatty acids. When intake of omega-3 fatty acids was high, 65- to 69-year-olds performed best with lower ratios, indicating those who kept their intake of omega-6 fatty acids lower performed better. This pattern held for the more difficult spatial working memory and rapid visual processing tasks. In 75- to 79-year-olds, participants performed best with greater intake of both omega-3 and omega-6 fatty acids. When omega-3 intake was high, the oldest adults performed best with higher ratios, indicating that they performed better with greater omega-6 intake. These results were found for the simpler memory task (PAL) and for processing time on the simplest spatial working memory problems.

The results with the 7- to 12-year-olds also demonstrate the importance of fatty acids to executive functions in this age range. The recruitment strategy allowed specific group comparisons based on previous findings. The significant interaction between the ratio and omega-3 intake predicting performance on the most difficult planning problems for 7- to 9-year-olds found in the previous study was



replicated in the present study. In addition, specific differences were found for 7- to 9-year-olds who consumed a low omega-3 fatty acid diet. Those who consumed a low ratio/low omega-3 diet performed significantly better than those who consumed a high ratio/low omega-3 diet. The opposite effect was found for 10- to 12-year-olds who benefitted from a low ratio/high omega-3 diet on the most difficult planning problems. The specific differences for 10- to 12-year-olds were between the high omega-3 groups with the high ratio group performing significantly worse than the low ratio group. These results indicate possible differences in dietary requirements as children develop. Table 18 shows a summary of the significant findings with older adults and children.

Overall, the findings from Specific Aim 1 support the role of the ratio in executive functions in both children and older adults. These results indicate that optimal cognitive function is likely supported by different balances of fatty acids at different ages. These results also indicate that as we develop increasingly complex cognitive functions, we see the role of the ratio in increasingly difficult tasks. As we develop, the use of executive resources is no longer required for simpler problems, and the support of fatty acids is seen for the tasks that most require executive capacities. As we age and decline in our cognitive abilities, the effects of the ratio can be seen on simpler tasks. Executive resources may be required for these simpler tasks again, making the importance of the ratio evident in these simpler tasks.

#### **The Ratio, Cortical Activation, and Behavioral Performance (Specific Aims 3 and 4)**

Participants included in analyses of the ratio, cortical activation, and behavioral performance were those with clean NIRS data for the task in the analysis. For inclusion in any maze analyses, the participant had to have clean data for all four mazes. In the end, five participants had no NIRS data (3 refused before measurement for the cap, 2 refused after placement of the cap). If more than 4 channels were considered bad channels (details below), the participant was not included for that task (n=12 across all tasks). Sixty two participants were included for the SOC task (16.22% loss), 55 participants were included for Maze 1 (20.29% loss), 51 participants were included for Maze 2 (25% loss), 49 participants were included for Maze 3 (27.94% loss), 54 participants were included for Maze 4 (19.4% loss), and 54 participants were included for SWM (20.59% loss). This attrition was similar to other NIRS studies

(Fekete et al., 2014). The decrease in included participants represents loss from participants who wanted the cap removed ( $n = 7$ ), loss from data collection errors made ( $n=4$ ), and loss from bad channels during maze tasks because of movement extreme enough to interrupt NIRS data collection ( $n=2$ ).

### **Statistical analyses.**

NIRS data were analyzed using the MATLAB ‘nirxlab’ graphical user interface. For all tasks, the baseline was designated as the first five seconds of the recording. Table 19 shows how events were marked for each task. In general, the presentation of each new problem and the time after making an error were marked as time the participant would step back to consider the problem. The SOC task and the mazes included yoked ‘move’ conditions designed to require the participant to move identically but without any planning needed. These were marked as separate events. NIRS data files were processed according to recommendations in investigations that utilized NIRS (Nakao et al., 2013) and fMRI (Beckmann, Jenkinson, & Smith, 2003) as follows: 1) Raw data were checked to remove bad channels, which were defined as gain measurements above 8 or a coefficient of variation greater than 15%; 2) discontinuities, also known as step artifacts, were removed, which were defined as a ratio of the difference from the standard deviation of successive data points above 5; 3) spike artifacts were removed by imputing corrected values; 4) data were band-pass filtered using a high pass cutoff of 0.2 Hz, a low pass cutoff of 0.01 Hz, and a roll off width of 15. Spike artifacts were defined as the ratio between the difference in the maximum and minimum values and the standard deviation of the time series above 5. Values were imputed from the two nearest neighbors that did not have spike artifacts at that time point. The values of the two nearest neighbors were averaged and used to replace the spike artifact value.

After processing, the oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) values were calculated using a modified Beer-Lambert law for each channel at each frame. The oxy-Hb files were analyzed because they are considered the best match for fMRI blood oxygen level-dependent (BOLD) signal responses (Strangman, Culver, Thompson, & Boas, 2002). A hemodynamic response function with time derivative was applied as the basis function to account for the temporal discrepancy between brain activity and blood flow, and pre-coloring was performed to account for the

correlation between the noise components in the NIRS signal. Pre-coloring imposes a pre-defined serial correlation that is based on the hemodynamic response function. After these operations were applied, specific contrasts for the cortical activity of interest were calculated for each task. These contrasts were specified as t-statistic contrasts in which the activity during one event (say the ‘move’ condition) was compared to the activity during another event (say planning the 5-move SOC problems). The t-statistic contrasts were used because they are a direct comparison of the relative brain activity during the one event compared to the other event.

In these analyses, negative values indicate a greater brain activity during ‘move’ events, and positive values indicate greater brain activity during planning events. The differences between planning events and ‘move’ events were calculated for 5-move and 3-move SOC problems and for each maze. A contrast was also calculated between 5-move and 3-move SOC problems in order to isolate activity related to problems that required counterintuitive moves (stepping outside the problem). For that contrast, negative values indicate a larger response for 3-move SOC problems, and positive values indicate a larger response for 5-move SOC problems. Contrasts for the SWM task were calculated between all levels (4-box, 6-box, and 8-box). The negative values indicated greater brain activity during the simpler problem in the contrast (i.e., 4-box problems in a contrast with 8-box problems), and positive values indicated greater activity during the more difficult problems in the contrast. These contrasts were then calculated for left hemisphere channels (1-6), central channels (7-14), and right hemisphere channels (15-20). These hemisphere contrasts were then used in analyses investigating the role of the ratio in cortical activation and the relation between the cortical activation and performance on the mazes and standardized measures. The relation between cortical activation and behavioral performance is addressed first as this information informs the analyses of the role of the ratio.

### **Cortical activation and behavioral performance.**

The number of participants who could be included in maze analyses ranged from 58 on the SOC task to 34 for the working memory and inhibitory control manipulation calculations. Loss of data occurred because of software malfunctions or corrupt files (n=4) or the need for clean data on two or

more tasks. For instance, the 6-step maze contrast values are the average of the 1<sup>st</sup> and 3<sup>rd</sup> mazes because those were the 6-step mazes. When a participant was missing data for the 1<sup>st</sup> maze or the 3<sup>rd</sup> maze, he or she could not receive a 6-step maze contrast value. These issues were compounded when the working memory and inhibitory control contrast values were calculated because those required complete maze data (all four mazes). The reduction in sample size for several of these contrasts prevented the use of the ratio and omega-3 fatty acid grouping strategy. First, correlations between behavioral outcomes and contrasts at each channel were run to examine the cortical activity associated with performance on the SOC task, SWM task, and EMT.

Table 20 shows the correlations between SOC task brain activity contrasts and SOC behavioral outcomes. The contrasts created were used to compare brain activity related to solving the 3-move SOC problems and the ‘move’ condition (simplest problems, Table 20), the brain activity related to solving the 5-move SOC problems and the ‘move’ condition (most difficult problems, not shown), and the brain activity related to solving the 5-move SOC problems and the 3-move SOC problems (stepping outside the problem, Table 21). The contrast comparing the 5-move and 3-move SOC problems represents the additional processing required to solve problems with counterintuitive moves and more information held in mind. The pattern of correlations with the 3-move SOC problems indicated a positive correlation between brain activity while solving 3-move problems and solving SOC problems in the minimum number of moves across the right and central prefrontal cortex. Greater brain activity while solving 3-move SOC problems compared to the ‘move’ condition was related to solving more problems in the minimum number of moves (central,  $r = 0.34$ ,  $p < 0.05$ ; right hemisphere,  $r = 0.35$ ,  $p < 0.05$ ). Conversely, greater brain activity while solving 5-move SOC problems compared to 3-move SOC problems was related to solving fewer problems in the minimum number of moves across the whole prefrontal cortex (left hemisphere,  $r = -0.32$ ,  $p < 0.05$ ; central,  $r = -0.41$ ,  $p < 0.05$ ; right hemisphere,  $r = -0.43$ ,  $p < 0.05$ ). These correlations indicate that participants who processed the simplest planning problems similar to the yolked ‘move’ condition performed worse on the SOC task overall, and those who required additional processing on the 5-move SOC problems (above and beyond the 3-move problems) also performed worse

on the SOC task overall. There was no discernable pattern of significant correlations for the 5-move SOC problem and ‘move’ condition contrast. SOC oxy-Hb contrasts for 7- to 9-year-olds were not significantly correlated with performance, but SOC oxy-Hb contrasts for 10- to 12-year-olds followed the pattern of the entire sample.

For the EMT, contrasts were calculated between the 6-step mazes and the ‘move’ condition, the 8-step mazes and the ‘move’ condition, 1<sup>st</sup> condition mazes and the ‘move’ condition, and 2<sup>nd</sup> condition mazes and the ‘move’ condition. There were no significant correlations between performance on the 1<sup>st</sup> or 2<sup>nd</sup> conditions and behavioral performance on the maze. This was not surprising as other analyses have indicated that the inhibitory control manipulation was not fully successful. The 6-step maze contrasts indicated that the brain activity related to solving 6-step mazes in the right and central prefrontal cortex were significantly related to performance on 6-step and 8-step mazes. Greater brain activity in these areas was related to making fewer total errors (6-step: central,  $r = -0.36$ ,  $p < 0.05$ ; right hemisphere,  $r = -0.33$ ,  $p < 0.05$ ), making fewer perseverative errors (6-step: central,  $r = -0.42$ ,  $p < 0.05$ ; 8-step: left hemisphere,  $r = -0.35$ ,  $p < 0.05$ , central,  $r = -0.35$ ,  $p < 0.05$ ; right hemisphere,  $r = -0.41$ ,  $p < 0.05$ ), making fewer rule errors (6-step: central,  $r = -0.4$ ,  $p < 0.05$ ; right hemisphere,  $r = -0.33$ ,  $p < 0.05$ ; 8-step: central,  $r = -0.43$ ,  $p < 0.05$ ), and a shorter latency to last error (6-step: central,  $r = -0.35$ ,  $p < 0.05$ ; right hemisphere,  $r = -0.33$ ,  $p < 0.05$ ), all indicators of better performance (Table 22). These results parallel the results with the simplest, 3-move SOC problems. Additionally, greater brain activity in the right prefrontal cortex when solving 8-step mazes compared to 6-step mazes was related to poorer performance in the form of more perseverative errors on 8-step mazes ( $r = 0.39$ ,  $p < 0.05$ , Table 23). This result was also similar to the result comparing 5-move and 3-move SOC problems. Greater brain activity when solving more difficult mazes compared to less difficult mazes was related to worse maze performance. Table 21 shows the correlations between maze performance and maze brain activity contrasts.

For the SWM task, greater brain activity when solving 8-box problems compared to 4-box problems was related to making fewer between errors across the whole prefrontal cortex (left hemisphere,  $r = -0.49$ ,  $p < 0.05$ ; central,  $r = -0.5$ ,  $p < 0.05$ ; right hemisphere,  $r = -0.47$ ,  $p < 0.05$ ), and to reduced time

to first response in some areas (4-box: central,  $r = -0.36$ ,  $p < 0.05$ ; 6-box: central,  $r = -0.35$ ,  $p < 0.05$ ; left hemisphere,  $r = -0.37$ ,  $p < 0.05$ ). These patterns indicate improved performance with greater brain activity while solving more difficult problems compared to less difficult problems. This pattern could be the result of lacking a ‘move’ condition for SWM problems. The outcomes from the SWM are not a direct comparison of activity related to solving the problems but also include the coordination of a motor response for the 4-box and 8-box problems. This pattern of brain activity could also be a reflection of the different task demands for the SWM task compared to the mazes and the SOC task. The SWM task is a working memory task for which the use of a strategy can improve performance. One issue with the task is that high levels of performance can be attained through greater working memory capacity or through efficient strategy use. The differences in cortical activation could reflect that these participants were relying upon working memory capacity for the SWM task instead of strategy use. Placing greater demands on working memory capacity would likely increase the use of prefrontal cortical resources, and being able to use that capacity would result in better performance on more difficult SWM problems. Table 22 shows the correlations between 8-box and 4-box SWM cortical activation and SWM task performance.

There were few differences between 7- to 9-year-olds and 10- to 12-year-olds in brain activity across the contrasts that predicted task performance. Table 25 shows the t-test results for comparisons between age groups in the left, central, and right prefrontal cortex. In general, the 7- to 9-year-olds exhibited reduced brain activity when solving 3-move SOC problems compared to 10- to 12-year-olds. This result indicates that their processing of these problems was similar to their processing of the yolked ‘move’ condition. Reduced brain activity predicted worse performance on the SOC task, which is an indication that reduced brain activity during the simplest planning problems meant the children were not employing executive resources to solve the problems. The lack of use of executive resources produced poor performance. In the contrast between 5-move and 3-move SOC problems, the 10- to 12-year-olds had larger negative numbers indicating increased brain activity when solving 3-move SOC problems instead of 5-move SOC problems compared to 7- to 9-year-olds (although insignificant). This pattern was

associated with better performance, indicating that the need to marshal additional resources to solve 5-move SOC problems was associated with worse performance. This pattern could exist because the task was very difficult across this age range, and those who were able to succeed at the task were able to efficiently use executive resources. Those who were not successful did not even attempt to use appropriate resources, and the behavioral performance supports the idea that many younger children may have simply abandoned attempts at planning on the most difficult 5-move tasks.

The 6-step maze contrast indicated that 10- to 12-year-olds had reduced brain activity compared to 7- to 9-year-olds (significant in the left hemisphere and a trend in the right hemisphere), which was associated with worse performance. The 6-step mazes were so simple that older children likely did not need to use resources much beyond those needed to walk the correct maze. Decreased brain activity when solving the 6-step mazes was associated with worse performance, which does not match behavioral differences found between 7- to 9-year-olds and 10- to 12-year-olds. The brain activity comparing 8-step and 6-step mazes did not show a particular pattern of age group differences. The brain activity among 10- to 12-year-olds comparing 8-box to 4-box SWM problems was more positive than 7- to 9-year-olds. Greater brain activity when solving 8-box SWM problems compared to 4-box SWM problems was associated with improved performance.

### **The ratio and cortical activation.**

Multivariate regressions were run including the ratio, omega-3 intake, omega-6 intake, maternal education, and physical activity predicting cortical activation in the left, central, and right prefrontal cortex. Regressions were run for the entire sample (controlling for age) and for each age group. The ratio, omega-3 intake, and omega-6 intake were not significant predictors of any cortical activation for the entire sample. There was a variance inflation issue between omega-3 and omega-6 intake in 10- to 12-year-olds. Omega-3 and omega-6 intake were run separately for the analyses by age group. For 7- to 9-year-olds, the ratio and omega-3 intake predicted brain activity in the right prefrontal cortex when solving 3-move SOC problems. The ratio had a negative relation to brain activity, indicating that lower ratios predicted greater brain activity in the right prefrontal cortex when solving 3-move SOC problems (Table

24). Greater brain activity when solving 3-move SOC problems was associated with better SOC task performance, as was a lower ratio in 7- to 9-year-olds. Lower omega-3 intake predicted greater brain activity when solving 3-move SOC problems in the right prefrontal cortex, which was associated with better performance. This result matches the behavioral results in which the low ratio and low omega-3 group performed significantly better than all other groups on the 5-move SOC problems. In 10- to 12-year-olds, only the ratio predicted brain activity in the left prefrontal cortex when solving 3-move SOC problems when omega-6 intake was included (Table 25). Higher ratios predicted greater brain activity, which was associated with better performance. This finding follows the behavioral results in which higher ratios were beneficial to 10- to 12-year-olds. Lower ratios also predicted greater brain activity in the right prefrontal cortex (omega-3, Table 26, and omega-6, Table 27) and the left prefrontal cortex (Table 27, omega-6 included) when solving 5-move compared to 3-move SOC problems. Greater brain activity for this contrast was related to worse performance, as were lower ratios in 10- to 12-year-olds. Similar to the behavioral results, the 7- to 9-year-olds and 10- to 12-year-olds exhibited opposite patterns.

The brain activity when solving the EMT had similar patterns to the SOC task. Omega-6 intake predicted brain activity in the left prefrontal cortex for 6-step mazes. Greater omega-6 intake predicted increased brain activity in 7- to 9-year-olds (Table 28). Greater brain activity for 6-step mazes was associated with better performance. Omega-6 intake predicted brain activity when solving 8-step compared to 6-step mazes in the central prefrontal cortex in 10- to 12-year-olds (Table 29). Greater omega-6 intake predicted increased brain activity, which was associated with worse performance. There were no other associations between the ratio and cortical activation for the mazes, and there were no associations between the ratio and cortical activation during the SWM task.

### **The ratio and cortical activation during the working memory and inhibitory control manipulations of the EMT.**

Specific aim 4 was designed to test the role of the ratio when working memory demands and inhibitory control demands were systematically altered in the EMT. Unfortunately, the evidence thus far indicates that inhibitory control was not successfully manipulated in the EMT. Specific aim 4, therefore,



can't be fully addressed. However, multivariate regressions were run comparing the contrast in brain activity after the rule switch (the 2<sup>nd</sup> condition compared to the 1<sup>st</sup> condition). Omega-3 intake predicted brain activity after the rule switch in 7- to 9-year-olds across the prefrontal cortex (Table 30). Lower omega-3 intake predicted greater brain activity after the rule switch. In 10- to 12-year-olds, omega-3 intake (Table 31) and omega-6 intake (Table 32) predicted brain activity across the whole prefrontal cortex. Greater omega-3 intake and omega-6 intake predicted greater brain activity after the rule switch. The brain activity after the rule switch was not associated with performance on any mazes, which means these findings can't be linked to behavioral performance. It is unknown if increased brain activity after a rule switch would be related to improved performance on rule switch tasks.

As mentioned earlier, increased brain activity after the increase in the number of steps (the working memory manipulation), was associated with worse performance on the mazes. These findings indicate that balanced fatty acids may contribute to inhibitory control performance more than working memory performance on tasks that require flexible use of both abilities. Even without a successful manipulation, the effect of omega-6 and omega-3 fatty acids was seen across the prefrontal cortex for inhibitory control. It may be that the inhibitory control manipulation on the EMT was not difficult enough to elicit differences in behavioral performance but did require the recruitment of different cortical resources for success. The differences in cortical activation were found particularly for the older participants in this study. This, again, could have been the result of the lack of a successful manipulation. It could also be an indication that older participants were able to apply these additional resources to the task, and younger children did not recruit these additional resources. Behavioral performance was not significantly different, but the two age groups could have been solving the mazes in different ways. The magnitude of the brain activity in the prefrontal cortex may not be the important element of the use of inhibitory control for these planning tasks. It could be that timing (Schroeter et al, 2004) or functional connections to other brain areas (Diamond, 2000) are more important aspects of cortical activation that relate to inhibitory control performance. Table 33 shows a summary of the findings for the relation between the ratio, cortical activation, and behavioral performance.

### **Summary of the relation between the ratio, cortical activation, and behavioral performance.**

Overall, these findings suggest a role for the ratio, omega-3 intake, and omega-6 intake in brain activity related to EF task performance. The cortical activation associated with performance on the standardized SOC planning task exhibited a similar pattern to that seen in the behavioral results. In 7- to 9-year-olds, lower ratios predicted greater activity in the right prefrontal cortex when solving the 3-move SOC problems, which in turn was related to better performance through solving more problems in the minimum number of moves. Lower ratios were beneficial to 7- to 9-year-olds in solving the most difficult 5-move planning problems. In 10- to 12-year-olds, higher ratios predicted greater activity in the central prefrontal cortex when solving 3-move SOC problems, which in turn was related to better performance. The associations between fatty acid intake and brain activity during the EMT were not straightforward, and more investigations with this task are needed to understand why. Brain activity when solving 6-step mazes and when moving from 6-step to 8-step mazes did predict performance, but only omega-6 intake in 7- to 9-year-olds was related to any brain activity that was in turn related EMT performance. The associations between omega-6 and omega-3 intake and brain activity related to the rule switch deserve further inquiry.

## CHAPTER 4: DISCUSSION

In the present study, I addressed the role of the omega-6 to omega-3 fatty acid ratio in executive functions in children and older adults. The main objective was to address some gaps in the literature on fatty acids and executive functions and to test a new task designed to allow systematic alteration of planning task demands. The main findings included the importance of the ratio in cognitive function in both children and older adults. The role of the ratio differed with age and with task demands. In children developing executive function skills, the ratio significantly predicted planning task performance on the most difficult planning tasks. In older adults whose executive function capacities are declining, the ratio significantly predicted increasingly simpler tasks across age (from difficult working memory tasks to simpler working memory and memory tasks). This pattern indicates that the balance of fatty acids is important to tasks that require executive capacity to be successful. The optimal balance was also different for different age groups with younger children performing best with balanced omega-6 and omega-3 intake (low ratio/low omega-3 intake), and older children performing best with an imbalanced omega-6 and omega-3 intake (high ratio/low omega-3 intake). A similar pattern was found among older adults with the oldest age group (75- to 79-year-olds) performing best with balanced fatty acid intake, and the youngest age group (65- to 69-year-olds) performing best with imbalanced fatty acid intake.

The present study adds to the literature on fatty acids and cognitive function in a few ways. First, the present study lends support to the notion that the dearth of findings of an effect of omega-3 fatty acid supplementation could be explained by lack of consideration of the ratio. Not only was the ratio often a predictor of behavioral performance and cortical activation, but omega-3 intake predicted both behavioral performance and cortical activation in the presence of the ratio and sometimes in interaction with it. In animal studies, the findings of beneficial effects of omega-3 supplementation often came from groups with extremely discrepant ratios (Aid et al., 2003; Delion et al., 1994; Zimmer et al., 2000). Human work

was not able to create such stark differences and often failed to find a direct effect of omega-3 fatty acids (Cheatham & Colombo, 2006). The underlying ratio likely confounded the animal results and masked effects that could have been found in the human work. The present study demonstrated that more omega-3 fatty acids are not always beneficial, and some groups performed best with reduced intake of omega-3 fatty acids (7- to 9-year-olds). Supplementing to a very low ratio by unbalancing fatty acid intake through the addition of more omega-3 fatty acids may actually produce worse performance. Ikemoto et al. (2001) found similar effects on monoamine transmission in the two unbalanced groups (ratio below 1 and ratio above 300). The present study supports the idea that the balance of fatty acids is relevant in both children and older adults.

Second, the present study adds some potential developmental considerations. The 7- to 9-year-olds and 10- to 12-year-old exhibited almost opposite effects of the ratio on executive functions. Across this time, children improve in their inhibitory control (Rubia et al., 2006; Schroeter et al., 2004), working memory (Conklin et al., 2007; Luciana et al., 2005), and planning (Luciana et al., 2009; Welsh et al., 1991) abilities. However, these changes reflect both a movement towards adult performance and brain activation and distinct differences (Schroeter et al., 2004; Tsujimoto, 2008). Some of these differences are related to pubertal changes in hormones and concomitant changes in brain structure and function. The present study did not measure puberty, and future studies need to address this developmental period. Omega-3 fatty acids have been found to increase neurite outgrowth and dendritic branching (Ahmad, Murthy, et al., 2002; Calderon & Kim, 2004) that is important during periods of brain growth. High omega-6 intake may inhibit the metabolism and use of omega-3 fatty acids that are important to brain growth. The 7- to 9-year-olds, whose brains are not undergoing the rapid growth associated with puberty, may require a balanced diet because both omega-6 and omega-3 fatty acids are important for neuronal communication (Delion et al., 1994; Fang et al., 2011; Kim et al., 2010). The support of neuronal communication may be more important for cognitive performance during this period. The 7- to 9-year-olds in the present study performed best with low ratios and low omega-3 intake, a diet in which both

omega-3 and omega-6 fatty acids are kept low, preventing one fatty acid family from overwhelming the metabolic pathway.

Conversely, the 10- to 12-year-olds benefited most from an imbalanced intake of omega-6 and omega-3 fatty acids. Children at these ages were more likely to have started puberty. Puberty brings with it changes in brain structure and function that could be best supported with a balance of omega-6 and omega-3 fatty acids that provides more omega-3 fatty acids. Omega-3 fatty acids support neurite growth in the frontal cortex and hippocampus (Calderon & Kim, 2004; Innis & De La Presa Owens, 2001), and DHA has been found to affect monoamine neurotransmission during puberty in rats (Weiser, Wynalda, Salem, & Butt, 2015). Monoamine neurotransmission has been shown to be affected by hormones (Epperson, Wisner, & Yamamoto, 1999; Rubinow, Schmidt, & Roca, 1998) and omega-6 and omega-3 fatty acids (Delion et al., 1994; Zimmer et al., 2000; Zimmer et al., 2002). In the present study, 10- to 12-year-olds performed significantly better with high omega-3 intake and a low ratio (indicating lower omega-6 intake). This finding is in line with the research in animals because higher omega-3 was important during puberty. This could be related to alterations in both monoamine function and brain growth that are supported by increased omega-3 fatty acid intake.

In the older adults, executive functions are declining. An imbalanced intake promoting more omega-3 fatty acids may support brain growth and monoamine function as it did in children going through puberty, but in older adults it would play a protective role. Increased neurite growth could protect against age-related declines in gray matter (Zimmerman et al., 2006), and improved monoamine function would improve communication between brain areas during complex tasks. There isn't any direct evidence as to why changes in the balance of omega-6 and omega-3 fatty acids may be beneficial across aging. However, some evidence from investigations of working memory performance and brain activity may provide a hypothesis worth further testing. Healthy aging is associated with increased brain activity in the prefrontal cortex and hippocampus during working memory tasks (Pudas et al., 2013) and improved performance and transfer of working memory skills (Borella et al., 2014), a pattern that is part of the compensation-related utilization of neural circuits hypothesis (CRUNCH, Schneider-Garces et al., 2010).

CRUNCH posits that older adults use more cortical resources than younger adults in order to perform at the same level. However, with the most difficult executive function tasks, the oldest older adults will often exhibit reduced cortical activation, very poor performance, and no ability to transfer learned skills. A reasonable hypothesis would be that during the process of normal aging, brain growth and communication can be supported by high omega-3 fatty acid intake in the youngest older adults when increased brain activity can compensate and produce similar performance to younger adults. However, in the oldest older adults, compensation does not occur as readily, and this change may result in the need for a different dietary balance of fatty acids.

Third, the present study supports the link between fatty acids, brain activity, and cognitive function. The ratio, omega-3 intake, and omega-6 intake predicted brain activity related to solving the simplest planning problems, related to increasing the difficulty of the planning problems, and related to increasing the working memory demands of the maze. In the case of the simplest planning problems, a lower ratio and greater omega-3 intake among 7- to 9-year-olds predicted increased brain activity in the right prefrontal cortex, which was in turn related to solving more SOC problems in the minimum number of moves. The bilateral prefrontal cortex is consistently found to be activated during planning tasks (Baker et al., 1996; Fincham et al., 2002; Morris et al., 1993; Ruocco et al., 2014; Tsujii et al., 2009). Tsujii et al. (2009) found right hemisphere dominance during working memory tasks in older children, with increased lateralization being linked to improved performance. Supporting right prefrontal cortex activity during planning tasks could indicate a role for fatty acids in supporting developing working memory skills that are key to planning success. In 10- to 12-year-olds, higher ratios were related to increased brain activity in the central prefrontal cortex when solving the simplest planning problems and decreased brain activity in the left and right prefrontal cortex when solving the most difficult planning problems compared to the simplest planning problems. Both of those patterns of brain activity were associated with solving more problems in the minimum number of moves. The older children in the present study were more likely to be approaching adult levels of performance on EF tasks. Efficiency increases in older children as they develop their EF skills, and this efficiency could be represented by

decreased prefrontal cortex activity required to solve the more difficult planning problems. Additionally, supporting bilateral prefrontal activity would indicate supporting more adult-like patterns of brain activity during planning tasks (Baker et al., 1996).

The difference in brain activity related to going from 3-move to 5-move SOC problems could be said to represent the brain activity related to thinking about the whole problem, or stepping “outside” the problem. The 3-move SOC problems were all perceptually supported, and all the 5-move SOC problems required making counterintuitive moves to solve the problems in the minimum number of moves. These counterintuitive moves are not only integral to planning (Kaller et al., 2008), they are likely supported by improved inhibitory control capacity due to the need to avoid making the perceptually supported (but incorrect) move. There is evidence that the younger children struggled considerably with the 5-move SOC problems and were not able to step outside the problem to make counterintuitive moves. However, the 10- to 12-year-olds were likely able to be successful on at least some of the problems requiring counterintuitive moves. The ratio supported brain activity related to these counterintuitive moves only in the older children, indicating that the ratio was likely also supporting inhibitory control skills. The change in the optimal ratio could also be related to developing the ability to step outside the problem. Inhibitory control typically recruits the bilateral prefrontal cortex (Hwang et al., 2010; Rubia et al., 2006) along with several non-prefrontal brain areas that are supported by different balances of omega-6 and omega-3 fatty acids. The development of these new skills with counterintuitive moves could signal a shift in the underlying nutritional needs.

The novel EMT task provided a new way to examine the ratio and planning performance among 7- to 12-year-olds. The success of the task at eliciting planning was supported by both the behavioral and neuroimaging results. The ratio predicted performance on the SOC task and the mazes similarly, and similar patterns of cortical activation supported better performance on both the SOC and maze tasks. The EMT offers a flexible task for measuring planning, and future research can capitalize on the findings here. First, more mazes can be used with 7- to 12-year-olds. The task was the unanimous favorite among participants, and all would have gladly participated in more than four mazes. More mazes would allow for

more testing of the manipulations used. Second, 8-step mazes were appropriately challenging to 7- to 12-year-olds, and 6-step mazes were too simple. This offers a benchmark for investigations with additional age groups. Third, the inhibitory control manipulation was too simple. In the future, I would propose either a three-dimensional task in which shape, color, and number varied among the squares (similar to the Wisconsin Card Sort task) or to use a Go/No-go design. In such a design, the presence of a specific symbol, say a blue fish, would tell the participant which game to play (the color game or the shape game). The symbol could then be switched such that the blue fish indicated the opposite game. This would be taxing because of the need to hold the rule about the symbol in mind. Instead of offering perceptual clues as to the correct path (the marked starting and ending squares), the participant would need to hold the correct rule in mind. This would still allow for control of working memory demands as the need to hold the correct rule in mind would be similar across all mazes. Stevens et al. (2009) found that Go/No-go tasks were still able to elicit differences in cortical activation between adolescents and adults.

Despite the overall promising use of the EMT, the ratio did not support any cortical activation related to performance on the EMT despite the ratio supporting behavioral performance. Only omega-6 and omega-3 intake were found to predict cortical activation related to EMT performance, and the most findings were for brain activity related to the inhibitory control manipulation that was not related to performance on any mazes. This difference between the SOC and EMT task may be related to the fact that the EMT was found to be simpler than the SOC planning task or could be due to the differences in response modality (touching a screen compared to walking) or overall task set-up (mazes compared to matching two patterns) between the planning tasks. Further research is needed, in particular by using mazes that match the difficulty of the SOC problems.

The EMT did provide some indication that inhibitory control manipulations would be worthwhile and possibly relate more strongly to the ratio. Inhibitory control requires flexible coordination between multiple brain areas. The balance of fatty acids would likely be important for that flexibility, and both omega-6 and omega-3 predicted brain activity after the rule switch among 10- to 12-year-olds in the present investigation. The omega-6 and omega-3 fatty acids had opposite effects with increased omega-3



fatty acids predicting decreased prefrontal activity and increased omega-6 fatty acids predicting increased prefrontal activity. This pattern is consistent with the generally opposite effects of omega-6 and omega-3 fatty acids in neuronal growth and communication (Calderon & Kim, 2004; Ikemoto et al., 1997; Novak, Dyer, & Innis, 2008). Given the specific importance of the ratio to counterintuitive moves in 10- to 12-year-olds, the relations between omega-6 and omega-3 fatty acids after the rule switch are similar to the relation between the ratio and brain activity related to counterintuitive moves. Greater omega-3 and reduced omega-6 intake would result in an imbalanced ratio and reduced overall activity after the rule switch. It is possible that the lack of difficulty masked any behavioral results, but that 10- to 12-year-olds still recruited inhibitory control resources to handle the rule switch.

There are several limitations that must be considered with any interpretation of the results of the present study. First, the dietary grouping strategy was not fully successful. This study was able to recruit a broader array of diets than the previous study on which it was based. This lends confidence in the results, especially because the findings with 7- to 9-year-olds replicated the previous study results. However, the small cell sizes hindered some analyses, especially as those cell sizes continued to shrink for NIRS analyses. Second, the inhibitory control manipulation on the EMT was not fully successful. This hindered the analyses of the EMT manipulations and made it more difficult to confirm our ability to control the underlying demands of the planning task. Third, NIRS is a new cortical imaging tool that offers many benefits. However, there is little consensus on how to analyze the data and what the oxy-Hb and deoxy-Hb measurements from NIRS mean across development. Often, NIRS data are compared to fMRI data as the closest analog, but even direct comparison studies find considerable differences, including the general conclusion that changes in deoxy-Hb measured by NIRS are difficult to interpret (Y. Moriguchi & Hiraki, 2013; Strangman et al., 2002). Finally, the current results are based on dietary measures of fatty acid intake. The blood analyses are ongoing, and it possible that the blood analyses will turn out quite differently from the diet analyses. Blood measurements are more accurate because they also reflect additional metabolic processing that occurs before nutrients reach the brain. A person who consumes a large quantity of omega-3 fatty acids but whose body does not efficiently metabolize fatty acids may have

similar blood levels of omega-3 fatty acids as a person who consumes less omega-3 fatty acids but more efficiently metabolizes those fatty acids.

The present study also had several strengths worth mentioning. First, recruiting participants with the goal of finding a variety of diets was a good goal that should be used in research focused on diet and cognitive performance. A person's diet is also a reflection of cultural practices, education about nutrition, and socioeconomic status. Sampling for diverse diets also helps create an overall diverse sample. Second, the EMT was a strength because it was a novel task that allowed for systematic control of task demands. The EMT was validated against standardized measures, and the basic task allows for a variety of manipulations. This task will likely be useful in longitudinal investigations because the fundamental task can remain the same while creating developmentally appropriate manipulations. Finally, the NIRS data collected as part of this study offers a rich database from which additional hypotheses related to nutrition and executive function could be explored. The analyses presented here represent the use of straightforward analysis tools designed for NIRS data analysis. New papers presenting new approaches to NIRS data are being published quickly, and these new approaches can be explored to help understand the link between fatty acids, brain function, and cognitive function.

## **Conclusions**

The present study adds to our understanding of the ratio and executive function in children and older adults. The pattern of findings indicate a clear need for developmentally informed longitudinal investigations of the role of the ratio in executive function development. The age of the participant and the function of interest were relevant to the role of balanced omega-3 and omega-6 intake. The maze offers a promising new task for future investigations, and more work with more age ranges and different manipulations could be fruitful. The present study supports many ideas in the fatty acid literature that have been not been directly investigated before, and at an absolute minimum, researchers need to keep the underlying balance of omega-3 and omega-6 fatty acids in mind when designing future investigations. The omega-6 to omega-3 fatty acid ratio supports executive functions in 7- to 12-year-olds and 65- to 79-year-olds. Executive functions require flexible use of multiple brain areas, and complex functions such as

planning require the flexible use of underlying executive functions. The ratio, as a measure of balance, supports this flexible use differently across development, and work stemming from the present study can further elucidate how diet can support optimal cognitive function at all ages.

# TABLES

Table 1.

*Descriptive statistics for a) 7- to 12-year-olds and b) 65- to 79-year-olds.*

<b>a) 7- to 12-year-olds</b>	<b>Entire sample Mean (SD) or Freq. (N)</b>	<b>7- to 9-year-olds Mean (SD) or Freq. (N)</b>	<b>10- to 12-year-olds Mean (SD) or Freq. (N)</b>	
N	78	41	37	
Age (years)	9.5 (1.63)	8.1 (.78)	10.97 (.75)	
Female	51.28% (40)	52.5% (21)	50% (19)	
Percent breast-fed	65.29 (40.38)	61.73 (42.29)	69.05 (38.48)	
All formula fed	18.42% (14)	20.51% (8)	16.22% (6)	
All breast-fed	46.05% (35)	43.59% (17)	48.65% (18)	
Ethnicity				
Hispanic/Latino	9.33% (7)	7.89% (3)	10.81% (4)	
Not Hispanic/Latino	90.67% (68)	92.11% (35)	89.19% (33)	
Race				
Caucasian	91.89% (68)	86.84% (33)	97.22% (35)	
African American	4.05% (3)	7.89% (3)	0%	
American Indian/Alaska Native	1.35% (1)	2.63% (1)	0%	
Asian	2.7% (2)	2.63% (1)	2.78% (1)	
Income				
0 to 29,999	6.85% (5)	5.13% (2)	8.82% (3)	
30,000 to 59,999	20.55% (15)	23.08% (9)	17.65% (6)	
60,000 to 89,999	30.14% (22)	23.08% (9)	38.24% (13)	
90,000 to 119,999	23.29% (17)	25.64% (10)	20.59% (7)	
120,000 +	19.18% (14)	23.08% (9)	14.71% (5)	
Maternal Education				
Less than high school diploma	1.33% (1)	0%	2.78% (1)	
High school diploma	21.33% (16)	23.08% (9)	19.44% (7)	
Associates Degree/Some college	10.67% (8)	12.82% (5)	8.33% (3)	
College degree	42.67% (32)	43.59% (17)	41.67% (15)	
Masters	22.67% (17)	20.51% (8)	25% (9)	
Doctorate/Professional Degree	1.33% (1)	0%	2.78% (1)	
Physical Activity (C-PAQ)				
Vigorous Activity (min)	336.16 (262.36)	306.28 (243.57)	370.44 (282.14)	
Moderate Activity (min)	664.19 (463.05)	685.64 (447.64)	640.96 (484.48)	
Light activity (min)	81.47 (102.66)	75.9 (103.71)	87.5 (102.63)	
Sedentary Time (min)	2721.33 (1437.91)	2624.36 (1365.51)	2826.39 (1524.85)	
<b>b) 65- to 79-year-olds</b>	<b>Entire sample Mean (SD) or Freq. (N)</b>	<b>65- to 69-year-olds Mean (SD or Freq. (N)</b>	<b>70- to 74- year-olds Mean (SD or Freq. (N)</b>	<b>75- to 79-year- olds Mean (SD) or Freq. (N)</b>
N	88	31	32	25
Age (years)	72.18 (4.17)	67.5 (1.42)	72.67 (1.31)	77.35 (1.34)
Female	60.23% (53)	64.52% (20)	62.5% (20)	52% (13)
Ethnicity				

Hispanic/Latino	0%	0%	0%	0%
Not Hispanic/Latino	100%	100%	100%	100%
Race				
Caucasian	96.59% (85)	96.77% (30)	96.88% (31)	96% (24)
African American	2.27% (2)	3.23% (1)	3.13% (1)	0%
American Indian/Alaska Native	1.14% (1)	0%	0%	4% (1)
Current Occupation				
Retired	83.12% (64)	77.78% (21)	89.29% (25)	81.82% (18)
Homemaker	1.2% (1)	0%	3.57% (1)	0%
Office/Food Service/Retail	6.49% (5)	7.41% (2)	3.57% (1)	9.09% (2)
Skilled Trade/Technical	2.6% (2)	0%	3.57% (1)	4.55% (1)
Nursing/Health Services	2.6% (2)	7.41% (2)	0%	0%
Professional/Managerial	3.9% (3)	7.41% (2)	0%	4.55% (1)
Pre-retirement Occupation				
Office/Food Service/Retail	20.31% (13)	5% (1)	34.78% (8)	19.05% (4)
Skilled Trade/Technical	12.5% (8)	10% (2)	17.39% (4)	9.52% (2)
Nursing/Health Services	9.38% (6)	15% (3)	13.04% (3)	0%
Professional/Managerial	39.06% (25)	45% (9)	21.74% (5)	52.38% (11)
Education				
Less than high school diploma	1.14% (1)	0%	0%	4% (1)
High school diploma	13.64% (12)	9.68% (3)	9.38% (3)	24% (6)
Associates Degree/Some college	45.45% (40)	35.48% (11)	53.13% (17)	48% (12)
College degree	18.18% (16)	19.35% (6)	25% (8)	8% (2)
Masters	18.18% (16)	29.03% (9)	9.38% (3)	16% (4)
Doctorate/Professional Degree	3.41% (3)	6.45% (2)	3.13% (1)	0%
Physical Activity (PASE)	147.9 (58.88)	153.01 (58.22)	144.84 (63.01)	145.48 (56.13)

Table 2.

*7- to 12-year-old participant recruitment strategy and final sample diet characteristics.*

Diet Group	Cutoffs	Sample Mean (SD)	Goal Recruitment	Actual Recruitment		
	Ratio / Omega-3	Ratio / Omega-3	Entire Sample	Entire Sample	7- to 9-year-olds	10- to 12-year-olds
High ratio/high omega-3	$\geq 10.43 / \geq 1.64$	11.59 (1.22) / 2.2 (0.34)	9	5	2	3
High ratio/mean omega-3	$\geq 10.43 / 1.1 - 1.64$	11.76 (1.17) / 1.37 (0.16)	9	12	6	6
High ratio/low omega-3	$\geq 10.43 / \leq 1.1$	13.83 (2.15) / 0.81 (0.16)	9	15	7	8
Mean ratio/high omega-3	$7.61 - 10.43 / \geq 1.64$	8.93 (0.71) / 2.07 (0.5)	9	8	6	2
Mean ratio/mean omega-3	$7.61 - 10.43 / 1.1 - 1.64$	9.13 (0.92) / 1.33 (0.12)	9	12	6	6
Mean ratio/low omega-3	$7.61 - 10.43 / \leq 1.1$	9.12 (1.00) / 0.87 (0.13)	9	6	4	2
Low ratio/high omega-3	$\leq 7.61 / \geq 1.64$	5.7 (1.95) / 2.51 (0.77)	9	12	5	7
Low ratio/mean omega-3	$\leq 7.61 / 1.1 - 1.64$	6.68 (0.63) / 1.24 (0.08)	9	4	2	2
Low ratio/high omega-3	$\leq 7.61 / \leq 1.1$	5.85 (0.79) / 0.93 (0.08)	9	4	2	2

Table 3.

*65- to 79-year-old final sample diet characteristics.*

Diet Group	Cutoffs	Sample Mean (SD)	N			
	Ratio/Omega-3	Ratio/Omega-3	Entire Sample	65- to 69-year-olds	70- to 74-year-olds	75- to 79-year-olds
High ratio/high omega-3	$\geq 8.44 / \geq 2.21$	9.68 (1.26) / 2.61 (0.4)	8	2	3	3
High ratio/mean omega-3	$\geq 8.44 / 1.67 - 2.21$	9.27 (0.87) / 1.89 (0.21)	5	2	2	1
High ratio/low omega-3	$\geq 8.44 / \leq 1.67$	11.46 (2.85) / 1.08 (0.33)	16	7	5	4
Mean ratio/high omega-3	$6.69 - 8.44 / \geq 2.21$	7.51 (0.52) / 3.22 (0.7)	11	4	3	4
Mean ratio/mean omega-3	$6.69 - 8.44 / 1.67 - 2.21$	7.62 (0.57) / 1.93 (0.16)	14	6	7	1
Mean ratio/low omega-3	$6.69 - 8.44 / \leq 1.67$	7.6 (0.68) / 1.24 (0.22)	6	2	1	3
Low ratio/high omega-3	$\leq 6.69 / \geq 2.21$	4.82 (1.11) / 2.96 (0.72)	11	2	7	2
Low ratio/mean omega-3	$\leq 6.69 / 1.67 - 2.21$	5.7 (0.72) / 1.93 (0.18)	10	2	4	4
Low ratio/low omega-3	$\leq 6.69 / \leq 1.67$	5.51 (0.71) / 1.21 (0.3)	7	4	0	3

Table 4.

*Cronbach's alphas for maze variables for the entire sample and by age group.*

	Entire Sample	7- to 9-year-olds	10- to 12-year-olds
All maze variables	0.92	0.89	0.83
6-step mazes	0.89	0.88	0.86
8-step mazes	0.88	0.88	0.87
1 <sup>st</sup> game	0.89	0.89	0.85
2 <sup>nd</sup> game	0.87	0.87	0.86
Difference scores	0.85	0.85	0.79



Table 5.

*Maze performance and independent samples t-test age group comparisons.*

<b>6-step Mazes</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	2.77 (2.76)	3.61 (3.07)	1.93 (2.14)**
Perseverative Errors <sup>#</sup>	0.33 (0.73)	0.43 (0.73)	0.22 (0.73)
Maze Errors <sup>#</sup>	0.08 (0.22)	0.11 (0.27)	0.06 (0.16)
Rule Errors <sup>#</sup>	0.65 (1.18)	1 (1.4)	0.29 (0.79)*
Latency to First Error <sup>^</sup>	10.07 (6.64)	11.47 (7.42)	8.58 (5.42)
Latency to Last Error <sup>^</sup>	29.23 (34.13)	39.48 (42.68)	18.38 (16.39)**
Percent Duration on Correct Path	58.87 (16.14)	58.89 (16.47)	58.85 (16.04)
<b>8-step Mazes</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	5.06 (3.69)	6.54 (4.25)	3.57 (2.24)**
Perseverative Errors <sup>#</sup>	1.03 (1.46)	1.47 (1.72)	0.6 (1)*
Maze Errors <sup>#</sup>	0.13 (0.35)	0.21 (0.47)	0.04 (0.14)*
Rule Errors <sup>#</sup>	0.98 (1.91)	1.6 (2.42)	0.36 (0.87)**
Latency to First Error <sup>^</sup>	10.56 (14.53)	12.68 (19.87)	8.44 (4.94) <sup>†</sup>
Latency to Last Error <sup>^</sup>	51.52 (45.05)	68.32 (50.74)	34.72 (31.02)**
Percent Duration on Correct Path	51.87 (12.2)	52.45 (11.69)	51.3 (12.82)
<b>First Game Mazes</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	4.2 (4.03)	5.58 (4.93)	2.82 (2.17)**
Perseverative Errors <sup>#</sup>	0.68 (1.22)	1.03 (1.52)	0.33 (0.67)*
Maze Errors <sup>#</sup>	0.15 (0.35)	0.22 (0.45)	0.07 (0.18) <sup>†</sup>
Rule Errors <sup>#</sup>	0.98 (2.01)	1.58 (2.53)	0.38 (1)*
Latency to First Error <sup>^</sup>	11.79 (15.15)	14.65 (20.37)	8.93 (5.82)
Latency to Last Error <sup>^</sup>	48.27 (49.25)	65.99 (61.46)	30.56 (22.3)**
Percent Duration on Correct Path	54.06 (13.44)	55.97 (11.93)	52.14 (14.71)
<b>Second Game Mazes</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	3.63 (2.71)	4.58 (3.08)	2.68 (1.88)**
Perseverative Errors <sup>#</sup>	0.68 (1.03)	0.88 (1.19)	0.49 (0.82)
Maze Errors <sup>#</sup>	0.06 (0.22)	0.1 (0.29)	0.03 (0.12)

Rule Errors <sup>#</sup>	0.65 (1.31)	1.01 (1.65)	0.28 (0.69)*
Latency to First Error <sup>^</sup>	8.74 (5.29)	9.82 (6.19)	7.67 (4) <sup>‡</sup>
Latency to Last Error <sup>^</sup>	39.82 (59.52)	51.57 (68.87)	28.07 (46.47) <sup>‡</sup>
Percent Duration on Correct Path	55.18 (14.21)	54.42 (15.64)	55.95 (12.79)

Note. <sup>#</sup> The percent of participant who made none of each type error for the entire sample, 7- to 9-year-olds, and 10- to 12-year-olds, respectively, were: Perseverative errors (6-step) = 77.78%, 69.44%, 86.11%, Maze errors (6-step) = 86.11%, 83.33%, 88.89%, Rule errors (6-step) = 62.5%, 44.44%, 80.56%, Perseverative errors (8-step) = 41.67%, 27.78%, 55.56%, Maze errors (8-step) = 84.72%, 77.78%, 91.67%, Rule errors (8-step) = 62.5%, 41.67%, 83.33%, Perseverative errors (1<sup>st</sup> game) = 51.39%, 36.11%, 66.67%, Maze errors (1<sup>st</sup> game) = 80.56%, 75%, 86.11%, Rule errors (1<sup>st</sup> game) = 58.33%, 36.11%, 80.56%, Perseverative errors (2<sup>nd</sup> game) = 52.78%, 44.44%, 61.11%, Maze errors (2<sup>nd</sup> game) = 90.28%, 86.11%, 94.44%, Rule errors (2<sup>nd</sup> game) = 65.28%, 47.22%, 83.33%. <sup>^</sup>These latencies are to the first and last error of any type. <sup>‡</sup> $p < 0.1$ , \* $p < 0.05$ , \*\* $p < 0.01$  indicate significant differences between 7- to 9-year-olds and 10- to 12-year-olds.

Table 6.

*Performance after manipulations for the entire sample and by age group.*

<b>Working Memory Manipulation</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	2.28 (3.77)***	2.93 (4.31)**	1.64 (3.07)**
Perseverative Errors	0.71 (1.53)**	1.04 (1.66)**	0.38 (1.32) <sup>‡</sup>
Maze Errors	0.04 (0.3)	0.1 (0.37)	-0.01 (0.19)
Rule Errors	0.33 (1.85)	0.6 (2.44)	0.07 (0.92)
Latency to First Error <sup>^</sup>	0.57 (15.82)	1.21 (20.95)	-0.11 (7.53)
Latency to Last Error <sup>^</sup>	22.85 (50.68)**	28.84 (60.48)*	16.51 (37.54)*
Percent Duration on Correct Path	-7 (18.96)**	-6.45 (17.5)*	-7.55 (20.56)*
<b>Inhibitory Control Manipulation</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	-0.57 (4.35)	-1 (5.6)	-0.14 (2.57)
Perseverative Errors	0 (1.44)	-0.15 (1.8)	0.15 (0.96)
Maze Errors	-0.08 (0.29)*	-0.13 (0.37)*	-0.04 (0.18)
Rule Errors	-0.33 (2.19)	-0.57 (2.93)	-0.1 (1.02)
Latency to First Error <sup>^</sup>	-3.05 (15.66)	-4.84 (21.08)	-1.27 (6.82)
Latency to Last Error <sup>^</sup>	-8.46 (77.36)	-14.43 (96.39)	-2.49 (52.68)
Percent Duration on Correct Path	1.13 (17.36)	-1.54 (17.59)	3.8 (16.95)

Note. <sup>^</sup>These latencies are to the first and last error of any type. <sup>‡</sup> $p < 0.1$ , \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.0001$  indicates a significant difference between the 6-step and 8-step mazes (working memory manipulation) and the first condition and second condition (inhibitory control manipulation).

Table 7.

*Correlations between maze performance and standardized measures of executive functions.*

	SOC Mean Moves 5	SOC MST 5	SWM Btw Err 6	SWM Btw Err 8	PAL Total Err	PAL Mem Score	PAL Stage Cmp 1st	6-step Total Err	6-step Ltncy Last Err	6-step Persev Err	8-step Total Err	8-step Ltncy Last Err	8-step Persev Err	RS Total Err	RS Ltncy Last Err
SOC Solved Min Moves	-0.49***	-0.28*	-0.22τ	-0.23*	-0.15	0.16	0.03	-0.06	-0.11	-0.002	-0.36**	-0.35**	-0.35**	-0.01	0.04
SOC Mean Moves 5		0.37**	0.25*	0.22τ	-0.08	0.05	0.004	-0.01	0.13	-0.1	0.25*	0.3*	0.38**	0.07	0.09
SOC MST 5			0.06	0.06	0.11	-0.15	-0.11	0.23*	0.22τ	0.09	0.19	0.25*	0.24*	-0.2τ	-0.25*
SWM Btw Err 6				0.67***	0.22	-0.26*	-0.39**	0.24*	0.24*	0.21τ	0.23τ	0.23τ	0.21	-0.08	-0.11
SWM Btw Err 8					0.28*	-0.33*	-0.35*	0.22τ	0.28*	0.14	0.33**	0.31*	0.31*	-0.07	-0.1
PAL Total Err						-0.84***	-0.55***	0.24*	0.23τ	0.18	0.12	0.17	0.11	-0.06	-0.06
PAL Memory Score							0.77***	-0.41**	-0.34**	-0.33**	-0.21τ	-0.3*	-0.14	0.18	0.13
PAL Stages Comp 1st								-0.35**	-0.24*	-0.27*	-0.24*	-0.28*	-0.18	0.26*	0.2
6-step Total Err									0.78***	0.85***	0.35*	0.28*	0.17	-0.45***	-0.29*
6-step Ltncy Last Err										0.62***	0.21τ	0.22τ	0.07	-0.22τ	-0.18
6-step Persev Err											0.26*	0.14	0.16	-0.42**	-0.2
8-step Total Err												0.8***	0.78***	-0.22τ	0.07
8-step Ltncy Last Err													0.59***	-0.14	0.11
8-step Persev Err														-0.19	0.06
RS Total Err															0.69***

Notes. SOC: Stockings of Cambridge; SWM: Spatial Working Memory; PAL: Paired Associates Learning; Btw: between; Ltncy: Latency; RS: Rule Switch; \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001; Solid outline for 6-step and PAL correlations, and dashed outline for 8-step and SOC and SWM correlations.

Table 8.

*Age group comparisons for CANTAB tasks for a) children and b) older adults.*

<b>a) Children</b>	Between Age Group			Within Age Group		
	B	SE	t-value	B	SE	t-value
PAL Stages Completed 1 <sup>st</sup> Try	0.93	0.24	3.84*	7- to 9-year-olds 10- to 12-year-olds	0.03 0.01	0.02 0.02 1.87τ 0.58
SOC Mean Moves (5-move)	-0.43	0.28	-1.54	7- to 9-year-olds 10- to 12-year-olds	-0.04 0.002	0.02 0.02 -2.14* 0.08
SWM Total Between Errors	-20.63	3.74	-5.52***	7- to 9-year-olds 10- to 12-year-olds	-0.58 -0.52	0.23 0.29 -2.55* -1.82τ
Errors (8-step)	-0.7	0.34	-2.02*	7- to 9-year-olds 10- to 12-year-olds	-0.02 -0.01	0.03 0.02 -0.72 -0.47
Perseverative Errors (8-step)	-0.88	0.33	-2.65*	7- to 9-year-olds 10- to 12-year-olds	-0.03 -0.01	0.03 0.02 -1.25 -0.74
Latency to Last Error (8-step)	-33.6	9.91	-3.39**	7- to 9-year-olds 10- to 12-year-olds	-0.27 0.09	0.83 0.55 -0.33 0.16
<b>b) Older Adults</b>	Between Age Group			Within Age Group		
	B	SE	t-value	B	SE	t-value
PAL Stages Completed 1 <sup>st</sup> Try	-0.37	0.14	-2.66**	65- to 69-year-olds 70- to 74-year-olds 75- to 79-year-olds	-0.01 0.01 -0.001	0.01 0.01 0.02 -0.68 1.1 -0.05
SWM Mean Time to First Response (8-box)	958.88	427.1	2.25*	65- to 69-year-olds 70- to 74-year-olds 75- to 79-year-olds	28.82 -31.37 60.89	26.93 20.21 61.7 1.07 -1.55 0.99
SWM Total Between Errors	6.44	2.31	2.79**	65- to 69-year-olds 70- to 74-year-olds 75- to 79-year-olds	-0.07 0.37 -0.04	0.21 0.17 0.2 -0.33 2.14* -0.21
RVP A'	-0.01	0.01	-1.03	65- to 69-year-olds 70- to 74-year-olds 75- to 79-year-olds	-0.0002 -0.0005 0.0002	0.0005 0.0004 0.0005 -0.48 -1.09 0.42
RVP B''	-0.02	0.01	-2.13*	65- to 69-year-olds 70- to 74-year-olds 75- to 79-year-olds	-0.001 -0.002 -0.001	0.001 0.001 0.001 -1.11 -1.42 -1.52

Notes. SOC = Stockings of Cambridge; SWM = Spatial Working Memory; PAL = Paired Associates Learning; RVP = Rapid Visual Processing. τ p < 0.1, \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001.

Table 9.

*Relation between the ratio, omega-6 intake, and omega-3 intake predicting total errors made on the PAL task in 75- to 79-year-olds.*

Omega-3 model	B	SE	t-value	VIF
Intercept	30.98	18.65	1.66	0
Ratio	1.07	2.41	0.44	1.4
Omega-3 intake (g)	-7.6	3.67	-2.07*	1.11
Education	2.96	2.35	1.26	1.14
Physical activity	-0.03	0.07	-0.49	1.36
Omega-6 model	B	SE	t-value	VIF
Intercept	15.73	17.85	0.88	0
Ratio	3.41	2.74	1.24	1.87
Omega-6 intake (g)	-1.06	0.47	-2.24*	1.39
Education	3.08	2.32	1.33	1.14
Physical activity	-0.04	0.07	0.51	1.41

Note. Omega-3 model: Adjusted  $R^2 = 0.04$ , overall model,  $F(4,19) = 1.21$ ,  $p > 0.05$ ; Omega-6 model: Adjusted  $R^2 = 0.07$ , overall model,  $F(4,19) = 1.41$ ,  $p > 0.05$ . SE = standard error, VIF = variance inflation factor, \* $p < 0.05$ .

Table 10.

*Relation between the ratio, omega-6 intake, and omega-3 intake predicting mean time to first response on 4-box SWM problems in 75- to 79-year-olds.*

Omega-3 model	B	SE	t-value	VIF
Intercept	5476.69	3065.82	1.79	0
Ratio	-944.33	389.76	-2.42*	1.38
Omega-3 intake (g)	409.38	614.4	0.67	1.12
Education	401.89	392.17	1.02	1.13
Physical activity	18.15	10.98	1.65	1.34
Omega-6 model	B	SE	t-value	VIF
Intercept	6124.7	3004.65	2.04	0
Ratio	-958.97	458.36	-2.09*	1.87
Omega-6 intake (g)	20.41	81.41	0.25	1.42
Education	442.54	396.54	1.12	1.14
Physical activity	17.28	11.29	1.53	1.39

Notes. Omega-3 model: Adjusted  $R^2 = 0.19$ , overall model  $F(4,20) = 2.38$ ,  $p > 0.05$ . Omega-6 model: Adjusted  $R^2 = 0.17$ , overall model  $F(4,20) = 2.25$ ,  $p > 0.05$ . SE = standard error; VIF = variance inflation factor. \* $p < 0.05$ .

Table 11.

*Interaction between the ratio and omega-3 intake predicting mean time to first response on SWM 4-box problems in 75- to 79-year-olds.*

	B	SE	t-value
Intercept	-14151	7075.45	-2.00
Ratio X Omega-3	-1312.72	440.83	-2.98*
Ratio	1905.58	1010.34	1.89
Omega-3 intake (g)	10283	3358.25	3.06*
Education	470.95	339.91	1.39
Physical activity	5.19	10.42	0.50

Notes. Adjusted  $R^2 = 0.41$ , overall model  $F(5,18) = 4.19$ ,  $p < 0.05$ . SE = standard error. \* $p < 0.05$ .



Table 12.

*Relation between the ratio, omega-6 intake, and omega-3 intake predicting mean time to first response on the 4-box SWM problems in 65- to 69-year-olds.*

Omega-3 model	B	SE	t-value	VIF
Intercept	376.01	1488.15	0.25	0
Ratio	46.92	87.17	0.54	1.08
Omega-3 intake (g)	827.8	299.51	2.76*	1.23
Education	106.12	154.7	0.69	1.04
Physical activity	-4.23	4.2	-1.01	1.21
Omega-6 model	B	SE	t-value	VIF
Intercept	1843.42	1270.37	1.45	0
Ratio	-85.72	96.33	-0.89	1.25
Omega-6 intake (g)	94.63	38.79	2.44*	1.28
Education	91.01	158.56	0.57	1.04
Physical activity	-5.47	4.19	-1.31	1.15

Notes. Adjusted  $R^2 = 0.2$ , overall model  $F(4,26) = 2.85$ ,  $p < 0.05$ . SE = standard error; VIF = variance inflation factor. \* $p < 0.05$ .

Table 13.

*Interaction between the ratio and omega-6 intake and the ratio and omega-3 intake predicting A' on the RVP task and total between errors on the SWM task in 65- to 69-year-olds.*

A'	B	SE	t-value
Intercept	0.98	0.07	13.83***
Ratio X Omega-6	0.001	0.0004	2.49*
Ratio	-0.02	0.01	-2.78*
Omega-6 intake (g)	-0.01	0.004	-1.89
Education	0.01	0.005	1.99
Physical activity	0.0002	0.0001	1.19
Between errors Omega-6	B	SE	t-value
Intercept	88.21	33.73	2.62*
Ratio X Omega-6	0.53	0.21	2.56*
Ratio	-7.89	3.81	-2.07*
Omega-6 intake (g)	-4.29	1.71	-2.51*
Education	1.74	2.38	0.73
Physical activity	0.03	0.06	0.43
Between errors Omega-3	B	SE	t-value
Intercept	138.01	46.64	2.96*
Ratio X Omega-3	8.95	3.27	2.74*
Ratio	-11.32	4.62	-2.45*
Omega-3 intake (g)	-73.32	25.87	-2.83*
Education	0.34	2.37	0.14
Physical activity	-0.03	0.07	-0.48

Notes. A' adjusted  $R^2 = 0.23$ , overall model  $F(5,25) = 2.76$ ,  $p < 0.05$ . Between errors Omega-6 adjusted  $R^2 = 0.11$ , overall model  $F(5,25) = 1.72$ ,  $p > 0.05$ . Between errors Omega-3 adjusted  $R^2 = 0.15$ , overall model  $F(5,25) = 2.03$ ,  $p > 0.05$ . SE = standard error. \* $p < 0.05$ , \*\*\* $p < 0.0001$ .

Table 14.

*Relation between the ratio, omega-3 intake, and omega-6 intake predicting mean moves on the 5-move SOC problems.*

Mean moves (5-move)	Sum of Squares	Mean Square	F-value
Ratio group	13.41	6.7	5.29*
Omega-3 group	4.53	2.27	1.79
Ratio X Omega-3	1.41	0.35	0.28
Age	3.42	3.42	2.69
Maternal education	0.35	0.35	0.27
Physical activity	0.44	0.44	0.35

Notes. Mean moves (5-move)  $R^2 = 0.24$ , overall model  $F(11,59) = 1.69$ ,  $p > 0.05$ .  $p < 0.05$ . \* $p < 0.05$

Table 15.

*Relation between the ratio and omega-3 intake predicting the mean moves on the 5-move SOC problems in 7- to 9-year-olds.*

Mean moves (5-move)	Sum of Squares	Mean Square	F-value
Ratio group	8.34	4.17	3.68*
Omega-3 group	5.97	2.98	2.63 $\tau$
Ratio X Omega-3	13.52	3.38	2.98*
Maternal education	1.15	1.15	1.01
Physical activity	0.65	0.65	0.58

Notes.  $R^2 = 0.49$ , overall model  $F(10,27) = 2.62$ ,  $p < 0.05$ . \* $p < 0.05$ ,  $\tau$   $p < 0.1$ .

Table 16.

*Relation between the ratio and omega-3 intake predicting mean moves on the 5-move SOC problems in 10- to 12-year-olds.*

	Sum of Squares	Mean Square	F-value
Ratio group	4.93	2.47	3.23 $\tau$
Omega-3 group	0.62	0.31	0.4
Ratio X Omega-3	11.15	2.79	3.66*
Maternal education	2.48	2.48	3.25 $\tau$
Physical activity	0.31	0.31	0.4

Notes.  $R^2 = 0.54$ , overall model  $F(10,20) = 2.55$ ,  $p > 0.05$ . \* $p < 0.05$ ,  $\tau$   $p < 0.1$ .

Table 17.

*Relation between the ratio and omega-3 intake predicting the latency to last error and errors made on 8-step mazes in 7- to 9-year-olds.*

Latency to last error	Sum of Squares	Mean Square	F-value
Ratio group	24179.64	12089.82	5.69*
Omega-3 group	4327.35	2163.68	1.02
Ratio X Omega-3	2259.55	564.89	0.27
Maternal education	1510.56	1510.56	0.71
Physical activity	6795.09	6795.09	3.2 $\tau$
Errors made	Sum of Squares	Mean Square	F-value
Ratio group	19.26	9.63	4.47*
Omega-3 group	15.74	7.87	3.65*
Ratio X Omega-3	3.03	0.76	0.35
Maternal education	0.45	0.45	0.21
Physical activity	0.09	0.09	0.04

Notes. Latency to last error  $R^2 = 0.44$ , overall model  $F(10,23) = 1.84$ ,  $p > 0.05$ . Errors made  $R^2 = 0.44$ , overall model  $F(10,23) = 1.79$ ,  $p > 0.05$ . \* $p < 0.05$ ,  $\tau p < 0.1$ .

Table 18.

*Summary of findings for the role of the ratio in EF.*

Older Adults			Children		
Entire Sample	No significant findings		Entire Sample	SOC Mean Moves (5-move)	Ratio
65- to 69-year-olds	SWM Total Between Errors	Omega-3 X Ratio Interaction Omega-6 X Ratio Interaction	7- to 9-year-olds	SOC Mean Moves (5-move)	Ratio Omega-3 X Ratio Interaction
	RVP A'	Omega-6 X Ratio Interaction		Latency to Last Error (8-step)	Ratio
				Errors (8-step)	Ratio Omega-3
70- to 74-year-olds	No significant findings		10- to 12-year-olds	SOC Mean Moves (5-move)	Omega-3 X Ratio Interaction
75- to 79-year-olds	PAL total errors made	Omega-6 Omega-3			
	SWM Mean Time to First Response (4-box)	Ratio Omega-3 X Ratio Interaction			

Table 19.

*Event marking process for NIRS data collection.*

Task	Event Marker Number	Event Marker Description
Stockings of Cambridge	1	Used to mark likely planning time for 3-move SOC problems. The beginning of a problem and after each mistake were considered times the participant would step back to consider the problem.
	2	Used to mark likely planning time for 4-move SOC problems. The beginning of a problem and after each mistake were considered times the participant would step back to consider the problem.
	3	Used to mark the yolked follow condition. A '3' was marked each time the computer showed the move that needed to be copied to capture time spent planning the motor move and the movement itself.
	4	Used to mark likely planning time for 5-move SOC problems. The beginning of a problem and after each mistake were considered times the participant would step back to consider the problem.
Electric Maze Task*	1	Used to mark likely planning time for each maze. Beginning the maze, and starting again after each error were considered times the participant would step back to consider the problem.
	2	Used to mark the 'move' condition. Each participant walked the correct maze path and '2' was marked as they began to walk the path.
Spatial Working Memory	1	Used to mark likely planning or strategy time for 4-box SWM problems. The presentation of the box array and each time a token was found were considered times the participant would step back to consider strategy or update found tokens.
	2	Used to mark likely planning or strategy time for 6-box SWM problems. The presentation of the box array and each time a token was found were considered times the participant would step back to consider strategy or update found tokens.
	3	Used to mark likely planning or strategy time for 8-box SWM problems. The presentation of the box array and each time a token was found were considered times the participant would step back to consider strategy or update found tokens.

Notes. \*Each maze was its own NIRS file. The entire SOC task was its own NIRS file, and the entire SWM task was its own NIRS file.



Table 20.

*Correlations between SOC brain activity contrasts and SOC performance*

	SOC Minimum Moves	SOC Moves 3	SOC Moves 4	SOC Moves 5	SOC MIT 3	SOC MIT 4	SOC MIT 5	SOC MST 3	SOC MST 4	SOC MST 5
3-move left hemisphere	0.22	-0.07	-0.1	-0.09	-0.18	-0.05	-0.03	-0.01	0.07	-0.01
3-move central	0.34*	-0.04	-0.21	-0.14	0.04	-0.09	0.12	0.12	0.04	0.07
3-move right hemisphere	0.35*	0.04	-0.2	-0.11	-0.11	0.09	-0.07	0.07	-0.04	-0.09
5-move left hemisphere	-0.08	-0.02	0.15	0.12	-0.09	-0.08	0.16	-0.08	0.11	-0.03
5-move central	-0.11	0.07	0.18	0.07	0.03	-0.06	0.26 $\tau$	-0.05	0.22 $\tau$	0.05
5-move right hemisphere	-0.05	0.1	0.19	0.07	-0.01	0.11	0.21	-0.04	0.18	-0.02
5 vs 3 left hemisphere	-0.32*	0.06	0.24 $\tau$	0.23 $\tau$	-0.04	-0.04	0.22 $\tau$	-0.04	0.02	-0.02
5 vs 3 central	-0.41**	0.12	0.31*	0.2	-0.04	0.03	0.15	-0.1	0.18	-0.01
5 vs 3 right hemisphere	-0.43**	0.07	0.36*	0.21	0.07	0.03	0.29*	-0.06	0.24 $\tau$	0.09

Notes. SOC = Stockings of Cambridge; MIT = mean initial thinking time; MST = mean subsequent thinking time.  $\tau$   $p < 0.1$ , \*  $p < 0.05$ , \*\*  $p < 0.01$ .

Table 21.

*Correlations between 6-step and 8-step maze brain activity contrasts and 6-step and 8-step maze performance.*

	6-step Dur Corr Path	6-step Total Error	6-step Persev Error	6-step Rule Error	6-step Ltncy First Error	6-step Ltncy Last Error	8- step Dur Corr Path	8-step Total Error	8-step Persev Error	8-step Rule Error	8-step Ltncy First Error	8-step Ltncy Last Error
6-step left hem	-0.11	-0.12	-0.12	-0.2	-0.1	-0.13	-0.19	-0.2	-0.35*	-0.15	0.04	-0.2
6-step central	-0.19	-0.36*	-0.42*	-0.4*	-0.16	-0.35*	-0.02	-0.32 $\tau$	-0.35*	-0.43*	-0.03	-0.08
6-step right hem	-0.28 $\tau$	-0.33*	-0.32 $\tau$	-0.33*	-0.34*	-0.33*	-0.19	-0.32	-0.41*	-0.31 $\tau$	-0.02	-0.18
8-step left hem	-0.15	-0.06	-0.07	-0.11	-0.16	-0.07	-0.05	-0.06	-0.03	-0.14	-0.2	0.01
8-step central	-0.21	-0.19	-0.29 $\tau$	-0.25	-0.24	-0.28 $\tau$	-0.04	-0.09	-0.07	-0.16	-0.03	-0.04
8-step right hem	-0.04	0.002	-0.09	-0.08	-0.29 $\tau$	-0.09	-0.03	-0.06	0.03	-0.13	-0.0004	0.001
8 vs 6 left hem	-0.03	0.05	0.04	0.07	-0.07	0.04	0.13	0.13	0.25	0.03	-0.2	0.23
8 vs 6 central	-0.06	0.08	0.04	0.07	-0.11	-0.02	-0.03	0.17	0.21	0.21	0.03	0.07
8 vs 6 right hem	0.26	0.3 $\tau$	0.16	0.21	0.08	0.19	0.16	0.24	0.39*	0.13	0.06	0.27

Notes. Hem = hemisphere;  $\tau$   $p < 0.1$ , \*  $p < 0.05$ , \*\*  $p < 0.01$ .

Table 22.

*Correlations between SWM brain activity contrasts and SWM task performance.*

	SWM Total Between Errors	SWM MTFR 4	SWM MTFR 6	SWM MTFR 8
8 vs 4 left hemisphere	-0.49**	-0.2	-0.37*	-0.11
8 vs 4 central	-0.5**	-0.36*	-0.35*	-0.22
8 vs 4 right hemisphere	-0.47**	-0.22	-0.27 $\tau$	-0.1
8 vs 6 left hemisphere	-0.31*	-0.06	-0.19	0.06
8 vs 6 central	-0.25	-0.07	-0.05	0.08
8 vs 6 right hemisphere	-0.3*	-0.15	-0.16	0.07
6 vs 4 left hemisphere	-0.11	-0.12	-0.17	-0.16
6 vs 4 central	-0.15	-0.22	-0.28	-0.27
6 vs 4 right hemisphere	-0.1	-0.09	-0.12	-0.15

Notes. SWM = Spatial Working Memory; MTFR = mean time to first response.  $\tau$   $p < 0.1$ , \*  $p < 0.05$ , \*\*  $p < 0.01$ .

Table 23.

*Age group differences in brain activity across tasks.*

	SOC 3-move		SOC 5 vs 3		Maze 6-step		Maze 8 vs 6		SWM 8 vs 4	
	7- to 9- year- olds	10- to 12- year- olds	7- to 9- year- olds	10- to 12- year- olds	7- to 9- year- olds	10- to 12- year- olds	7- to 9- year- olds	10- to 12- year- olds	7- to 9- year- olds	10- to 12- year- olds
Left hemisphere	-0.85	0.16	-1.64	-2.08	-0.21	-3.25*	-1.06	0.97	-1.37	0.93
Central	-0.84	1.1	-0.66	-2.33	-0.51	-2.09	0.01	-0.51	-1.13	0.91
Right Hemisphere	-1.24	0.43	-0.4	-1.77	-1.06	-2.68 $\tau$	0.19	-0.26	-0.93	0.69

Notes. SOC = Stockings of Cambridge, SWM = Spatial Working Memory.  $\tau p < 0.05$ ,  $*p < 0.05$ .

Table 24.

*The ratio and omega-3 predicting 3-move SOC brain activity in the right prefrontal cortex in 7- to 9-year-olds.*

	B	S.E.	t-value	VIF
Intercept	-5.27	10.98	-0.48	0
Omega-6 to Omega-3 ratio	-0.73	0.33	-2.25*	1.96
Omega-3 intake (g)	-2.94	1.32	-2.22*	1.92
Maternal Education	1.09	0.58	1.88 $\tau$	1.22
Vigorous Activity	-0.01	0.004	-1.99 $\tau$	1.33

Notes. SOC = Stockings of Cambridge, \* $p < 0.05$ .

Table 25.

*The ratio and omega-6 predicting 3-move SOC brain activity in the left prefrontal cortex in 10- to 12-year-olds*

	B	S.E.	t-value	VIF
Intercept	-9.39	7.2	-1.3	0
Omega-6 to Omega-3 ratio	0.76	0.36	2.11*	1.14
Omega-6 intake (g)	-0.11	0.18	-0.6	1.08
Maternal Education	0.19	0.41	0.45	1.15
Vigorous Activity	0.0001	0.003	0.03	1.18

Notes. SOC = Stockings of Cambridge, \* $p < 0.05$ .

Table 26.

*The ratio and omega-3 predicting 5-move compared to 3-move SOC brain activity in the right prefrontal cortex in 10- to 12-year-olds.*

	B	S.E.	t-value	VIF
Intercept	10.71	8.03	1.33	0
Omega-6 to Omega-3 ratio	-0.81	0.36	-2.26*	1.2
Omega-3 intake (g)	-0.43	1.68	-0.26	1.19
Maternal Education	-0.25	0.4	-0.61	1.15
Vigorous Activity	0.0005	0.003	0.16	1.18

Notes. SOC = Stockings of Cambridge, \* $p < 0.05$ .

Table 27.

*The ratio and omega-6 predicting 5-move compared to 3-move SOC brain activity in the left and right prefrontal cortex in 10- to 12-year-olds.*

Left PFC	B	S.E.	t-value	VIF
Intercept	0.75	6.08	0.12	0
Omega-6 to Omega-3 ratio	-0.69	0.3	-2.27*	1.14
Omega-6 intake (g)	0.08	0.15	0.56	1.08
Maternal Education	0.23	0.35	0.65	1.15
Vigorous Activity	-0.001	0.003	-0.52	1.18
Right PFC	B	S.E.	t-value	VIF
Intercept	9.58	7.01	1.37	0
Omega-6 to Omega-3 ratio	-0.78	0.35	-2.23*	1.14
Omega-6 intake (g)	-0.001	0.17	-0.00	1.08
Maternal Education	-0.23	0.4	-0.58	1.15
Vigorous Activity	0.001	0.003	0.17	1.18

Notes. SOC = Stockings of Cambridge, \* $p < 0.05$ .



Table 28.

*The ratio and omega-6 predicting 6-step EMT brain activity in the left prefrontal cortex in 7- to 9-year-olds.*

	B	S.E.	t-value	VIF
Intercept	-0.98	8.61	-0.11	0
Omega-6 to Omega-3 ratio	-0.46	0.23	-2.00 $\tau$	1.15
Omega-6 intake (g)	0.46	0.21	2.24*	1.23
Maternal Education	-0.14	0.48	-0.3	1.31
Vigorous Activity	0.01	0.003	2.11 $\tau$	1.36

Notes.  $\tau$   $p < 0.1$ , \* $p < 0.05$ .

Table 29.

*The ratio and omega-6 predicting 8-step compared to 6-step EMT brain activity in the central prefrontal cortex in 10- to 12-year-olds*

	B	S.E.	t-value	VIF
Intercept	-0.28	7.29	-0.04	0
Omega-6 to omega-3 ratio	-0.1	0.32	-0.31	1.04
Omega-6 intake (g)	0.51	0.22	2.37*	1.1
Maternal Education	-0.37	0.34	-1.09	1.22
Vigorous Activity	0.002	0.002	0.86	1.2

Notes. \* $p < 0.05$ .

Table 30.

*The ratio and omega-3 predicting rule switch EMT brain activity in the left, central, and right prefrontal cortex in 7- to 9-year-olds.*

Left PFC	B	S.E.	t-value	VIF
Intercept	15.87	13.55	1.17	0
Omega-6 to Omega-3 ratio	-0.35	0.44	-0.8	2.02
Omega-3 intake (g)	-4.33	1.84	-2.36*	1.91
Maternal Education	-0.43	0.73	-0.6	1.3
Vigorous Activity	-0.003	0.005	-0.55	1.3
Right PFC	B	S.E.	t-value	VIF
Intercept	28.55	13.53	2.11	0
Omega-6 to Omega-3 ratio	-0.36	0.44	-0.82	2.02
Omega-3 intake (g)	-5.3	1.83	-2.89*	1.91
Maternal Education	-0.98	0.73	-1.34	1.3
Vigorous Activity	-0.01	0.005	-1.19	1.3
Central PFC	B	S.E.	t-value	VIF
Intercept	6.53	15.22	0.43	0
Omega-6 to Omega-3 ratio	-0.28	0.49	-0.57	2.02
Omega-3 intake (g)	-4.86	2.06	-2.36*	1.91
Maternal Education	0.29	0.82	0.36	1.3
Vigorous Activity	-0.01	0.01	-1.39	1.3

Notes. \* $p < 0.05$ .

Table 31.

*The ratio and omega-3 predicting rule switch EMT brain activity in the left, central, and right prefrontal cortex in 10- to 12-year-olds.*

Left PFC	B	S.E.	t-value	VIF
Intercept	-31.06	15.92	-1.95 $\tau$	0
Omega-6 to Omega-3 ratio	1.1	0.68	1.62	1.6
Omega-3 intake (g)	11.15	3.81	2.93*	1.72
Maternal Education	0.4	0.58	0.69	1.23
Vigorous Activity	-0.01	0.004	-1.14	1.22
Right PFC	B	S.E.	t-value	VIF
Intercept	-37.63	19.66	-1.91 $\tau$	0
Omega-6 to Omega-3 ratio	1.59	0.84	1.89 $\tau$	1.6
Omega-3 intake (g)	12.24	4.71	2.6*	1.72
Maternal Education	0.17	0.71	0.24	1.23
Vigorous Activity	0.001	0.01	0.23	1.22
Central PFC	B	S.E.	t-value	VIF
Intercept	-34.77	15.69	-2.22 $\tau$	0
Omega-6 to Omega-3 ratio	1.15	0.67	1.72	1.6
Omega-3 intake (g)	11.15	3.76	2.97*	1.72
Maternal Education	0.57	0.57	0.99	1.23
Vigorous Activity	-0.004	0.004	-0.87	1.22

Notes.  $\tau$   $p < 0.1$ , \* $p < 0.05$ .

Table 32.

*The ratio and omega-6 predicting rule switch EMT brain activity in the left, central, and right prefrontal cortex in 10- to 12-year-olds.*

Left PFC	B	S.E.	t-value	VIF
Intercept	-13.65	13.78	-0.99	0
Omega-6 to Omega-3 ratio	-0.22	0.6	-0.37	1.04
Omega-6 intake (g)	0.97	0.41	2.38*	1.1
Maternal Education	0.33	0.63	0.51	1.22
Vigorous Activity	-0.006	0.005	-1.2	1.2
Right PFC	B	S.E.	t-value	VIF
Intercept	-19.29	16.29	-1.18	0
Omega-6 to Omega-3 ratio	0.13	0.71	0.19	1.04
Omega-6 intake (g)	1.11	0.48	2.3*	1.1
Maternal Education	0.1	0.75	0.14	1.22
Vigorous Activity	0.0005	0.01	0.08	1.2
Central PFC	B	S.E.	t-value	VIF
Intercept	-17.6	13.49	-1.3	0
Omega-6 to Omega-3 ratio	-0.17	0.59	-0.29	1.04
Omega-6 intake (g)	0.98	0.4	2.46*	1.1
Maternal Education	0.5	0.62	0.8	1.22
Vigorous Activity	-0.005	0.005	-0.95	1.2

Notes. \* $p < 0.05$ .

Table 33.

*Summary of findings for the ratio, cortical activation, and behavioral performance.*

Task	Significant diet predictors	Significant cortical activation	Significant behavioral outcomes
SOC Task	Ratio (10-12) (+)	3-move central	Problems solved minimum number of moves (+)
	Ratio (7-9) (-)	3-move right	Problems solved minimum number of moves (+)
	Omega-3 (7-9) (-)		
	Ratio (10-12) (-)	5-move to 3-move left	Problems solved minimum number of moves (-)
		5-move to 3-move central	4-move Mean Moves (+)
			Problems solved minimum number of moves (-)
			4-move Mean Moves (+)
	Ratio (10-12) (-)	5-move to 3-move Right	Problems solved minimum number of moves (-)
			4-move Mean Moves (+)
			5-move Mean Initial Thinking Time (+)
EMT	Omega-6 (7-9) (+)	6-step left	8-step Perseverative Errors (-)
		6-step central	6-step Total Errors (-)
			6-step Perseverative Errors (-)
			6-step Rule Errors (-)
			6-step Latency to Last Error (-)
			8-step Perseverative Errors (-)
			8-step Rule Errors (-)
		6-step right	6-step Total Errors (-)
			6-step Rule Errors (-)
			6-step Latency to First Error (-)
			6-step Latency to Last Error (-)
			8-step Perseverative Errors (-)
	Omega-6 (10-12) (+)	8-step to 6-step central	
		8-step to 6-step right	8-step Perseverative Errors (+)
		Rule switch left	
	Omega-3 (7-9, 10-12) (-)		
	Omega-6 (10-12) (+)		
	Omega-3 (7-9, 10-12) (-)	Rule switch central	
	Omega-6 (10-12) (+)		
	Omega-3 (7-9, 10-12) (-)	Rule switch right	
	Omega-6 (10-12) (+)		
SWM		8-box to 4-box left	Total Between Errors (-)
			6-box Mean Time to First Response (-)
		8-box to 4-box central	Total Between Errors (-)
			4-box Mean Time to First Response (-)
			6-box Mean Time to First Response (-)
		8-box to 4-box right	Total Between Errors (-)
		8-box to 6-box left	Total Between Errors (-)
		8-box to 4-box right	Total Between Errors (-)

Notes. The ratio was tested as a predictor of cortical activation separately from the relation between cortical activation and behavioral performance. For instance, in the first row, the ratio was found to be negatively associated with brain activity during 3-move SOC problems in the central prefrontal cortex. The central prefrontal cortex activity was found to be positively related to the number of problems solved in the minimum number of moves. (-) indicates a negative relation between the variables, (+) indicates a positive relation between the variables.

## FIGURES

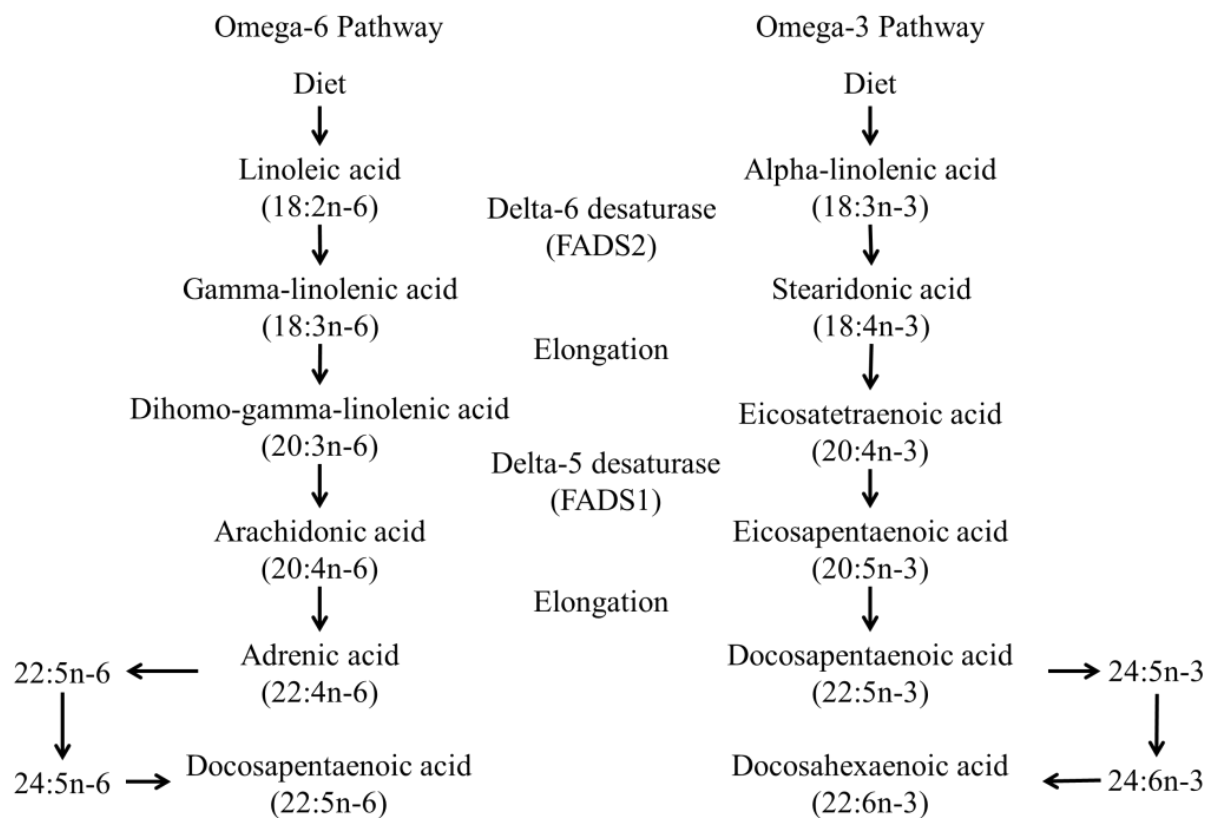


Figure 1. The omega-6 and omega-3 fatty acid metabolic pathway.

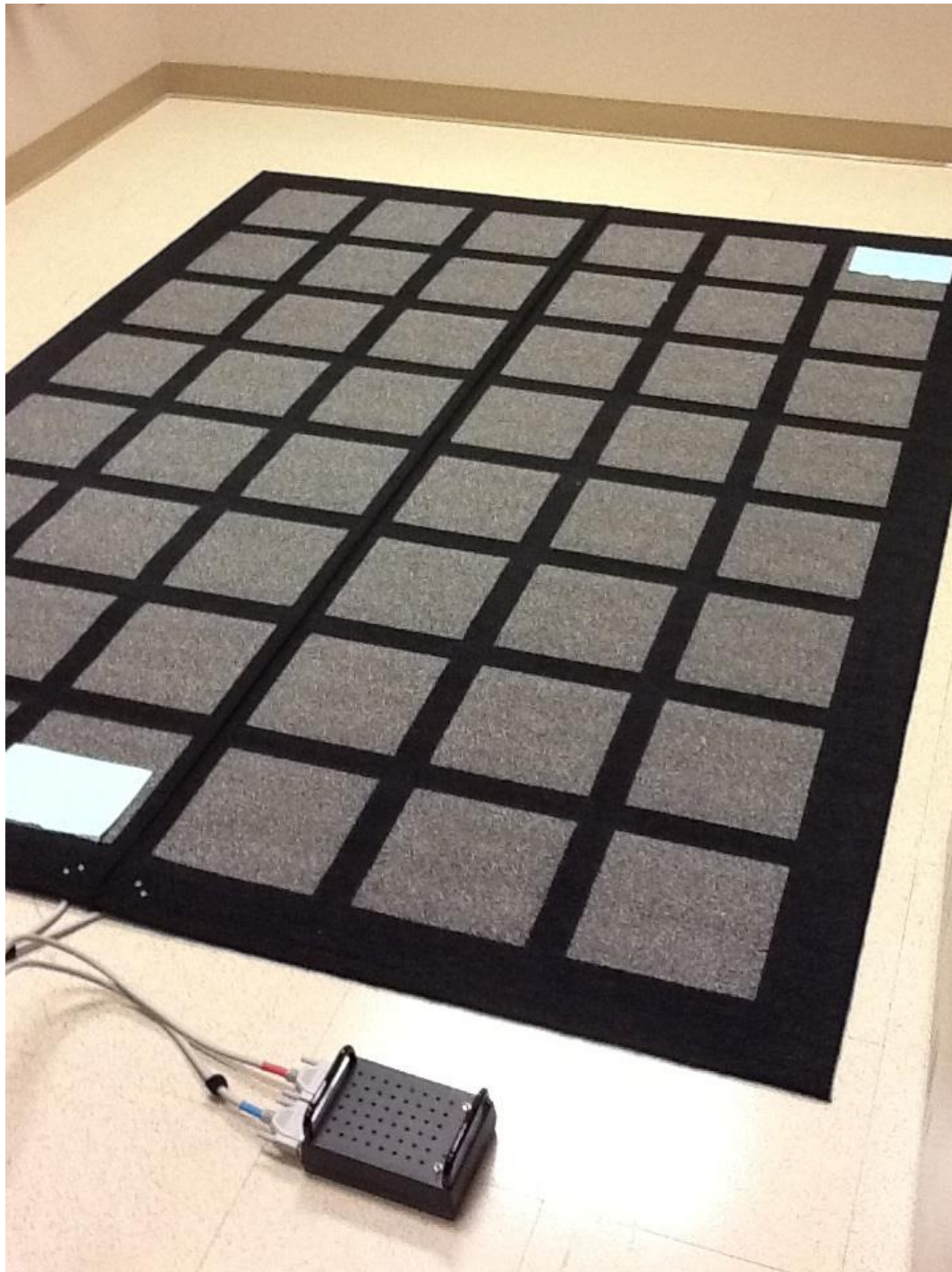


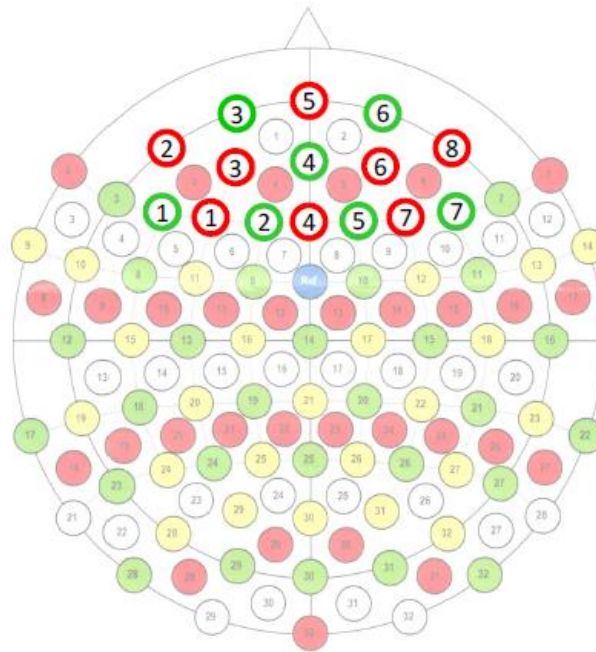
Figure 2. The electric maze.





Figure 3. The dimensional change card sort manipulation of the electric maze.

- ① Source No. 1, etc...
- ② Detector No. 1, etc...



a)

b)

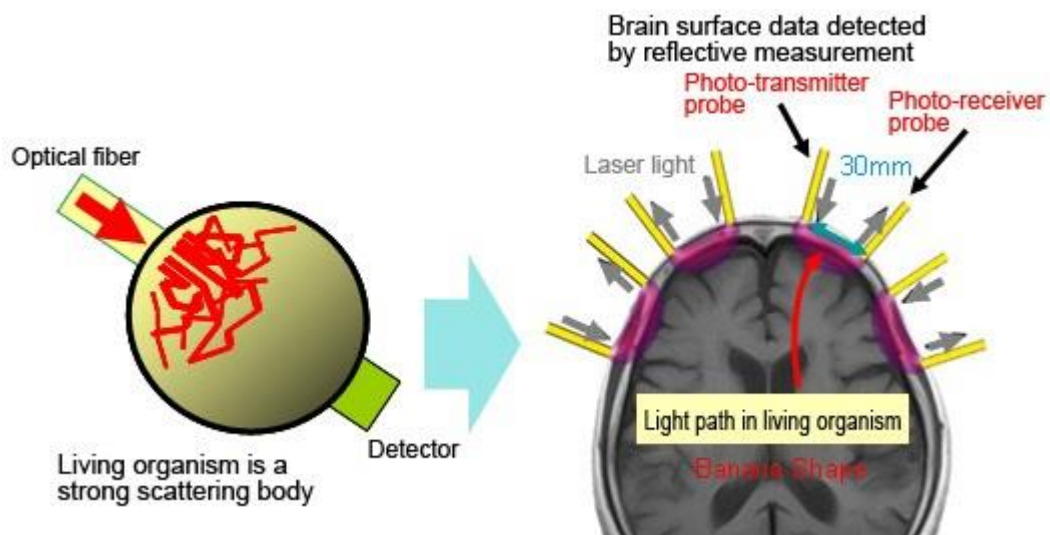


Figure 4. a) Standard prefrontal cortex array for near-infrared spectroscopy (NIRS) data collection and backpack set up; b) Graphical depiction of the basic premise of NIRS data collection.

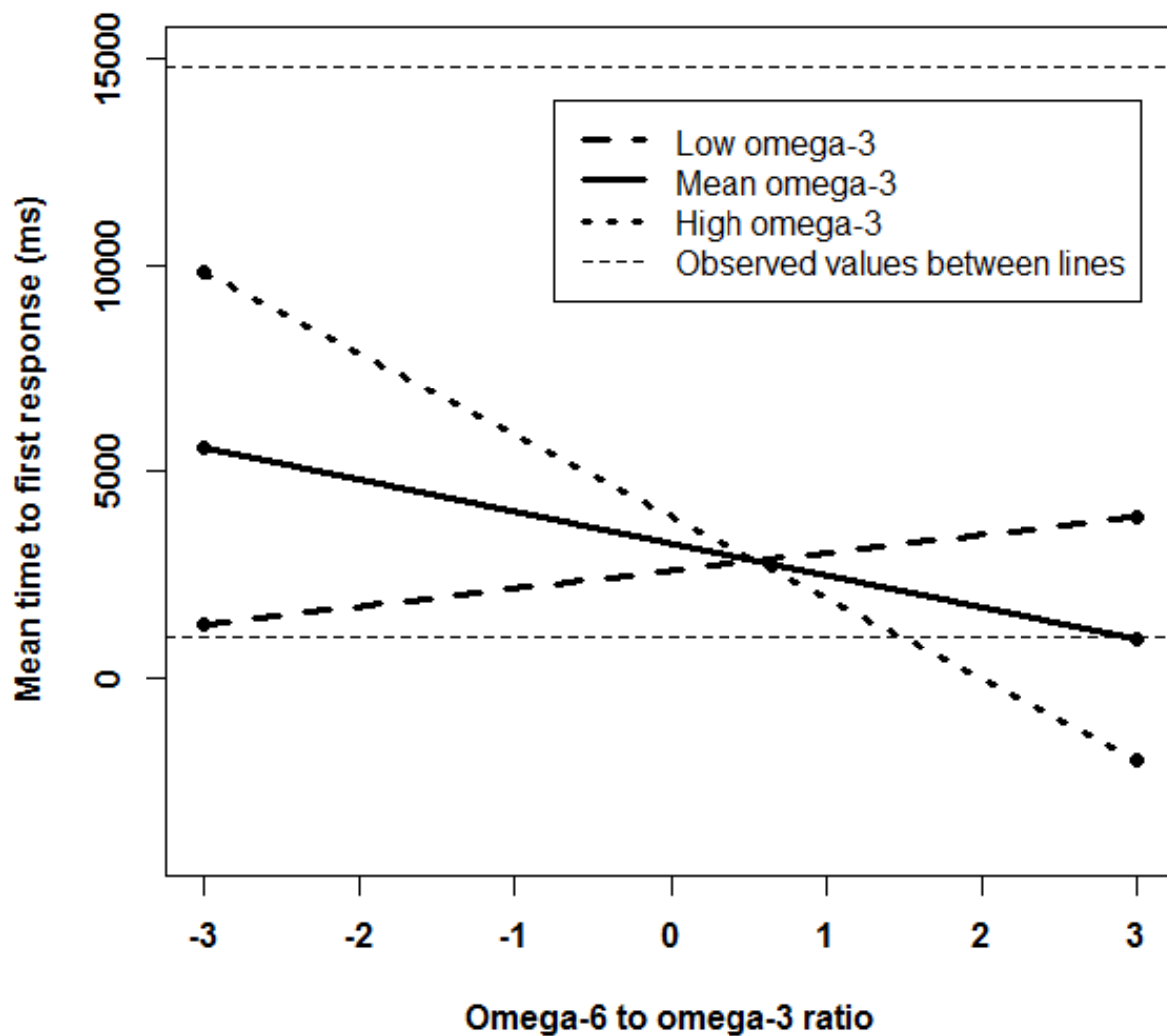


Figure 5. Simple slopes graph of significant interaction between the omega-6 to omega-3 ratio and omega-3 intake predicting mean time to first response on the 4-box SWM problems in 75- to 79-year-olds. The high omega-3 intake (n=6) slope is significant, the mean omega-3 intake (n=15) slope is a trend, and the low omega-3 intake (n=4) slope is not significant.

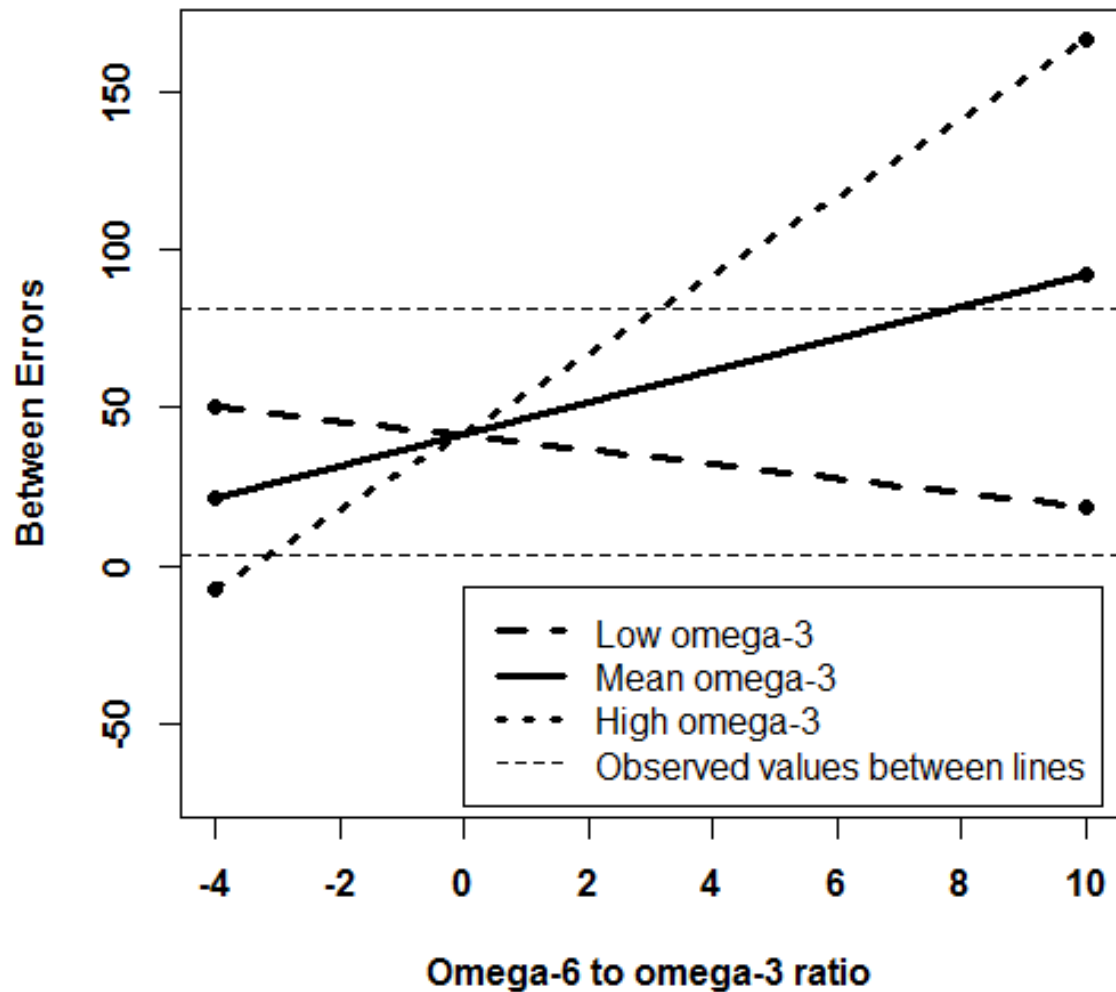


Figure 6. Simple slopes graph of the significant interaction between the omega-6 to omega-3 ratio and omega-3 intake predicting total between errors on the SWM task in 65- to 69-year-olds. The high omega-3 intake (n=4) slope is significant, the mean omega-3 intake (n=26) slope is significant, and the low omega-3 intake (n=2) slope is not significant.

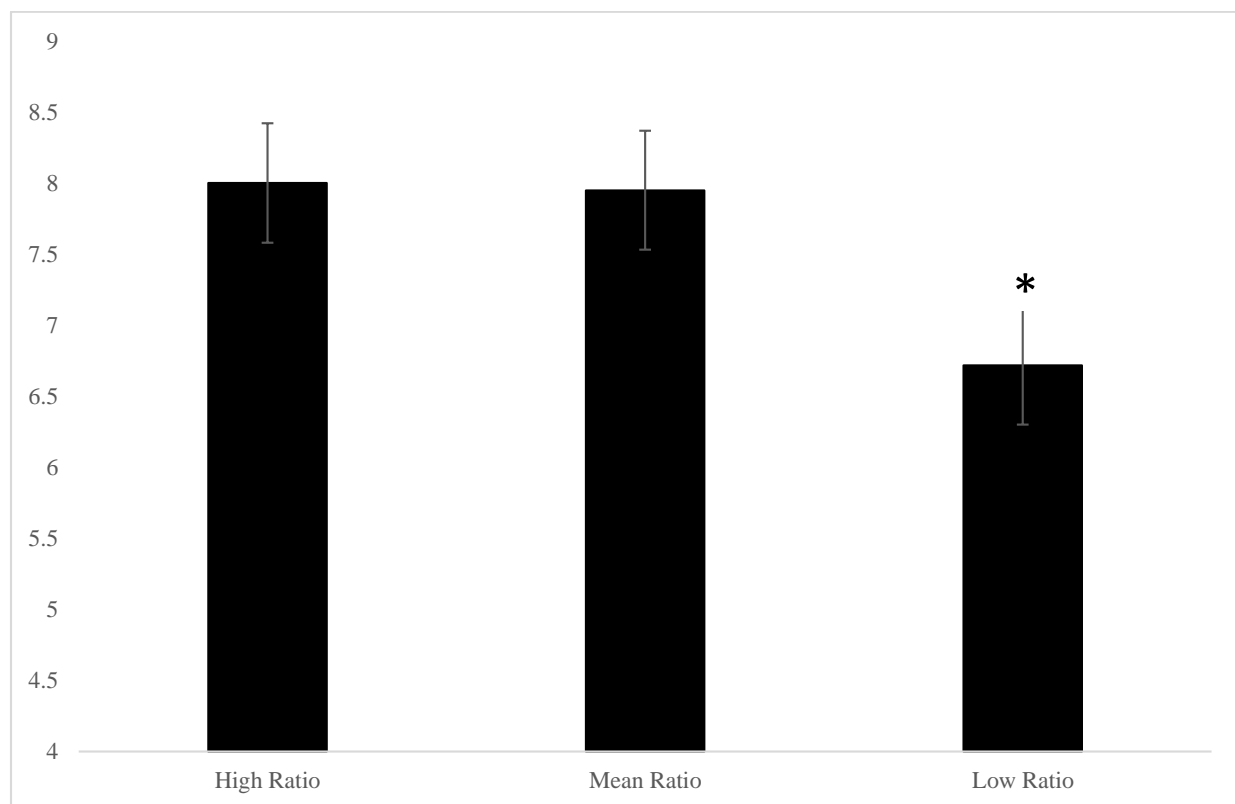


Figure 7. The omega-6 to omega-3 ratio predicting mean moves on the 5-move SOC problems in 7- to 12-year-olds. \* $p < 0.05$ , the low ratio group made significantly fewer moves than the high and mean ratio groups.

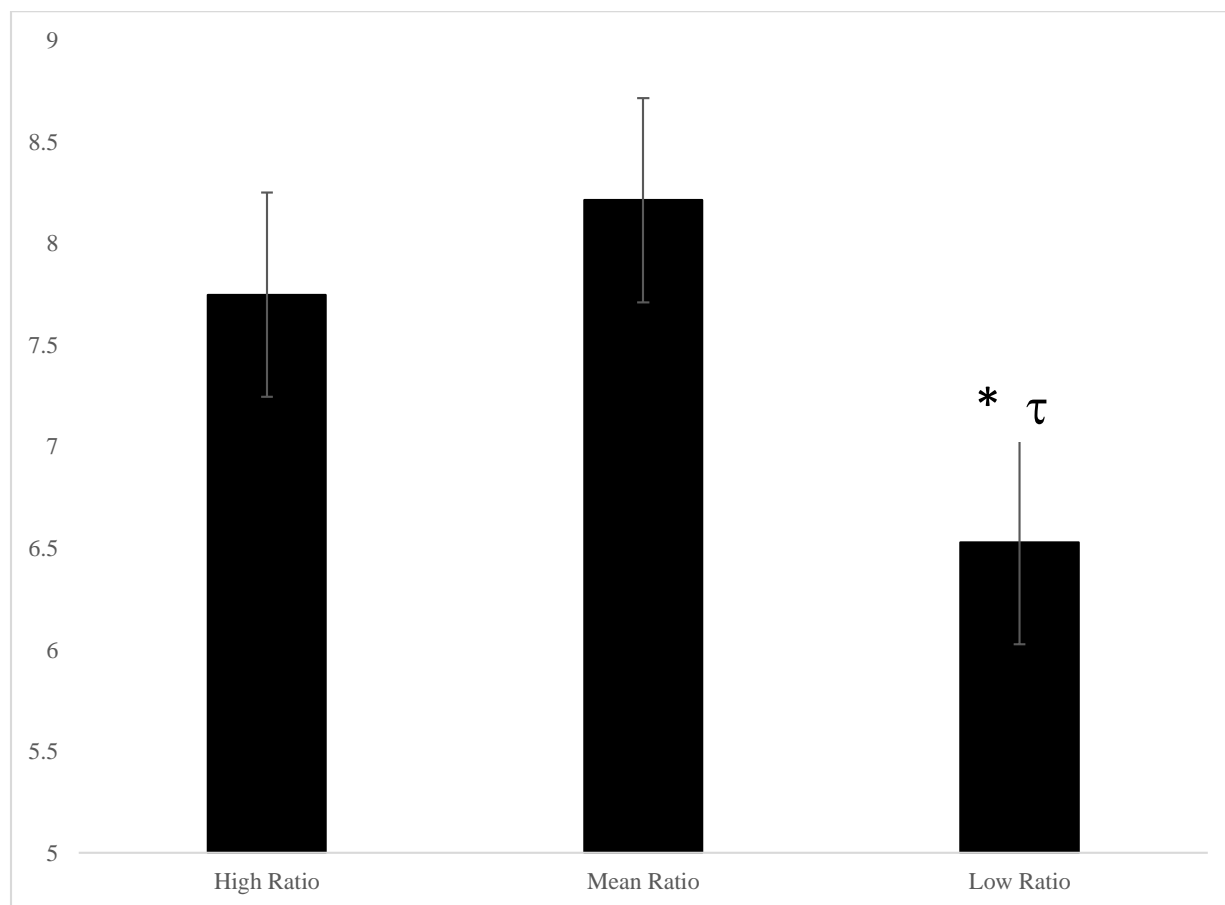


Figure 8. The omega-6 to omega-3 ratio predicting mean moves on the 5-move SOC problems in 7- to 9-year-olds, \*  $p < 0.05$ ,  $\tau p < 0.1$ , the low ratio group made significantly fewer moves than the mean ratio group and tended to make fewer moves than the high ratio group.

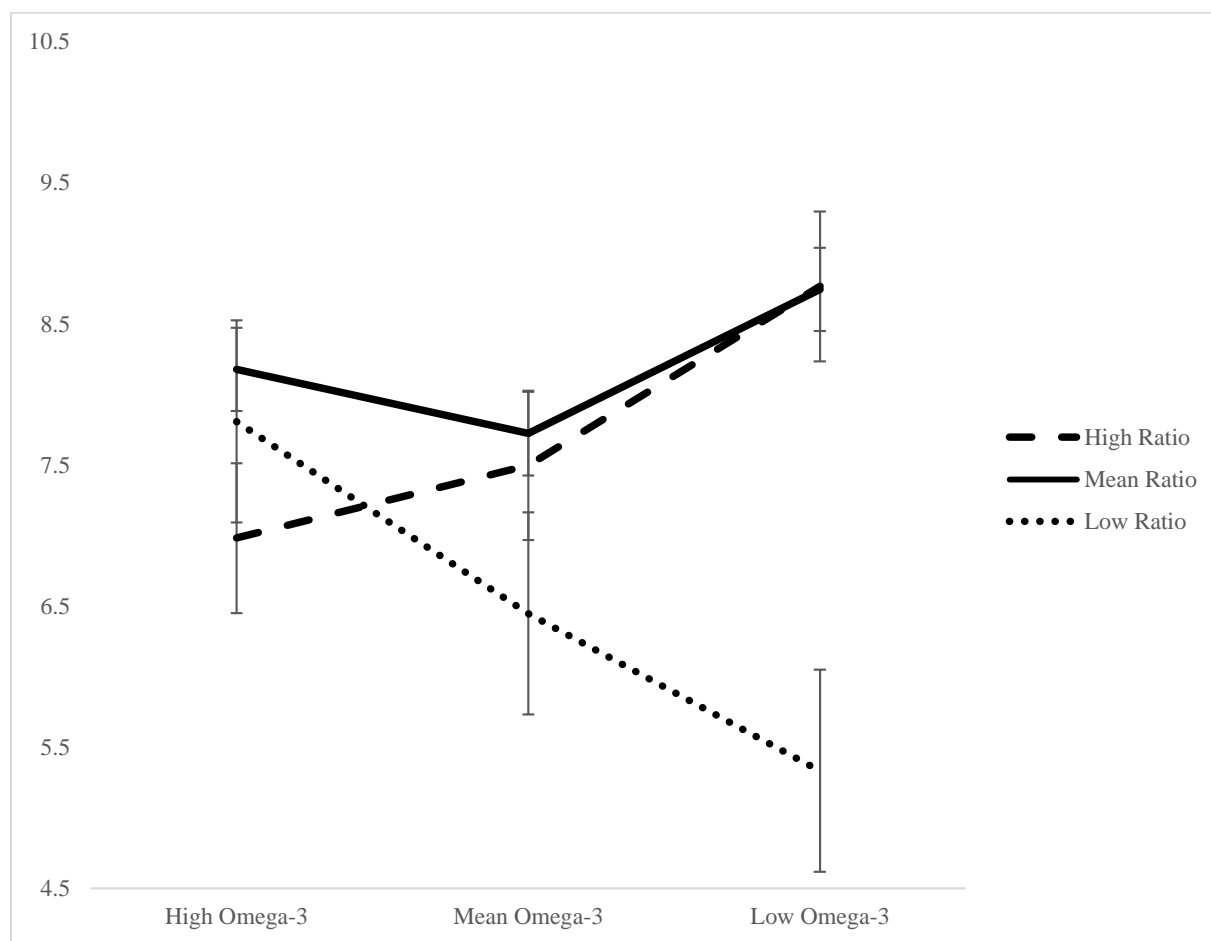


Figure 9. Interaction between the ratio and omega-3 intake predicting mean moves on the 5-move SOC problems in 7- to 9-year-olds.

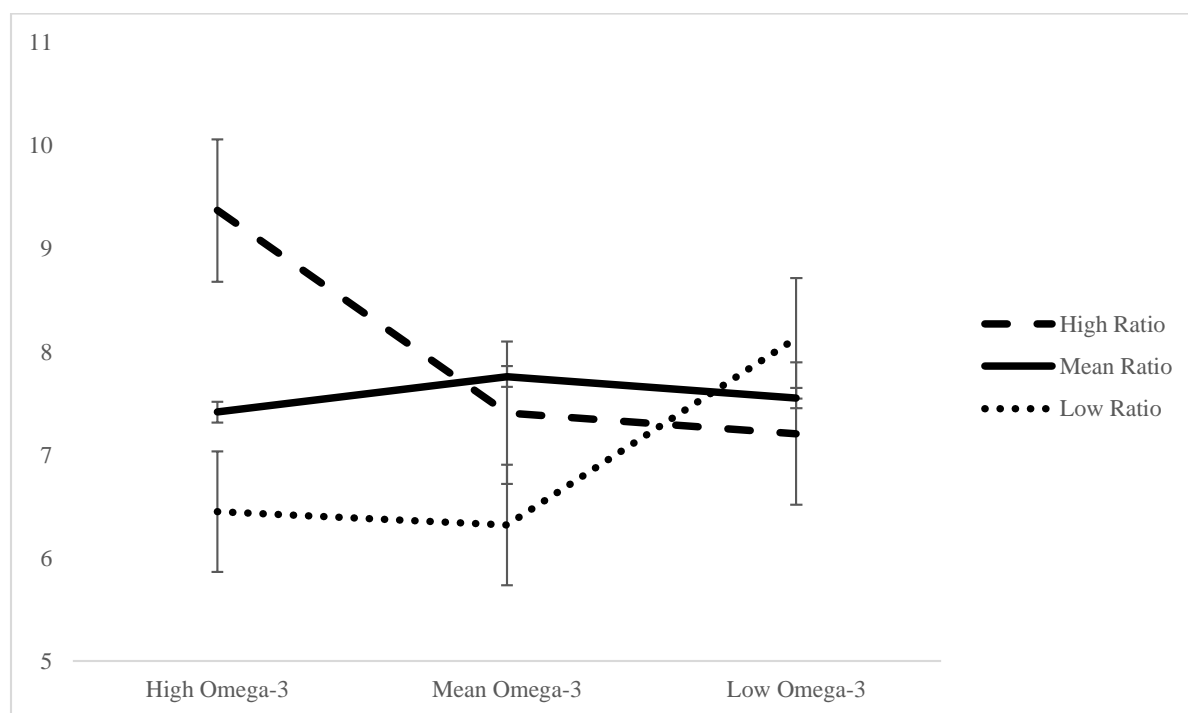


Figure 10. Interaction between the ratio and omega-3 intake predicting mean moves on the 5-move SOC problems in 10- to 12-year-olds.



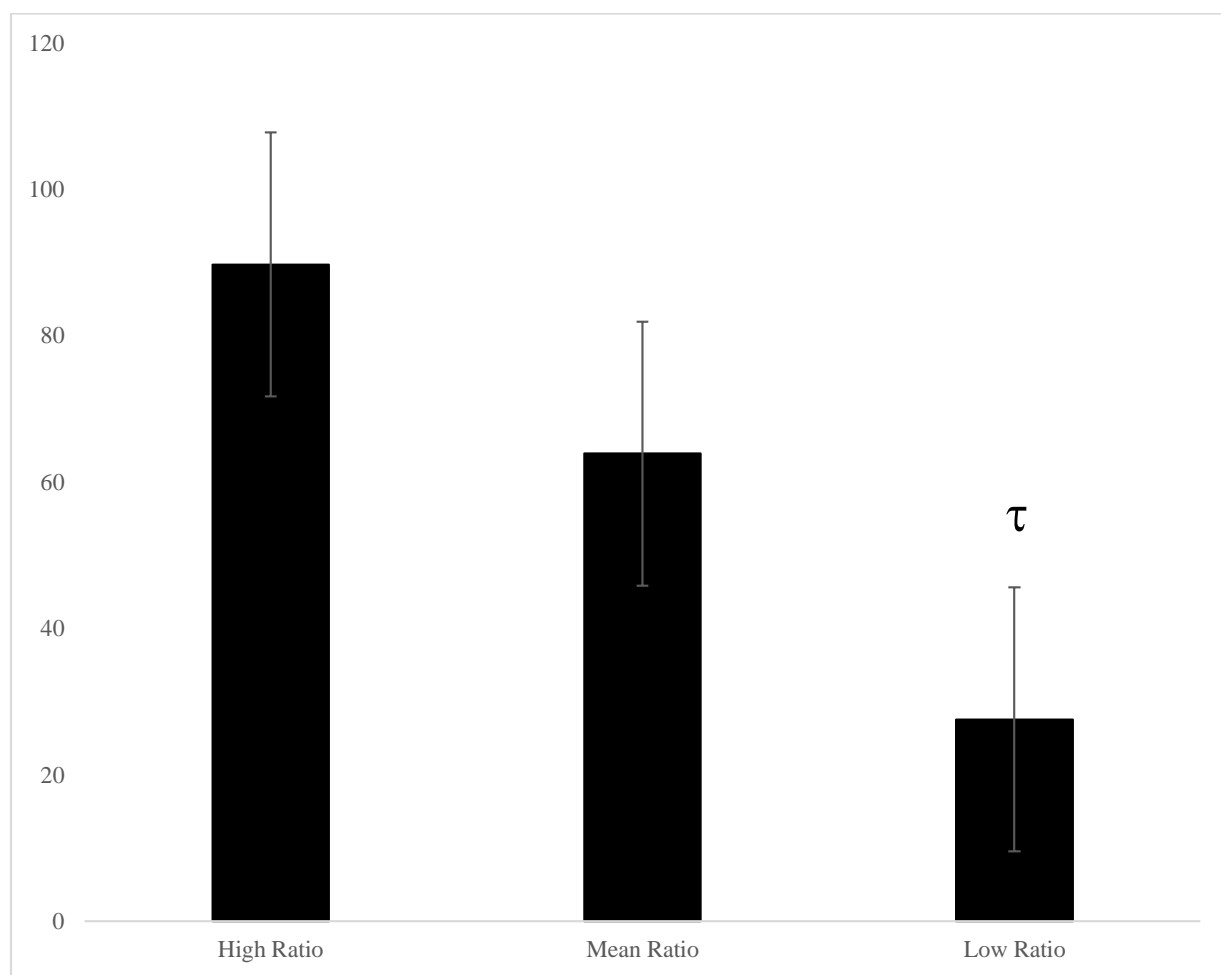


Figure 11. Ratio group predicting latency to last error 8-step mazes in 7- to 9-year-olds.  $\tau p < 0.1$ , the low ratio group tended to make fewer errors than the high ratio group.

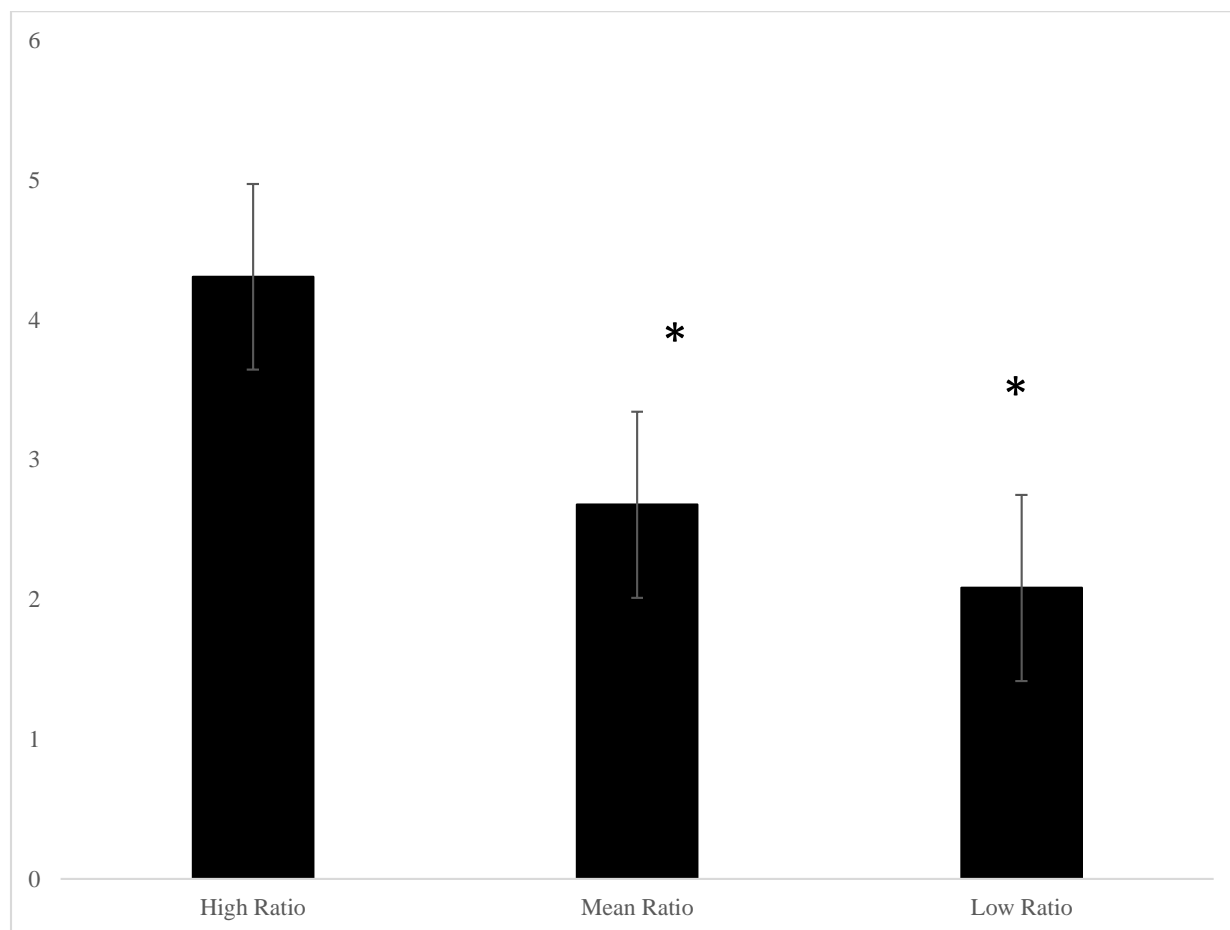


Figure 12. Ratio group predicting errors made on 8-step mazes in 7- to 9-year-olds.

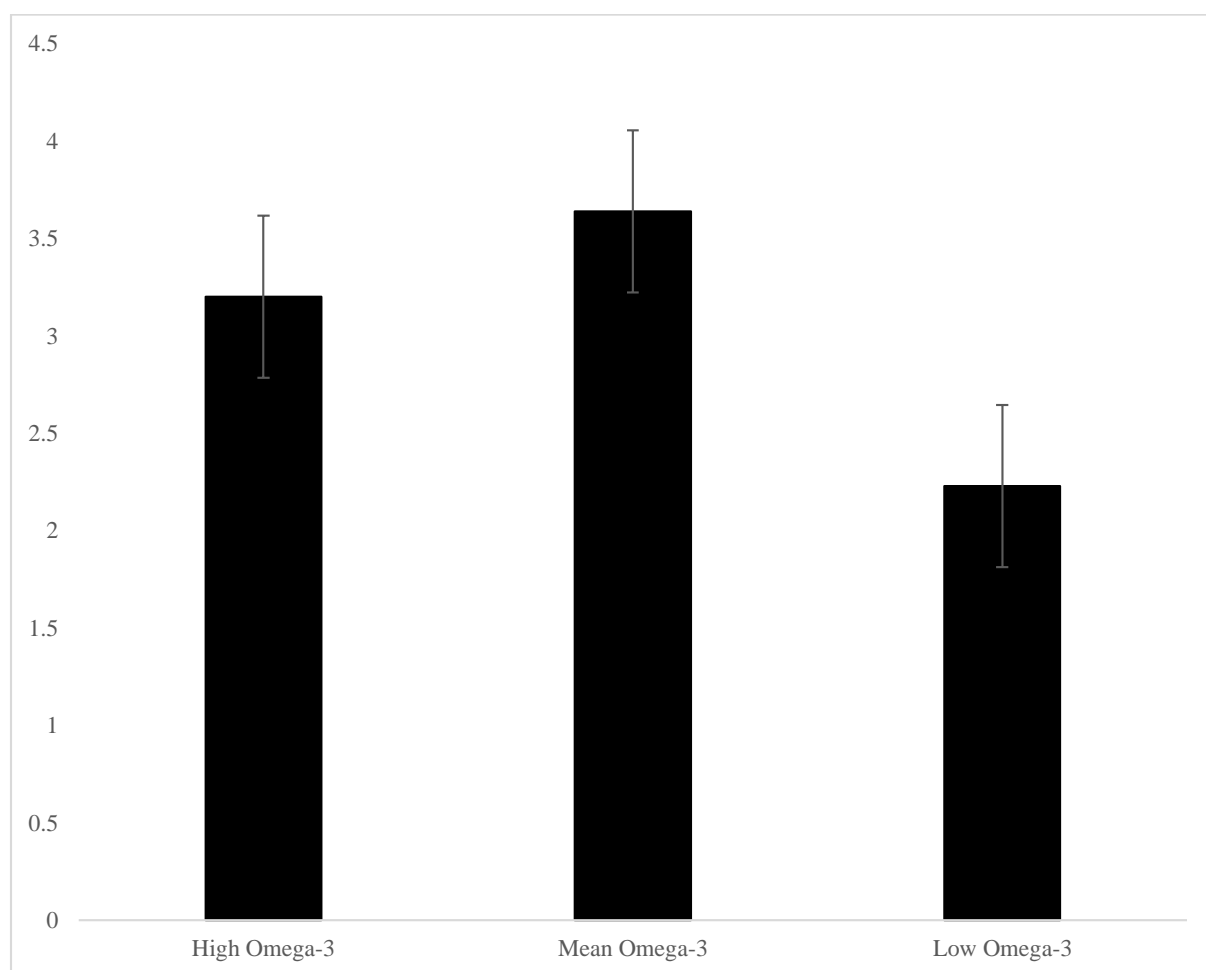


Figure 13. Omega-3 group predicting errors made on 8-step mazes in 7- to 9-year-olds.

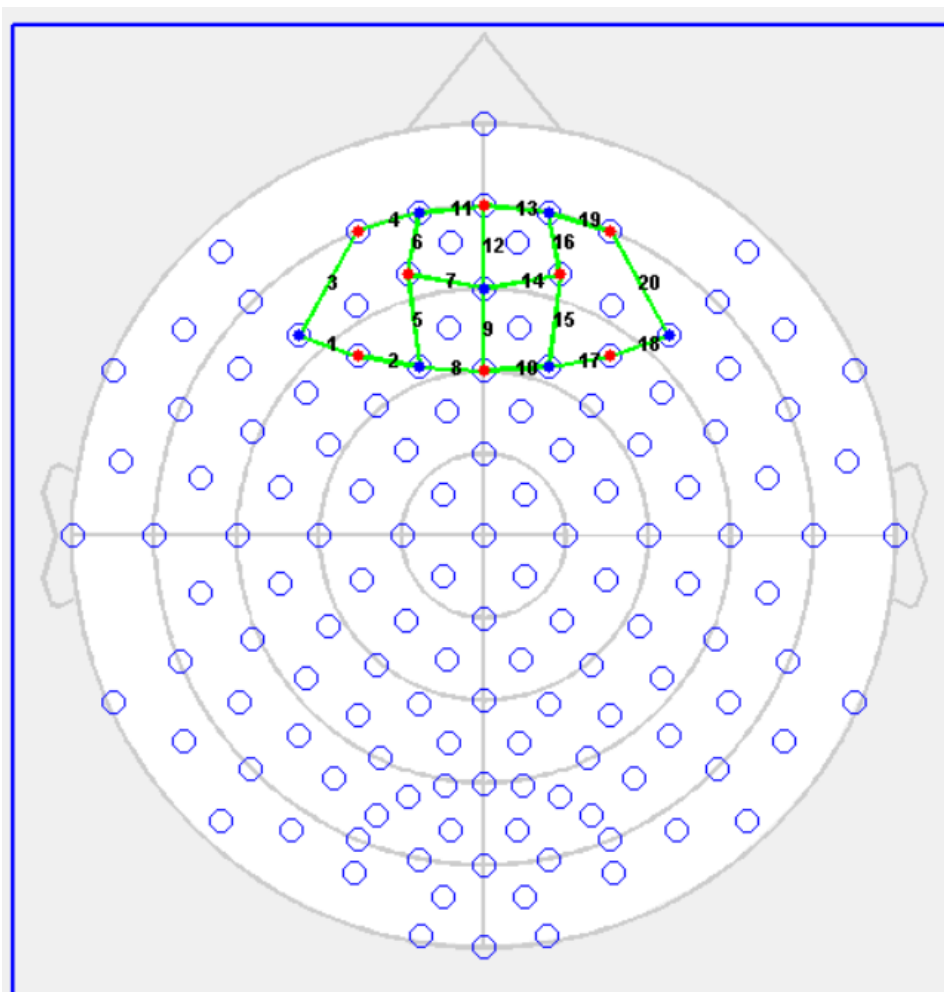


Figure 14. Channel map for NIRs data collection from the prefrontal cortex.

## APPENDIX 1

### **Specific Aim 2: Validating the Electric Maze Task**

Specific aim 2 was designed to validate the Electric Maze task (EMT) as a measure of planning. Outcome measures from the mazes included errors made, duration spent on the correct path and in error zones on the maze, and latency to first and last errors made. All outcome measures were calculated automatically by Noldus Ethovision XT version 8.0. Errors were coded as regular errors (stepping on an incorrect squares), perseverative errors (stepping on an the same incorrect square two or more times in a row), rule errors (stepping on a square that broke the rules of the current condition, shape or color), or maze errors (breaking a rule that applied to all mazes, such as stepping on a non-adjacent square or not returning to the starting square after making an error). Maze errors were rare and were corrected by the researcher immediately to ensure that errors made reflected the challenges of the task and not confusion over the rules. Average errors were calculated for 6-step mazes, 8-step mazes, mazes from the first condition, and mazes from the second condition. The errors made during the first condition were subtracted from the errors made during the second condition to produce a score reflecting the change in performance due to the rule switch. There were no significant differences in performance based on maze start location (1 or 2) or maze starting condition (color or shape). Table A2 shows maze performance for the entire sample and by age group.

Cronbach's alphas were calculated for the entire sample, each age group, and each maze manipulation (6-step, 8-step, first game, second game, and rule switch scores). The maze was a reliable task for the entire sample (Cronbach's  $\alpha = 0.92$ ), 7- to 9-year-olds (Cronbach's  $\alpha = 0.89$ ), and 10- to 12-year-olds (Cronbach's  $\alpha = 0.83$ ). A factor analysis revealed that the 6-step and 8-step mazes loaded onto separate factors,  $\chi^2(85) = 132.34$ ,  $p < 0.05$ , CFI = 0.94, TLI = 0.92, RMSEA = 0.09. The 6-step mazes were reliable for the entire sample (Cronbach's  $\alpha = 0.89$ ), 7- to 9-year-olds (Cronbach's  $\alpha = 0.88$ ), and 10- to 12-year-olds (Cronbach's  $\alpha = 0.86$ ), and the 8-step mazes were reliable for the entire sample (Cronbach's  $\alpha = 0.88$ ), 7- to 9-year-olds (Cronbach's  $\alpha = 0.88$ ), and 10- to 12-year-olds (Cronbach's  $\alpha = 0.87$ ). A factor analysis also indicated that the 1<sup>st</sup> and 2<sup>nd</sup> conditions loaded onto separate factors, although

not as strongly,  $\chi^2(98) = 188.52, p < 0.05$ , CFI = 0.88, TLI = 0.86, RMSEA = 0.11. The first condition was reliable for the entire sample (Cronbach's  $\alpha = 0.89$ ), 7- to 9-year-olds (Cronbach's  $\alpha = 0.89$ ), and 10- to 12-year-olds (Cronbach's  $\alpha = 0.85$ ), and the second condition was reliable for the entire sample (Cronbach's  $\alpha = 0.87$ ), 7- to 9-year-olds (Cronbach's  $\alpha = 0.87$ ), and 10- to 12-year-olds (Cronbach's  $\alpha = 0.86$ ). Table A1 shows the Cronbach's alphas for all versions of the EMT.

Independent samples t-tests were run to examine differences in maze performance between the two age groups. For the working memory manipulation, older children made fewer total errors on the 6-step mazes,  $t(62.56) = 2.69, p < 0.05^2$ , and 8-step mazes,  $t(53.06) = 3.71, p < 0.05$ . The older children also made fewer rule errors on the 6-step mazes,  $t(55.14) = 2.65, p < 0.05$ , and the 8-step mazes,  $t(43.84) = 2.89, p < 0.05$ . The older children had a shorter latency to last error on the 6-step mazes,  $t(45.61) = 2.76, p < 0.05$ , and the 8-step mazes,  $t(57.96) = 3.39, p < 0.05$ . The 8-step mazes increased the difficulty for the younger children as they also made more perseverative errors,  $t(56.29) = 2.65, p < 0.05$  and maze errors,  $t(41.21) = 2.04, p < 0.05$ , than older children. It is important to note that maze errors were rare on the 6-step and 8-step mazes with 86.11% and 84.72% of participants, respectively, not making any maze errors. The latency to last error measure is an indication of the errors made after the participant began attempting a solution. This is an indication of planning because participants who planned their routes would make errors early as they eliminated potential options, and they would use information about errors to update potential paths through the maze. Later errors are an indication of trial-and-error solution methods or an inability to fully use any plans made.

For the inhibitory control manipulation, older children made fewer total errors in the first condition,  $t(48) = 3.08, p < 0.05$ , and the second condition,  $t(57.9) = 3.17, p < 0.05$ , than younger children. Older children made fewer rule errors on the first,  $t(45.55) = 2.66, p < 0.05$ , and second conditions,  $t(46.98) = 2.47, p < 0.05$ , than younger children. Older children also made fewer perseverative errors,  $t(47.93) = 2.51, p < 0.05$ , and had a shorter latency to last error,  $t(44.06) = 3.25, p < 0.05$ , than

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<sup>2</sup> The Satterthwaite-corrected degrees of freedom are reported when the Folded F test indicated there were significantly unequal variances between groups.

younger children in the first condition. Rule errors were also relatively rare on the first and second conditions with 58.33% and 65.28% of participants, respectively, making no rule errors. The inhibitory control manipulation may not have been fully successful as more children made no perseverative errors in the second condition, 52.78%, than the first condition, 51.39%, and there was no significant difference between the age groups in perseverative errors made in the second condition despite a significant difference between the age groups in the first condition. Table A2 shows all age group comparisons for maze performance.

Paired t-tests were also run for the sample as a whole and for each age group to determine if there were significant differences in performance created by each manipulation. For the working memory manipulation, all groups made significantly more errors on the 8-step mazes than on the 6-step mazes (entire sample:  $t(71) = 5.15, p < 0.0001$ ; 7- to 9-year-olds:  $t(35) = 4.08, p < 0.01$ ; 10- to 12-year-olds:  $t(35) = 3.21, p < 0.05$ ). All groups also had longer latency to last error on the 8-step mazes than on the 6-step mazes (entire sample:  $t(69) = 3.77, p < 0.01$ ; 7- to 9-year-olds:  $t(35) = 2.86, p < 0.01$ ; 10- to 12-year-olds:  $t(33) = 2.56, p < 0.05$ ) and spent a lower percentage of their time on the correct path (entire sample:  $t(71) = -3.13, p < 0.05$ ; 7- to 9-year-olds:  $t(35) = -2.21, p < 0.05$ ; 10- to 12-year-olds:  $t(35) = -2.2, p < 0.05$ ). The entire sample and 7- to 9-year-olds also made more perseverative errors when the number of steps increased (entire sample:  $t(71) = 3.93, p < 0.01$ ; 7- to 9-year-olds:  $t(35) = 3.76, p < 0.01$ ). In another indication that the inhibitory control manipulation was not fully successful, there was only one significant difference from the first to the second condition. The entire sample and 7- to 9-year-olds made fewer maze errors after the rule switch (entire sample:  $t(71) = -2.43, p < 0.05$ ; 7- to 9-year-olds:  $t(35) = -2.05, p < 0.05$ ). Table A3 shows all comparisons of maze performance after the working memory and inhibitory control manipulations.

Correlations were run between performance on the mazes and outcomes on the standardized measures, the PAL memory task, the SWM working memory task, and the SOC planning task. Correlations were run separately for the 6-step mazes, the 8-step mazes, and the difference scores between the first and second conditions. The 6-step mazes correlated most with outcomes from the PAL

task. For the entire sample, the PAL memory score was correlated with the total errors made on the 6-step mazes,  $r(72) = -0.41$ ,  $p < 0.05$ , perseverative errors made on 6-step mazes,  $r(72) = -0.33$ ,  $p < 0.05$ , maze errors on 6-step mazes,  $r(72) = -0.32$ ,  $p < 0.05$ , rule errors on 6-step mazes,  $r(72) = -0.3$ ,  $p < 0.05$ , latency to last error on 6-step mazes,  $r(72) = -0.34$ ,  $p < 0.05$ , and duration on the correct path for 6-step mazes  $r(72) = -0.29$ ,  $p < 0.05$ . The memory score is the total number of patterns correctly recalled across all trials. A higher score means better performance. The number of PAL stages completed on the first try was also correlated with total errors on 6-step mazes,  $r(72) = -0.35$ ,  $p < 0.05$ , perseverative errors on 6-step maze,  $r(72) = -0.27$ ,  $p < 0.05$ , maze errors on 6-step mazes  $r(72) = -0.26$ , and rule errors on 6-step mazes,  $r(72) = -0.28$ . Completing more stages on the first try is also an indication of better memory and possibly of the use of a strategy to remember where patterns are located on difficult 6-box and 8-box levels.

Interestingly, the correlations between PAL and maze performance for 10- to 12-year-olds were similar to results for the entire sample with the PAL memory score correlated with total errors,  $r(36) = -0.57$ ,  $p < 0.05$ , perseverative errors,  $r(36) = -0.48$ ,  $p < 0.05$ , rule errors,  $r(36) = -0.34$ ,  $p < 0.05$ , latency to last error,  $r(36) = -0.44$ ,  $p < 0.05$ , and the duration on the correct path  $r(36) = -0.37$ ,  $p < 0.05$ . However, the correlations for 7- to 9-year-olds were different. PAL measures were most often correlated with the latency to first error on the 6-step mazes, which was correlated with PAL errors to success  $r(38) = 0.46$ ,  $p < 0.05$ , trials to success  $r(38) = 0.34$ ,  $p < 0.05$ , total errors,  $r(38) = 0.47$ ,  $p < 0.05$ , and errors on the 8-box stage,  $r(38) = 0.66$ ,  $p < 0.05$ . The latency to first error measure is an indication of the initial amount of time spent considering possible maze paths and then time spent solving before an error is made. These significant correlations among 7- to 9-year-olds could indicate that younger children who spent more time considering maze paths were not using that time efficiently. The additional paths they considered could have actually made incorrect possible paths more distracting or created too much information to hold in mind. They could also not have been considering additional paths through the mazes but instead spending additional time because they were overwhelmed by the task demands. Tables A4, A5, and A6 show the correlation results for 6-step mazes and the standardized measures for the entire sample and each age group.



Performance on the 8-step mazes correlated more strongly with SOC and SWM outcome measures. For the entire sample, the mean number of moves on the 5-move SOC problems was correlated with total errors made on the 8-step mazes,  $r(72) = 0.25$ ,  $p < 0.05$ , perseverative errors made on 8-step mazes,  $r(72) = 0.38$ ,  $p < 0.05$ , latency to last error,  $r(72) = 0.3$ ,  $p < 0.05$ , and duration on the correct path,  $r(72) = 0.29$ . The problems solved in the minimum number of moves was correlated with total errors on the 8-step mazes,  $r(72) = -0.36$ ,  $p < 0.05$ , perseverative errors,  $r(72) = -0.35$ ,  $p < 0.05$ , latency to last error,  $r(72) = -0.35$ ,  $p < 0.05$ , and the duration on the correct path,  $r(72) = -0.39$ ,  $p < 0.05$ . The problems solved in the minimum number of moves is an indication of planning because the problems with counterintuitive moves are unlikely to be solved in the minimum number of moves using trial-and-error solution methods. More problems solved in the minimum number of moves is an indication that a participant has thought through the solution before making any moves. The between errors made on the 4-box and 8-box SWM problems also correlated with the total errors on the 8-step mazes (4-box:  $r(72) = 0.35$ , 8-box:  $r(72) = 0.33$ ,  $ps < 0.05$ ) and the latency to last error (4-box:  $r(72) = 0.34$ , 8-box:  $r(72) = 0.31$ ,  $ps < 0.05$ ). Between errors are the errors made by going back to a box in which a token was already found, indicating either an inability to hold all found tokens in mind or inefficient use of search strategy to avoid returning to boxes.

The pattern of correlations for 7- to 9-year-olds on the 8-step mazes was similar to the entire sample with the mean moves on the 5-move problems correlating with perseverative errors on the 8-step maze,  $r(38) = 0.49$ ,  $p < 0.05$ , and the problems solved in the minimum number of moves correlating with perseverative errors,  $r(38) = -0.38$ ,  $p < 0.05$ , the latency to last error,  $r(38) = -0.33$ ,  $p < 0.05$ , and the duration on the correct path,  $r(38) = -0.32$ ,  $p < 0.05$ . There were fewer correlations for the 10- to 12-year-olds with only the duration on the correct path correlating with the problems solved in the minimum number of moves,  $r(36) = -0.37$ ,  $p < 0.05$ . This could be an indication that younger children approached the 8-step mazes and the SOC task in a similar manner, required similar skills, and found the two tasks to be similarly challenging. The 10- to 12-year-olds may have found that they could rely on their working memory capacity or other skills more with the 8-step mazes than with the SOC task. This idea is supported by the correlations between 8-step maze performance and the mean time to first response and

mean time to last response on the 6-box and 8-box SWM problems found only for 10- to 12-year-olds (6-box first response:  $r(36) = 0.39$ , 6-box last response:  $r(36) = 0.43$ , 8-box first response:  $r(36) = 0.53$ , 8-box last response:  $r(36) = 0.44$ ,  $ps < 0.05$ ), but not for younger children. These measures indicate the amount of time spent creating a strategy to find all the tokens (mean time to first response) and time spent finding tokens (mean time to last response). Tables A7, A8, and A9 show the correlation results for the 8-step mazes and standardized measures for the entire sample and each age group.

Performance after the rule switch did not correlate with SOC or SWM performance for the entire sample. The number of PAL stages completed on the first try was weakly correlated with the change in total errors after the rule switch,  $r(72) = 0.26$ ,  $p < 0.05$ , the change in perseverative errors,  $r(72) = 0.22$ ,  $p < 0.05$ , the change in maze errors,  $r(72) = 0.24$ ,  $p < 0.05$ , and the change in rule errors,  $r(72) = 0.26$ ,  $p < 0.05$ . For 7- to 9-year-olds, the mean subsequent thinking time on the 5-move SOC problems was correlated with the change in total errors made after the rule switch,  $r(38) = -0.43$ ,  $p < 0.05$ , the change in rule errors made,  $r(38) = -0.34$ ,  $p < 0.05$ , the change in latency to last error,  $r(38) = -0.45$ ,  $p < 0.05$ , and the change in the duration on the correct path  $r(38) = -0.37$ ,  $p < 0.05$ . For 10- to 12-year-olds, the mean number of moves made on the 5-move SOC problems was correlated with the change in total errors,  $r(36) = 0.5$ ,  $p < 0.05$ , the change in perseverative errors,  $r(36) = 0.47$ ,  $p < 0.05$ , the change in latency to last error,  $r(36) = 0.49$ ,  $p < 0.05$ , and the change in duration on the correct path,  $r(36) = 0.48$ ,  $p < 0.05$ .

The opposite direction of the correlations for the younger and older children may be an indication of the difficulty of the 5-move problems for the younger children. The mean subsequent thinking time is an indication of the time they participant spent thinking through the solution to the problem after starting to make moves. Less time spent after making the first move is an indication of planning because following a plan should require less thinking time once the plan is being implemented. The younger children who did not struggle with the rule switch in the maze task may nevertheless have found the 5-move SOC problems so challenging that they abandoned all attempts at planning. They would have therefore spent more time solving the problems after making the first move because they were not

following a considered plan. Tables A10, A11 and A12 show the correlation results for performance after the rule switch and standardized measures for the entire sample and each age group.

### **Specific Aim 2: Summary and Discussion**

Overall, the correlations between the standardized measures and maze performance indicate that the maze task can effectively elicit planning from 7- to 12-year-olds. The working memory and inhibitory control demands of the maze can also be effectively manipulated. Additional testing with more age groups and some new manipulations (i.e., 10-step mazes, 3 dimension rule switch) will be required to fully understand the maze. This initial analysis of the maze task indicates that the 6-step mazes were quite simple for 7- to 12-year-olds and may have been mostly solved using memory resources as indicated by correlations with the simpler PAL memory task. The 8-step mazes appear to have required planning skill as performance was correlated most with SOC and SWM measures. In particular, 8-step maze performance was correlated with performance on difficult SOC problems for younger children (5-move problems) and difficult SWM problems for older children (6-box and 8-box problems). There were other indications that the rule switch did not successfully increase inhibitory control demands, and the correlation pattern further supported this conclusion. The pattern of correlations did indicate more correlations between the SOC task and performance after the rule switch. The SOC task requires flexible use of working memory and inhibitory control abilities, and therefore increasing the inhibitory control requirements on the mazes would have been expected to correlate more with the SOC task than the other tasks. However, the correlations were quite different for the 7- to 9-year-olds and 10- to 12-year-olds making it difficult to conclude that a clear-cut manipulation of inhibitory control demands was accomplished.

Table A1.

*Cronbach's alphas for maze variables for the entire sample and by age group.*

	Entire Sample	7- to 9-year-olds	10- to 12-year-olds
All maze variables	0.92	0.89	0.83
6-step mazes	0.89	0.88	0.86
8-step mazes	0.88	0.88	0.87
1 <sup>st</sup> game	0.89	0.89	0.85
2 <sup>nd</sup> game	0.87	0.87	0.86
Difference scores	0.85	0.85	0.79

Table A2.

*Maze performance and independent samples t-test age group comparisons.*

<b>6-step Mazes</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	2.77 (2.76)	3.61 (3.07)	1.93 (2.14)**
Perseverative Errors <sup>#</sup>	0.33 (0.73)	0.43 (0.73)	0.22 (0.73)
Maze Errors <sup>#</sup>	0.08 (0.22)	0.11 (0.27)	0.06 (0.16)
Rule Errors <sup>#</sup>	0.65 (1.18)	1 (1.4)	0.29 (0.79)*
Latency to First Error <sup>^</sup>	10.07 (6.64)	11.47 (7.42)	8.58 (5.42)
Latency to Last Error <sup>^</sup>	29.23 (34.13)	39.48 (42.68)	18.38 (16.39)**
Percent Duration on Correct Path	58.87 (16.14)	58.89 (16.47)	58.85 (16.04)
<b>8-step Mazes</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	5.06 (3.69)	6.54 (4.25)	3.57 (2.24)**
Perseverative Errors <sup>#</sup>	1.03 (1.46)	1.47 (1.72)	0.6 (1)*
Maze Errors <sup>#</sup>	0.13 (0.35)	0.21 (0.47)	0.04 (0.14)*
Rule Errors <sup>#</sup>	0.98 (1.91)	1.6 (2.42)	0.36 (0.87)**
Latency to First Error <sup>^</sup>	10.56 (14.53)	12.68 (19.87)	8.44 (4.94) <sup>†</sup>
Latency to Last Error <sup>^</sup>	51.52 (45.05)	68.32 (50.74)	34.72 (31.02)**
Percent Duration on Correct Path	51.87 (12.2)	52.45 (11.69)	51.3 (12.82)
<b>First Game Mazes</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	4.2 (4.03)	5.58 (4.93)	2.82 (2.17)**
Perseverative Errors <sup>#</sup>	0.68 (1.22)	1.03 (1.52)	0.33 (0.67)*
Maze Errors <sup>#</sup>	0.15 (0.35)	0.22 (0.45)	0.07 (0.18) <sup>†</sup>
Rule Errors <sup>#</sup>	0.98 (2.01)	1.58 (2.53)	0.38 (1)*
Latency to First Error <sup>^</sup>	11.79 (15.15)	14.65 (20.37)	8.93 (5.82)
Latency to Last Error <sup>^</sup>	48.27 (49.25)	65.99 (61.46)	30.56 (22.3)**
Percent Duration on Correct Path	54.06 (13.44)	55.97 (11.93)	52.14 (14.71)
<b>Second Game Mazes</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	3.63 (2.71)	4.58 (3.08)	2.68 (1.88)**
Perseverative Errors <sup>#</sup>	0.68 (1.03)	0.88 (1.19)	0.49 (0.82)
Maze Errors <sup>#</sup>	0.06 (0.22)	0.1 (0.29)	0.03 (0.12)

Rule Errors <sup>#</sup>	0.65 (1.31)	1.01 (1.65)	0.28 (0.69)*
Latency to First Error <sup>^</sup>	8.74 (5.29)	9.82 (6.19)	7.67 (4) <sup>‡</sup>
Latency to Last Error <sup>^</sup>	39.82 (59.52)	51.57 (68.87)	28.07 (46.47) <sup>‡</sup>
Percent Duration on Correct Path	55.18 (14.21)	54.42 (15.64)	55.95 (12.79)

Note. <sup>#</sup> The percent of participant who made none of each type error for the entire sample, 7- to 9-year-olds, and 10- to 12-year-olds, respectively, were: Perseverative errors (6-step) = 77.78%, 69.44%, 86.11%, Maze errors (6-step) = 86.11%, 83.33%, 88.89%, Rule errors (6-step) = 62.5%, 44.44%, 80.56%, Perseverative errors (8-step) = 41.67%, 27.78%, 55.56%, Maze errors (8-step) = 84.72%, 77.78%, 91.67%, Rule errors (8-step) = 62.5%, 41.67%, 83.33%, Perseverative errors (1<sup>st</sup> game) = 51.39%, 36.11%, 66.67%, Maze errors (1<sup>st</sup> game) = 80.56%, 75%, 86.11%, Rule errors (1<sup>st</sup> game) = 58.33%, 36.11%, 80.56%, Perseverative errors (2<sup>nd</sup> game) = 52.78%, 44.44%, 61.11%, Maze errors (2<sup>nd</sup> game) = 90.28%, 86.11%, 94.44%, Rule errors (2<sup>nd</sup> game) = 65.28%, 47.22%, 83.33%. <sup>^</sup>These latencies are to the first and last error of any type. <sup>‡</sup> $p < 0.1$ , \* $p < 0.05$ , \*\* $p < 0.01$  indicate significant differences between 7- to 9-year-olds and 10- to 12-year-olds.

Table A3.

*Performance after manipulations for the entire sample and by age group.*

<b>Working Memory Manipulation</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	2.28 (3.77)***	2.93 (4.31)**	1.64 (3.07)**
Perseverative Errors	0.71 (1.53)**	1.04 (1.66)**	0.38 (1.32) <sup>‡</sup>
Maze Errors	0.04 (0.3)	0.1 (0.37)	-0.01 (0.19)
Rule Errors	0.33 (1.85)	0.6 (2.44)	0.07 (0.92)
Latency to First Error <sup>^</sup>	0.57 (15.82)	1.21 (20.95)	-0.11 (7.53)
Latency to Last Error <sup>^</sup>	22.85 (50.68)**	28.84 (60.48)*	16.51 (37.54)*
Percent Duration on Correct Path	-7 (18.96)**	-6.45 (17.5)*	-7.55 (20.56)*
<b>Inhibitory Control Manipulation</b>	<b>Entire Sample</b>	<b>7- to 9-year-olds</b>	<b>10- to 12-year-olds</b>
Total Errors	-0.57 (4.35)	-1 (5.6)	-0.14 (2.57)
Perseverative Errors	0 (1.44)	-0.15 (1.8)	0.15 (0.96)
Maze Errors	-0.08 (0.29)*	-0.13 (0.37)*	-0.04 (0.18)
Rule Errors	-0.33 (2.19)	-0.57 (2.93)	-0.1 (1.02)
Latency to First Error <sup>^</sup>	-3.05 (15.66)	-4.84 (21.08)	-1.27 (6.82)
Latency to Last Error <sup>^</sup>	-8.46 (77.36)	-14.43 (96.39)	-2.49 (52.68)
Percent Duration on Correct Path	1.13 (17.36)	-1.54 (17.59)	3.8 (16.95)

Note. <sup>^</sup>These latencies are to the first and last error of any type. <sup>‡</sup> $p < 0.1$ , \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.0001$  indicates a significant difference between the 6-step and 8-step mazes (working memory manipulation) and the first condition and second condition (inhibitory control manipulation).

Table A4. *Correlations between SOC task performance and 6-step maze performance for the entire sample and by age group.*

Entire Sample	SOC Move (4)	SOC Move (5)	SOC MIT (3)	SOC MIT (4)	SOC MIT (5)	SOC MST (3)	SOC MST (4)	SOC MST (5)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
SOC Min Moves	-0.39**	-0.49***	-0.2τ	-0.08	0.18	-0.26*	-0.42**	-0.28*	-0.05	-0.002	-0.09	-0.11	-0.19	-0.11	-0.23*
SOC Move (4)		-0.08	0.17	0.15	0.11	0.08	0.58***	0.1	-0.02	-0.08	0.21τ	-0.08	0.13	0.05	0.16
SOC Move (5)			0.06	0.09	-0.15	0.19τ	0.14	0.37**	-0.01	-0.1	-0.05	-0.02	0.07	0.13	0.22τ
SOC MIT (3)				0.35**	0.26*	0.13	0.38**	0.28*	0.09	0.07	-0.03	0.13	0.18	0.28*	0.43**
SOC MIT (4)					0.25*	0.19	0.37**	0.18	-0.13	-0.14	-0.02	-0.07	-0.01	-0.05	0.02
SOC MIT (5)						0.02	0.27*	0.27*	-0.16	-0.17	-0.03	-0.11	-0.02	-0.13	-0.06
SOC MST (3)							0.4**	0.2τ	-0.02	0.03	0.25*	-0.01	0.16	-0.001	0.03
SOC MST (4)								0.46***	0.08	0.02	0.23*	0.1	0.19	0.23τ	0.3*
SOC MST (5)									0.23*	0.09	0.06	0.35*	0.15	0.22τ	0.37**
Maze Total Errors										0.85***	0.27*	0.85***	0.07	0.78***	0.7***
Maze Persev Errors											0.11	0.78***	0.06	0.62***	0.49***
Maze Rule Errors												0.06	0.01	0.13	0.21τ
Maze Ltncy 1 <sup>st</sup> Error													0.06	0.57***	0.61***
Maze Ltncy Last Error														0.29*	0.26*
															0.75***





10- to 12-year- olds	SOC Move (4)	SOC Move (5)	SOC MIT (3)	SOC MIT (4)	SOC MIT (5)	SOC MST (3)	SOC MST (4)	SOC MST (5)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
SOC Min Moves	-0.32*	-0.45**	-0.02	0.02	0.29 $\tau$	-0.18	-0.27	-0.16	0.14	0.1	-0.15	0.04	0.02	0.15	-0.02
SOC Move (4)		-0.17	0.16	0.1	0.15	-0.11	0.57**	0.24	-0.03	0.04	0.01	0.02	-0.07	-0.15	0.05
SOC Move (5)			-0.05	0.14	-0.27	0.29 $\tau$	0.1	0.46**	-0.38*	-0.4*	-0.03	-0.4*	0.28	-0.14	0.04
SOC MIT (3)				0.23	0.26	0.11	0.29 $\tau$	0.17	-0.04	-0.03	-0.07	-0.05	0.23	-0.07	0.12
SOC MIT (4)					0.11	0.08	0.35*	0.09	-0.14	-0.13	-0.15	-0.16	0.06	-0.11	-0.15
SOC MIT (5)						0.03	0.45**	0.3 $\tau$	-0.08	-0.08	-0.03	-0.1	0.21	-0.09	-0.05
SOC MST (3)							0.28 $\tau$	0.26	-0.17	-0.08	0.13	-0.18	0.06	-0.15	-0.05
SOC MST (4)								0.57**	-0.21	-0.15	-0.1	-0.18	0.18	-0.18	-0.04
SOC MST (5)									0.14	0.1	-0.15	0.04	0.02	0.15	0.23
Maze Total Errors										0.93***	0.16	0.87***	-0.26	0.75***	0.65***
Maze Persev Errors											0.01	0.86***	-0.22	0.68***	0.51**
Maze Rule Errors												-0.02	-0.15	-0.1	0.18
Maze Ltncy 1 <sup>st</sup> Error													-0.21	0.55**	0.51**
Maze Ltncy Last Error														0.1	0.17
															0.63***

Notes. SOC = Stockings of Cambridge; MIT = Mean initial thinking time; MST = Mean subsequent thinking time, Persev = Perseverative; Ltncy = Latency; Dur = Duration; Corr = Correct.

Table A5. *Correlations between SWM task performance and 6-step maze performance for the entire sample and by age group.*

[illegible]



10- to 12- year-olds	SWM Btw Err (6)	SWM Btw Err (8)	SWM MTFR (4)	SWM MTLR (4)	SWM MTFR (6)	SWM MTLR (6)	SWM MTFR (8)	SWM MTLR (8)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
SWM Btw Err (4)	0.42**	0.042**	-0.17	0.35*	0.07	0.23	0.05	0.15	0.06	0.02	0.33	-0.09	0.1	-0.06	0.07
SWM Btw Err (6)		0.69***	-0.02	0.33*	0.22	0.52**	0.13	0.44**	0.15	0.19	0.06	0.06	0.17	0.24	0.11
SWM Btw Err (8)			-0.19	-0.004	-0.02	0.16	-0.19	0.33*	0.18	0.17	0.1	0.07	0.23	0.24	0.2
SWM MTFR (4)				0.65***	0.57**	0.57**	0.49**	0.68***	0.09	0.17	-0.11	0.19	0.07	0.12	0.13
SWM MTLR (4)					0.67***	0.83***	0.59***	0.66***	0.01	0.03	0.18	-0.06	0.13	0.06	0.18
SWM MTFR (6)						0.76***	0.77***	0.66***	-0.02	-0.03	-0.13	-0.12	0.2	0.23	0.28
SWM MTLR (6)							0.59***	0.82***	-0.03	0.06	-0.001	0.06	0.31 $\tau$	0.1	0.19
SWM MTFR (8)							0.59***		0.08	0.09	-0.24	0.03	0.05	0.17	0.18
SWM MTLR (8)									0.19	0.26	-0.13	0.21	0.22	0.24	0.25
Maze Total Errors										0.93***	0.16	0.87***	-0.26	0.75***	0.65***
Maze Persev Errors											0.01	0.86***	-0.22	0.68***	0.51**
Maze Errors												-0.02	-0.15	-0.1	0.18
Maze Rule Errors													-0.21	0.55**	0.51**
Maze Ltncy 1 <sup>st</sup> Error														0.1	0.17
Maze Ltncy Last Error															0.63***

Notes. SWM = Spatial working memory; MTFR = Mean time to first response; MTLR = Mean time to last response; Persev = Perseverative; Ltncy = Latency; Dur = Duration; Corr = Correct.

Table A6. *Correlations between PAL task performance and 6-step maze performance for the entire sample and by age group.*

[illegible]

[illegible]

10- to 12- year-olds	PAL Errs Success	PAL Trials Success	PAL Stages Comp 1 <sup>st</sup>	PAL Total Errors	PAL Errors (3)	PAL Errors (6)	PAL Errors (8)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
PAL Mem Score	-0.84***	-0.79***	0.84***	-0.84***	-0.54**	-0.59***	-0.72***	-0.57**	-0.48**	-0.3τ	-0.34*	0.24	-0.44*	-0.37*
PAL Errs Success		0.95***	-0.68***	1.00***	0.33*	0.57**	0.95***	0.34*	0.29τ	0.12	0.13	-0.09	0.32τ	0.23
PAL Trials Success			-0.79***	-0.95***	0.34*	0.69***	0.84***	0.29τ	0.25	0.08	0.14	-0.07	0.24	0.14
PAL Stages Comp 1 <sup>st</sup>				-0.68***	-0.52**	-0.68***	-0.49**	-0.37*	-0.29τ	-0.22	-0.23	0.22	-0.21	0.15
PAL Total Errors					0.33*	0.57**	0.95***	0.34*	0.29τ	0.12	0.13	-0.09	0.32τ	0.23
PAL Errors (3)						0.28τ	0.13	0.33*	0.27	0.21	0.21	0.07	0.26	0.38*
PAL Errors (6)							0.31τ	0.5**	0.5**	0.19	0.35*	-0.19	0.34*	0.18
PAL Errors (8)								0.2	0.15	0.05	0.01	-0.04	0.24	0.16
Maze Total Errors									0.93***	0.16	0.87***	-0.26	0.75***	0.65***
Maze Persev Errors										0.01	0.86***	-0.22	0.68***	0.51**
Maze Errors											-0.02	-0.15	-0.1	0.18
Maze Rule Errors												-0.21	0.55**	0.51**
Maze Ltncy 1 <sup>st</sup> Error													0.1	0.17
Maze Ltncy Last Error														0.63***

Notes. PAL = Paired associates learning; Comp = Completed; Persev = Perseverative; Ltncy = Latency; Dur = Duration; Corr = Correct.



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10- to 12-year- olds	SOC Move (4)	SOC Move (5)	SOC MIT (3)	SOC MIT (4)	SOC MIT (5)	SOC MST (3)	SOC MST (4)	SOC MST (5)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
SOC Min Moves	-0.32*	-0.45**	-0.02	0.02	0.29 $\tau$	-0.18	-0.27	-0.16	-0.23	-0.14	0.11	0.02	-0.05	-0.22	-0.37*
SOC Move (4)		-0.17	0.16	0.1	0.15	-0.11	0.57**	0.24	-0.04	-0.13	0.01	0.07	0.07	-0.05	-0.1
SOC Move (5)			-0.05	0.14	-0.27	0.29 $\tau$	0.1	0.46**	0.02	0.12	0.02	-0.22	0.19	0.27	0.28 $\tau$
SOC MIT (3)				0.23	0.26	0.11	0.29 $\tau$	0.17	0.08	-0.05	0.01	0.33*	0.32 $\tau$	0.02	0.03
SOC MIT (4)					0.11	0.08	0.35*	0.09	-0.18	-0.11	-0.09	-0.001	0.09	-0.06	-0.1
SOC MIT (5)						0.03	0.45**	0.3 $\tau$	-0.14	-0.07	-0.15	-0.05	-0.01	-0.08	-0.18
SOC MST (3)							0.28 $\tau$	0.26	-0.19	-0.17	-0.03	-0.04	0.24	-0.09	-0.15
SOC MST (4)								0.57**	-0.17	-0.07	-0.11	-0.09	0.06	-0.05	-0.06
SOC MST (5)									-0.1	0.06	-0.04	-0.18	0.15	0.07	-0.08
Maze Total Errors									0.72***	0.31 $\tau$	0.53**	0.0001	0.73***	0.73***	
Maze Persev Errors										0.38*	0.16	-0.03	0.43*	0.39*	
Maze Errors											0.05	-0.1	0.06	-0.07	
Maze Rule Errors												0.3 $\tau$	0.29 $\tau$	0.26	
Maze Ltncy 1 <sup>st</sup> Error													0.26	0.14	
Maze Ltncy Last Error														0.83***	

Notes. SOC = Stockings of Cambridge; MIT = Mean initial thinking time; MST = Mean subsequent thinking time, Persev = perseverative; Ltncy = Latency; Dur = Duration; Corr = Correct.

[illegible]



10- to 12- year-olds	SWM Btw Err (6)	SWM Btw Err (8)	SWM MTFR (4)	SWM MTLR (4)	SWM MTFR (6)	SWM MTLR (6)	SWM MTFR (8)	SWM MTLR (8)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
SWM Btw Err (4)	0.42*	0.42*	-0.17	0.35*	0.07	0.23	0.05	0.15	0.29 $\tau$	0.41*	0.26	-0.2	-0.13	0.12	0.17
SWM Btw Err (6)		0.69***	-0.02	0.33*	0.22	0.52***	0.13	0.44**	-0.18	-0.03	-0.11	-0.26	0.21	-0.07	-0.04
SWM Btw Err (8)			-0.19	-0.004	-0.02	0.16	-0.19	0.33*	0.02	0.07	-0.02	-0.19	-0.01	0.03	-0.001
SWM MTFR (4)				0.65***	0.57***	0.57***	0.49***	0.68***	-0.23	-0.35*	-0.21	-0.04	0.32 $\tau$	-0.11	-0.02
SWM MTLR (4)					0.67***	0.83***	0.59***	0.66***	-0.18	-0.26	-0.11	-0.1	0.27	-0.09	0.004
SWM MTFR (6)						0.76***	0.77***	0.66***	-0.26	-0.27	-0.19	-0.14	0.39*	-0.003	-0.03
SWM MTLR (6)							0.59***	0.82***	-0.23	-0.19	-0.18	-0.11	0.43*	-0.01	0.03
SWM MTFR (8)							0.59***		-0.18	-0.2	-0.19	0.03	0.53**	0.06	-0.02
SWM MTLR (8)									-0.17	-0.2	-0.15	-0.09	0.44**	0.03	0.03
Maze Total Errors										0.72***	0.31 $\tau$	0.53**	0.0002	0.73***	0.73***
Maze Persev Errors											0.38*	0.16	-0.03	0.43**	0.39*
Maze Errors												0.05	-0.1	0.06	-0.07
Maze Rule Errors													0.3 $\tau$	0.29 $\tau$	0.25
Maze Ltncy 1 <sup>st</sup> Error														0.26	0.14
Maze Ltncy Last Error															0.83***

Notes. SWM = Spatial working memory; MTFR = Mean time to first response; MTLR = Mean time to last response; Persev = Perseverative; Ltncy = Latency; Dur = Duration; Corr = Correct.

Table A9. *Correlations between PAL task performance and 8-step maze performance for the entire sample and by age group.*

[illegible]





10- to 12- year-olds	PAL Errs Success	PAL Trials Success	PAL Stages Comp 1 <sup>st</sup>	PAL Total Errors	PAL Errors (3)	PAL Errors (6)	PAL Errors (8)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
PAL Mem Score	-0.84***	-0.79***	0.84***	-0.84***	-0.54***	-0.59***	-0.72***	0.02	0.17	-0.04	0.18	0.2	-0.09	-0.1
PAL Errs Success		0.95***	-0.68***	1.00***	0.33*	0.57***	0.94***	0.01	0.03	0.2	-0.19	-0.23	0.01	-0.05
PAL Trials Success			-0.79***	0.95***	0.34*	0.69***	0.83***	0.05	0.08	0.24	-0.23	-0.14	0.07	0.001
PAL Stages Comp 1 <sup>st</sup>				-0.68***	-0.52***	-0.68***	-0.49**	0.01	0.14	-0.09	0.32τ	0.08	-0.15	-0.17
PAL Total Errors					0.33*	0.57***	0.95***	0.01	0.03	0.2	-0.19	-0.23	0.01	-0.05
PAL Errors (3)						0.28τ	0.13	-0.01	-0.12	-0.14	-0.1	0.06	0.13	0.23
PAL Errors (6)							0.31τ	0.08	0.05	0.16	-0.12	0.13	0.09	0.03
PAL Errors (8)								-0.01	0.05	0.22	-0.17	-0.33*	-0.03	-0.11
Maze Total Errors									0.72***	0.31τ	0.53***	0.0002	0.73***	0.73***
Maze Persev Errors										0.38*	0.16	-0.03	0.43**	0.39*
Maze Errors											0.05	-0.1	0.06	-0.07
Maze Rule Errors												0.3τ	0.29τ	0.26
Maze Ltncy 1 <sup>st</sup> Error													0.26	0.14
Maze Ltncy Last Error														0.83***

Notes. PAL = Paired associates learning; Comp = Completed; Persev = Perseverative; Ltncy = Latency; Dur = Duration; Corr = Correct.

Table A10. *Correlations between SOC task performance and maze performance after the rule switch (inhibitory control manipulation) for the entire sample and by age group.*

Entire Sample	SOC Move (4)	SOC Move (5)	SOC MIT (3)	SOC MIT (4)	SOC MIT (5)	SOC MST (3)	SOC MST (4)	SOC MST (5)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
SOC Min Moves	-0.39***	-0.49***	-0.21τ	-0.08	0.18	-0.26*	-0.42***	-0.28*	-0.01	-0.06	0.02	-0.03	0.01	0.04	0.02
SOC Move (4)		-0.08	0.17	0.15	0.11	0.08	0.58***	0.1	0.1	0.11	0.16	0.04	-0.15	0.03	0.05
SOC Move (5)			0.06	0.09	-0.15	0.19τ	0.14	0.37**	0.07	0.15	0.03	0.06	-0.11	0.09	0.005
SOC MIT (3)				0.35**	0.26*	0.13	0.38**	0.28*	0.04	0.07	0.07	0.06	-0.01	-0.1	-0.06
SOC MIT (4)					0.25*	0.19	0.37**	0.18	-0.01	0.06	0.13	0.01	0.03	0.04	0.01
SOC MIT (5)						0.02	0.27*	0.28*	-0.02	0.01	0.09	-0.02	-0.07	-0.04	-0.06
SOC MST (3)							0.4**	0.2τ	0.11	0.16	0.12	-0.03	0.17	0.27*	0.2
SOC MST (4)								0.46**	0.09	0.17	0.17	0.02	-0.07	0.02	0.1
SOC MST (5)									-0.2τ	-0.06	-0.08	-0.21	-0.05	-0.25*	-0.18
Maze Total Errors										0.81***	0.19	0.88***	0.18	0.69***	0.83***
Maze Persev Errors											0.06	0.62***	0.06	0.72***	0.69***
Maze Rule Errors												0.15	0.01	0.19	0.28*
Maze Ltncy 1 <sup>st</sup> Error													0.29*	0.48***	0.71***
Maze Ltncy Last Error														0.24*	0.5***
Maze Dur Corr Path															0.74***



10- to 12-year- olds	SOC Move (4)	SOC Move (5)	SOC MIT (3)	SOC MIT (4)	SOC MIT (5)	SOC MST (3)	SOC MST (4)	SOC MST (5)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
SOC Min Moves	-0.32*	-0.45**	-0.02	0.02	0.29 $\tau$	-0.18	-0.27	-0.16	-0.08	-0.14	-0.08	-0.11	-0.11	-0.14	-0.09
SOC Move (4)		-0.17	0.16	0.1	0.15	-0.11	0.57***	0.24	-0.12	-0.12	0.38*	0.05	-0.1	-0.18	0.04
SOC Move (5)			-0.05	0.14	-0.27	0.29 $\tau$	0.1	0.46**	0.5**	0.47**	-0.001	0.34*	-0.004	0.49**	0.48**
SOC MIT (3)				0.23	0.26	0.11	0.29 $\tau$	0.17	-0.11	0.06	-0.03	-0.18	-0.004	0.03	-0.05
SOC MIT (4)					0.11	0.08	0.35*	0.09	-0.05	0.04	0.12	0.02	0.08	-0.01	-0.07
SOC MIT (5)						0.03	0.45**	0.3 $\tau$	0.09	0.05	0.09	0.1	-0.15	-0.01	-0.06
SOC MST (3)							0.28 $\tau$	0.26	0.03	-0.03	-0.08	-0.03	0.11	0.07	-0.05
SOC MST (4)								0.57***	0.01	0.12	0.19	-0.04	-0.03	0.01	0.09
SOC MST (5)									0.31 $\tau$	0.3 $\tau$	0.07	0.11	-0.19	0.12	0.38*
Maze Total Errors										0.84***	-0.07	0.75***	-0.1	0.69***	0.77***
Maze Persev Errors											-0.12	0.5**	-0.05	0.62***	0.68***
Maze Rule Errors												0.05	0.1	-0.06	0.05
Maze Ltncy 1 <sup>st</sup> Error													-0.09	0.46**	0.42*
Maze Ltncy Last Error														0.15	0.1
															0.71***

Notes. SOC = Stockings of Cambridge; MIT = Mean initial thinking time; MST = Mean subsequent thinking time, Persev = perseverative; Ltncy = Latency; Dur = Duration; Corr = Correct.

Table A11. *Correlations between SWM task performance and maze performance after the rule switch (inhibitory control manipulation) for the entire sample and by age group.*

Entire Sample	SWM Btw Err (6)	SWM Btw Err (8)	SWM MTFR (4)	SWM MTLR (4)	SWM MTFR (6)	SWM MTLR (6)	SWM MTFR (8)	SWM MTLR (8)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
SWM Btw Err (4)	0.37**	0.4**	0.17	0.54***	0.29*	0.3*	0.15	0.25*	0.12	0.09	-0.15	0.07	-0.07	0.01	-0.02
SWM Btw Err (6)		0.67***	0.12	0.2τ	0.17	0.53***	0.05	0.36**	-0.08	-0.1	-0.14	-0.05	-0.07	-0.11	-0.13
SWM Btw Err (8)			0.22	0.28*	0.2τ	0.4**	0.01	0.56***	-0.07	-0.07	-0.11	-0.09	-0.07	-0.1	-0.14
SWM MTFR (4)				0.67***	0.4**	0.51***	0.48***	0.63***	-0.08	-0.09	0.05	-0.1	-0.26	-0.18	-0.17
SWM MTLR (4)					0.47***	0.73***	0.51***	0.71***	-0.02	-0.03	-0.04	-0.08	-0.17	-0.05	-0.11
SWM MTFR (6)						0.62***	0.67***	0.5***	0.01	0.03	-0.09	-0.06	0.05	-0.01	0.03
SWM MTLR (6)							0.54***	0.82***	-0.05	-0.04	-0.13	-0.12	-0.04	-0.03	-0.04
SWM MTFR (8)								0.5***	-0.15	-0.09	-0.13	-0.16	-0.05	-0.09	-0.14
SWM MTLR (8)									-0.05	-0.08	-0.01	-0.11	-0.05	-0.06	-0.03
Maze Total Errors										0.81***	0.19	0.88***	0.18	0.69***	0.83***
Maze Persev Errors											0.06	0.62***	0.06	0.72***	0.69***
Maze Errors												0.15	0.01	0.19	0.28*
Maze Rule Errors													0.29*	0.48***	0.71***
Maze Ltncy 1 <sup>st</sup> Error														0.24*	0.5***
Maze Ltncy Last Error															0.74***



10- to 12- year-olds	SWM Btw Err (6)	SWM Btw Err (8)	SWM MTFR (4)	SWM MTLR (4)	SWM MTFR (6)	SWM MTLR (6)	SWM MTFR (8)	SWM MTLR (8)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
SWM Btw Err (4)	0.42**	0.42**	-0.17	0.35*	0.07	0.23	0.05	0.15	0.23	0.19	-0.53**	0.14	-0.11	0.05	0.06
SWM Btw Err (6)		0.69***	-0.02	0.33*	0.22	0.52**	0.13	0.44**	-0.06	-0.13	-0.27	-0.13	-0.29τ	-0.1	-0.07
SWM Btw Err (8)			-0.19	-0.004	-0.02	0.16	-0.19	0.33*	-0.05	-0.13	-0.25	0.02	-0.09	-0.14	-0.1
SWM MTFR (4)				0.65***	0.57**	0.57**	0.49**	0.68***	-0.18	-0.28τ	0.12	-0.24	-0.26	-0.2	0.03
SWM MTLR (4)					0.67***	0.83***	0.59***	0.66***	-0.05	-0.16	-0.24	-0.17	-0.29τ	-0.12	-0.07
SWM MTFR (6)						0.76***	0.77***	0.66***	0.02	-0.1	-0.05	-0.1	-0.19	-0.05	0.18
SWM MTLR (6)							0.59**	0.82***	-0.01	-0.08	-0.2	-0.19	-0.3τ	-0.002	0.12
SWM MTFR (8)							0.59***		-0.02	-0.11	0.07	-0.11	-0.18	0.12	0.09
SWM MTLR (8)									-0.2	-0.25	-0.11	-0.29τ	-0.2	-0.18	0.002
Maze Total Errors										0.84***	-0.07	0.75***	-0.1	0.69***	0.77***
Maze Persev Errors											-0.12	0.5**	-0.05	0.62***	0.68***
Maze Errors												0.05	0.1	-0.06	0.05
Maze Rule Errors													-0.09	0.46**	0.42*
Maze Ltncy 1 <sup>st</sup> Error														0.15	0.1
Maze Ltncy Last Error															0.71***

Notes. SWM = Spatial working memory; MTFR = Mean time to first response; MTLR = Mean time to last response; Persev = Perseverative; Ltncy = Latency; Dur = Duration; Corr = Correct.







10- to 12- year-olds	PAL Errs Success	PAL Trials Success	PAL Stages Comp 1 <sup>st</sup>	PAL Total Errors	PAL Errors (3)	PAL Errors (6)	PAL Errors (8)	Maze Total Errors	Maze Persev Errors	Maze Errors	Maze Rule Errors	Maze Ltncy 1 <sup>st</sup> Error	Maze Ltncy Last Error	Maze Dur Corr Path
PAL Mem Score	-0.84***	-0.79***	0.84***	-0.84***	-0.54***	-0.59***	-0.72***	0.39*	0.37*	0.25	0.31τ	0.04	0.2	0.27
PAL Errs Success		0.95***	-0.68***	1.00***	0.33*	0.57***	0.94***	-0.22	-0.16	-0.34*	-0.14	-0.04	-0.08	-0.16
PAL Trials Success			-0.79***	0.95***	0.34*	0.69***	0.83***	-0.13	-0.1	-0.43**	-0.07	-0.11	-0.06	-0.07
PAL Stages Comp 1 <sup>st</sup>				-0.68***	-0.52***	-0.68***	-0.49**	0.2	0.24	0.38*	0.13	0.17	0.17	0.12
PAL Total Errors					0.33*	0.57***	0.95***	-0.22	-0.16	-0.34*	-0.14	-0.04	-0.08	-0.16
PAL Errors (3)						0.28τ	0.13	-0.1	-0.16	-0.22	-0.28	-0.03	-0.03	0.01
PAL Errors (6)							0.31τ	-0.29τ	-0.28τ	-0.48**	-0.24	-0.19	-0.24	-0.2
PAL Errors (8)								-0.16	-0.07	-0.23	-0.05	0.02	-0.002	-0.13
Maze Total Errors									0.84***	-0.07	0.75***	-0.1	0.69***	0.77***
Maze Persev Errors										-0.12	0.5**	-0.05	0.62***	0.68***
Maze Errors											0.05	-0.1	0.06	0.05
Maze Rule Errors												-0.09	0.46**	0.42*
Maze Ltncy 1 <sup>st</sup> Error													0.15	0.1
Maze Ltncy Last Error														0.71***

Notes. PAL = Paired associates learning; Comp = Completed; Persev = Perseverative; Ltncy = Latency; Dur = Duration; Corr = Correct.

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