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Behavioral and Neural Effects of Reasoning Training

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Behavioral and Neural Effects of Reasoning Training

by Allyson Mackey

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Abstract

Behavioral and Neural Effects of Reasoning Training
by Allyson Mackey
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My thesis research has focused broadly on how the environment shapes the structure and function of prefrontal cortex, for better or worse. I am interested in understanding in how experience-dependent plasticity can be harnessed to boost, or in some cases, remediate prefrontal function. I focused on training reasoning, the ability to solve novel problems, for two reasons: 1) reasoning is highly predictive of academic outcomes, and 2) reasoning was originally conceptualized as a fixed trait, and many people, both in science and in the general public, still believe that reasoning is set in stone. I conducted two studies, one in children and one in adults, to test the predictions that reasoning ability is malleable, and that repeated practice with reasoning problems strengthens connectivity within the frontoparietal network that supports high-level cognition.

In my first study, children from low socioeconomic status backgrounds participated in 8 weeks of training with computerized and non-computerized games that targeted either reasoning ability or cognitive speed. Training led to dissociable behavioral outcomes: children in the reasoning training group improved substantially on a matrix reasoning test, while children in the speed training group improved specifically on a measure of cognitive speed. Reasoning gains corresponded to roughly 10 points in performance IQ. These results indicated that reasoning is modifiable by training in this population.

In my second study, I capitalized on the fact that adults are taught reasoning skills by courses aimed at improving performance on the Law School Admissions Test (LSAT). I recruited young adults who were enrolled in an LSAT preparation course, and age- and IQ-matched controls intending to take the LSAT in the future. Magnetic resonance imaging (MRI) measures were collected for all subjects during two scanning sessions separated by 90 days. I first tested whether reasoning training altered functional connectivity at rest. I found strengthened fronto-parietal and parietal-striatal functional connectivity, particularly between hemispheres. I next investigated whether structural connectivity, as measured by diffusion in white matter, had been altered by training. I found training-related radial diffusivity (RD) decreases in white matter connecting frontal cortices, and mean diffusivity (MD) decreases closer to cortex in white matter in left frontal lobe and right parietal lobe. In conclusion, my thesis research has demonstrated that training can improve reasoning ability and, in adults, alter functional and structural connectivity. These results provide evidence for neural plasticity in large-scale networks supporting high-level cognition.

Dedication

To my high school biology teacher, Richard Irwin, who encouraged me to think like a scientist, and to aspire to be one.

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Co-author Contributions

Chapter 2: A.P.M. designed the experiment, collected data, analyzed data, and wrote the paper. S.S.H. collected data. S.I.S. performed statistical analyses and commented on drafts. S.A.B. designed the experiment and wrote the paper

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Chapter 1
Introduction: Environmental Influences on Prefrontal Development

It takes only a few years for a human child's sensory cortex to develop its full functionality. By contrast, it takes over two decades of experience and growth before prefrontal cortex (PFC) reaches its full maturity (Casey, Giedd, & Thomas, 2000; Fuster, 2002). A variety of studies have provided evidence that this prolonged period of development makes the PFC particularly sensitive to environmental influences – not only during the prenatal period and infancy, but also during childhood and adolescence (Andersen & Teicher, 2008; Crews, He, & Hodge, 2007). Among adults, as among children, there is a high degree of variability in cognitive functions that rely on PFC, including working memory (Vogel & Machizawa, 2004; Vogel, McCollough, & Machizawa, 2005) and cognitive control (Braver, Cole, & Yarkoni, 2010; Kane & Engle, 2002). Research on development and plasticity can provide important insights regarding the origins of individual differences in PFC-dependent cognitive functions. The focus of this chapter is on the role of the environment in shaping the development of the PFC – for better or for worse.

There is substantial evidence that the development of prefrontal cortex can be hindered by a variety of environmental factors, including chronic stress as well as physical and psychosocial deprivation. However, there is also a growing body of research showing that various interventions could have a positive influence on brain function, or at least mitigate the effects of negative influences. This chapter provides an overview of research that provides evidence for both negative and positive environmental influences on prefrontal function, with an emphasis on prefrontal development. It then introduces the work in this thesis on improving reasoning ability, a prefrontal skill that has long been thought to be immutable to environmental influences.

Negative environmental influences on prefrontal development

Children who experience detrimental or simply insufficient environments encounter obstacles to reaching their full potential. Two crucial questions are how these obstacles can be prevented beforehand, and whether or how, once encountered, they can be overcome. Here, we consider in turn various negative influences on the development of prefrontal cortex, including physical and psychosocial factors. Negative environmental influences tend to cluster together: children of lower socioeconomic status (SES) are at greater risk for many of these factors.

Physical factors in the prenatal environment

Research on the effects of prenatal exposure to teratogens (substances that increase the risk of birth defects, such as alcohol and other drugs) illustrates how

the prenatal environment influences brain development (Langlois & Mayes, 2008). The specific patterns of deficits observed in children who were exposed to drugs and alcohol *in utero* shed light on the vulnerability of PFC to insult even before birth. Dopamine-rich cortical and subcortical fetal brain structures are particularly susceptible to damage from intrauterine drug exposure, given the large number of psychoactive substances that influence dopaminergic transmission. We focus here on alcohol and cocaine because of the depth of the literature linking these substances to PFC dysfunction. However, there have also been studies suggesting that prefrontal development may be negatively impacted by prenatal exposure to other substances, including tobacco (Cornelius & Day, 2009) and marijuana (Campolongo, Trezza, Palmery, Trabace, & Cuomo, 2009). For an in-depth discussion of prenatal substance exposure, see (Shankaran et al., 2007) and (Derauf, Kekatpure, Neyzi, Lester, & Kosofsky, 2009).

Alcohol

For at least thirty years, it has been known that alcohol exposure *in utero* can lead to negative developmental outcomes. In 1973, extreme symptoms associated with prenatal alcohol exposure, namely growth deficiency, facial malformation and mental retardation, were grouped under the diagnosis of Fetal Alcohol Syndrome (FAS). Fetal Alcohol Spectrum Disorder (FASD) is a broader term that encompasses the full spectrum of negative outcomes associated with prenatal alcohol exposure (Norman, Crocker, Mattson, & Riley, 2009). Children with FASD have smaller brains than healthy children (Sowell et al., 2001) and an abnormal brain shape, specifically in frontal cortex and the left hemisphere (Sowell et al., 2002). Further, individuals with FASD show deficits in many PFC-dependent skills, including cognitive flexibility, working memory, planning, and reasoning (Mattson et al., 2010). Importantly, these deficits are found with and without facial dysmorphology, a hallmark symptom of FAS.

In a large study of executive function (EF) in four-year- old children, Noland and colleagues found a negative correlation between severity of prenatal alcohol exposure and performance on a test of cognitive inhibition (Noland, Singer, Mehta, & Super, 2003). This relationship held when they controlled for verbal IQ, other prenatal drug exposure, and postnatal environmental factors. They also tested two other PFC-dependent cognitive measures, category fluency and motor planning, but did not find an effect of alcohol exposure on either of these tests. It is important to note that these tests were administered at an age – 4 years – when the PFC is underdeveloped in all children.

Cognitive deficits resulting from prenatal alcohol exposure may be more evident later in development, when typically developing children begin to exhibit a variety of PFC-dependent skills. In fact, there is even some evidence that differences cognition can be detected even in adulthood. Adults who were exposed to alcohol *in utero* perform well below average on consonant trigrams, a test of working memory that requires suppression of interference (Kerns, Don, Mateer,

& Streissguth, 1997). To get an accurate picture of the long-term effects of prenatal alcohol exposure on the development of PFC-dependent skills in humans, it will be necessary to follow infants with FASD throughout childhood and adolescence.

Research in rats provides independent confirmation that prenatal alcohol exposure leads to deficits in PFC-dependent skills. For example, Mihalick and colleagues found that rats that had been exposed to alcohol *in utero* showed deficits in reversal learning, inhibition, and transfer of learning (Mihalick, Crandall, Langlois, Krienke, & Dube, 2001). The rats in this study had a significant decrease in the number of neurons in the medial prefrontal cortex compared to rats whose mothers had been fed a standard diet during pregnancy. A number of factors have been shown to exacerbate the neurotoxicity of alcohol. For example, genetic susceptibility linked to polymorphisms in alcohol dehydrogenase and the serotonin transporter gene promoter (Warren & Li, 2005) can interact with alcohol to derail neurodevelopment.

Cocaine

When cocaine use spiked in the 1980s, researchers expected the effects of intrauterine cocaine exposure to be disastrous (Lewis et al., 2009). Initial characterization of these effects, however, showed them to be remarkably subtle. More recently, though, long-term problems have been identified in children who were followed through the age of 15 years, including deficits in PFC-dependent functions.

In a large behavioral study involving a continuous performance test similar to a Go/No-Go task, Accornero and colleagues found that 7-year-old children who had been exposed to cocaine *in utero* were no more likely than non-exposed peers to correctly withhold responses to 'No-Go' stimuli, but were slower and less accurate at responding to 'Go' stimuli (Accornero et al., 2007). These results suggest that the drug-exposed group may have had to perform the task more cautiously than their peers to achieve the same level of response inhibition. Consistent with this interpretation, Sheinkopf and colleagues showed in an fMRI study that cocaine-exposed children engaged the right inferior frontal gyrus and striatum more strongly than controls on No-Go trials, despite similar levels of performance (Sheinkopf et al., 2009). These regions have been implicated in response control (Dodds, Morein-Zamir, & Robbins, 2010), suggesting that the cocaine-exposed children had to engage greater control to achieve the same level of performance as typically developing children.

Animal research has pointed to three main mechanisms underlying the effects of prenatal cocaine exposure: 1) interactions with neurotransmitter systems, including monoamine systems (dopamine, serotonin, noradrenaline), GABA, and glutamate, 2) vasoconstriction leading to intrauterine growth restriction, and 3)

alterations in expression of genes important to placental function which cause dysregulation of stress responsivity (Derauf et al., 2009).

While both prenatal alcohol and cocaine have been shown to affect PFC development, alcohol seems to have more catastrophic consequences for PFC function than does cocaine. In other words, the severity of effects of substances on adults may not predict their effects on fetuses (Welch-Carre, 2005). This finding highlights the importance of this line of work: the impacts of prenatal factors may be counterintuitive. Understanding exactly how, and whether, substances that a fetus may be exposed to *in utero* affect brain development is critical for policy-makers. Additionally, research on the neural and behavioral effects of prenatal substance exposure is critical because it may lead to the identification of biomarkers that can aid in the diagnosis and treatment of children who were exposed to drugs *in utero*.

Physical factors in a child's environment

Brain development during childhood can be negatively affected both by the absence of necessary nutrients (malnutrition), as well as by the presence of environmental toxins. The long developmental trajectory of PFC makes it vulnerable to environmental insult throughout childhood.

Malnutrition

Adequate nutrition is critical for normative cognitive and brain development. One of the most glaring examples of this truism is research on the effects of iron deficiency in infancy. Iron is important for neurological functioning and development, playing a role in neurotransmitter metabolism, myelin formation, and metabolism in the brain (Beard, 2003). Lukowski and colleagues have shown that chronic, severe iron deficiency in infancy leads to deficits in inhibitory control, set-shifting, and planning in adulthood (Lukowski et al., 2010). The researchers administered a series of neuropsychological tests designed to tap frontostriatal networks to young adults with and without iron deficiency as infants. Two tests showed particularly strong effects of lead exposure: Trails B and Stockings of Cambridge. Performance on both of these tasks is impaired in patients with frontal lobe lesions (Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Stuss et al., 2001). On the Trails B task, a task that requires the test-taker to draw a line to complete the pattern 1, A, 2, B, 3, C etc., young adults who had iron deficiency as infants made more switching errors relative to young adults with good early iron status. On the Stockings of Cambridge task, a task that requires participants to plan a series of moves to complete a problem, young adults with iron deficiency needed more time to plan for harder problems, and they needed more moves to complete these problems.

Animal research has shown that iron deficiency in early life impacts myelination, synaptogenesis, dendritogenesis, and neurotransmission, leading to long-term

changes in abilities such as spatial learning and attention (Lozoff et al., 2006). Iron deficiency also leads to increased extracellular dopamine and reduced dopaminergic activity in the striatum, which affects frontostriatal networks. Given the widespread effects of iron on brain function, it is no surprise that iron deficiency negatively affects PFC function.

Lead exposure

Exposure to heavy metals in food, chemical waste, and synthetic materials is known to interfere with biochemical processes necessary for normal brain development. Lead exposure, in particular, is dangerous because it disrupts synapse formation and myelination, and interferes with neurotransmitter systems. Exposure to lead during childhood, for example through contact with lead-based paints, has been shown to be devastating for the development of PFC-dependent cognitive functions. Canfield and colleagues tested 5.5-year-old lead-exposed children on a variety of PFC-dependent tasks. Even after controlling for factors such as SES, quality of caregiving, maternal and child intelligence, blood lead level significantly predicted performance on tests of planning, working memory, and set-shifting (Canfield, Gendle, & Cory-Slechta, 2004). PFC structure is also affected by lead exposure: adults with childhood lead exposure have reduced gray matter in PFC (Cecil et al., 2008). Brubaker and colleagues investigated the effects of the age of lead exposure within the age range of 1 to 6 years. They showed that lead exposure *later* in this range leads to a greater decrease in PFC gray matter volume than earlier exposure (Brubaker, Dietrich, Lanphear, & Cecil, 2010).

Research in monkeys and rats has shown that even low levels of lead exposure compromise PFC-dependent behaviors. Monkeys exposed to lead were shown to be impaired in learning a delayed alternation task, and failed to perform the task correctly when the delays were long (Rice & Karpinski, 1988). In rats, it has been shown that lead exposure disrupts neurodevelopmental processes such as neuron migration, synapse formation, and myelination, and also interferes with several neurotransmitter systems, including dopamine, glutamate, and acetylcholine (Costa, Aschner, Vitalone, Syversen, & Soldin, 2004).

Chronic stress

A stressor can be defined as real or perceived threat to homeostasis, and stress can be defines as the state of experiencing such stressors. Stressors can take many forms, including exposure to predators, physical restraint, and maternal separation. A neural pathway that includes the amygdala, hippocampus and medial prefrontal cortex (mPFC) has been implicated in the physiological response to stress (de Kloet, Joels, & Holsboer, 2005; Krugers, Hoogenraad, & Groc, 2010). These brain structures exert influence over the hypothalamic-pituitary-adrenal axis. The hypothalamus releases corticotropin-releasing hormone, which regulates secretion of adrenocorticotropic hormone (ACTH) from

the anterior pituitary gland. ACTH in turn acts upon the adrenal glands, which regulate the secretion of cortisol. PFC, hippocampus, and amygdala contain a high number of receptors for cortisol, glucocorticoid receptors, so it stands to reason that these regions are particularly sensitive to its levels (de Kloet et al., 2005; Joels, Pu, Wiegert, Oitzl, & Krugers, 2006).

Cortisol release is adaptive when orchestrating an acute stress response: it leads to the release of energy from storage and puts long term projects like reproduction and immune system maintenance on hold. However, chronically high levels of cortisol can wreak havoc on tissue systems throughout the body, including the brain (McEwen, 2004; Sapolsky, 2003). Chronic stress is a risk factor for many psychiatric illnesses (E. S. Brown, Varghese, & McEwen, 2004) but also takes a toll on cognition in healthy individuals. Here, we will consider animal research on the effects of stress *in utero* and postnatal development. This body of research provides a window into potential mechanisms underlying neural effects of deprivation. We will discuss the effects of stress at the molecular and cellular levels and then widen our view to consider how stress affects PFC-dependent behavior in rodents. Animal models of chronic stress provide insights regarding children dealing with chronic stress, including children who experience early deprivation and children from low socioeconomic status (SES) homes.

Chronic stress can change gene expression. When glucocorticoid receptors bind cortisol, they dimerize and become activated transcription factors. In addition to acting directly as a transcription factor, cortisol can also lead to histone acetylation and increased methylation. An example of a direct link between environment and these epigenetic effects comes from work on the relationship between maternal behavior and stress reactivity (Weaver et al., 2004). High quality maternal behavior, as measured by high levels of licking and grooming, alters the epigenomes of rat pups. This experience changes methylation patterns and histone acetylation to lead to reduced expression of glucocorticoid receptors (Szyf, Weaver, & Meaney, 2007). Rat pups that experience low quality maternal behavior, in contrast, have higher glucocorticoid receptor expression, and have higher levels of stress reactivity. These pups have abnormal behaviors, including impaired novelty seeking, spatial learning (Liu, Diorio, Day, Francis, & Meaney, 2000), and working memory (Barha, Pawluski, & Galea, 2007) that persist into adulthood. This finding from the animal literature parallels the finding deficient early caregiving in humans, as experienced in Romanian orphanages, could lead to long lasting brain changes.

In part through its epigenetic effects, stress can alter cellular morphology. For example, exposure to stress hormones *in utero* leads to decreases in spine density and dendritic complexity in dorsal anterior cingulate cortex, a subregion of mPFC, and orbitofrontal cortex (Murmu et al., 2006). These changes mirror cellular morphology changes in hippocampus, in which cells also show dendritic hypotrophy. Stress actually reshapes neurons in the mPFC, hippocampus, and amygdala, and by changing their structure, affects network connectivity.

Interestingly, mPFC seems to be more sensitive to the effects of stress either the hippocampus or the amygdala. Dendrites in PFC begin to change after just one week of stress (S. M. Brown, Henning, & Wellman, 2005), but structural changes in these other regions take several weeks (McEwen, 2005).

The effects of this remodeling are evident in behavior. In addition to deficits in behaviors dependent on the hippocampus and the amygdala (Conrad, Galea, Kuroda, & McEwen, 1996; de Kloet, Oitzl, & Joels, 1999; Vyas, Pillai, & Chattarji, 2004), stress causes clear deficits in PFC-dependent behaviors such as working memory (Mizoguchi et al., 2000) and attention. Liston and colleagues found that, in rodents, stress decreased apical dendrite length in PFC, and this was correlated with impairments in attention shifting (Liston et al., 2006). In summary, chronic stress leads to elevated cortisol levels, which in turn alter gene expression, neural structure and function, and PFC-dependent behaviors. In the next sections, we discuss how environments associated with chronic stress, early deprivation and low SES, impact PFC structure and function in children.

Psychosocial deprivation

Institutionalization in early childhood can drastically alter development. Institutional settings tend to be characterized by a low caregiver-to-child ratio, unresponsive caregiving, and impoverished sensory, cognitive, and linguistic stimulation (C. A. Nelson, 3rd et al., 2007). As a result, children who spend time in these orphanages suffer cognitive impairments spanning a wide variety of abilities, including language, social-emotional development, and cognitive control. The literature on children who have experienced profound and prolonged deprivation is substantial (Gunnar, Bruce, & Grotevant, 2000; Gunnar & van Dulmen, 2007). Here, we summarize the extant literature on deficits in PFC-dependent cognitive function and PFC structure and function in children who have experienced early environmental deprivation. Behavioral research indicates that adolescents who were adopted because of early caregiver deprivation have impaired cognitive control relative to age-matched controls (Mueller et al., 2010). Adolescents who had experienced early deprivation were slowed to switch from a prepotent (‘go’) response to an alternative (‘change’) response. These adolescents also showed greater activity in inferior PFC in response during task-switching trials.

An early PET study showed that children adopted from Romanian orphanages showed reduced orbitofrontal cortex (OFC) activity, as compared to adults and the nonepileptic hemispheres of childhood epilepsy controls (Chugani et al., 2001). These children also showed reduced activity in medial and lateral temporal lobe, and brainstem. More recently, a DTI study provided evidence of reduced white matter integrity in children who had been institutionalized (Govindan, Behen, Helder, Makki, & Chugani, 2010). These reductions in FA were localized to uncinate fasciculus, which connects medial temporal lobe to OFC, and superior longitudinal fasciculus, which connects frontal, parietal, and

temporal cortices. FA in the right uncinate fasciculus was correlated with duration of stay in an orphanage. Further, a structural MRI study revealed that OFC volumes were smaller in children who had suffered parental physical abuse (Hanson et al., 2010).

The deficits in PFC development associated with early institutional rearing have been attributed to the absence of "expectable" environmental inputs during sensitive periods, or periods of development during which certain neural systems are more plastic (C. A. Nelson & Sheridan, in press). This plasticity is adaptive in the sense that environmental input can shape the system to deal with the environment, but it leaves the system vulnerable in that the *absence* of positive environmental input can negatively impact development in a lasting way.

Low SES

Leaving aside extreme environments, like the Romanian orphanages described above, children's schooling and home environments vary in ways that influence a child's acquisition of knowledge and skills. These differences between neighborhoods may influence the developmental trajectory of the PFC and other brain regions. Although the long-term consequences of low SES on brain development are still largely unknown, this topic has begun to receive attention over the last few years (Hackman & Farah, 2009; Hackman, Farah, & Meaney, 2010; Raizada & Kishiyama, 2010)

It has been well documented that children from low SES backgrounds are at a higher risk of difficulties in school than their middle class peers (Bradley & Corwyn, 2002). The list of possible reasons for this difference is extensive. Low SES tends to be associated with lower levels of parental education, as well as a higher incidence of many of the physical factors described above such as exposure to environmental toxins like lead (Miranda, Edwards, Swamy, Paul, & Neelon, 2010). Additionally, the existence of socioeconomic disparities can lead to higher levels of chronic stress in lower SES individuals. In animal models, as described below, chronic stress is correlated with changes in structure and function of PFC. Regardless of the individual causal factors behind deficits in PFC-dependent cognition in children from low SES backgrounds, a better understanding of SES-related differences in brain and cognitive development is essential for designing effective brain-based interventions.

While there is a relationship between SES and performance on many tests of cognition (Bradley & Corwyn, 2002; Duncan, Brooks-Gunn, & Klebanov, 1994; Kiernan & Huerta, 2008; McLoyd, 1998), language and cognitive control appear to be influenced more strongly by childhood environment than other areas of cognition (Noble, McCandliss, & Farah, 2007). Here, we will briefly discuss SES-related differences in language skills, with a focus on inferior frontal gyrus (IFG), then turn our attention to studies that have shown differences in prefrontal structure, function, and cognition between high and low SES children. A broader

discussion of deficits across cognitive and emotional systems can be found elsewhere (Hackman & Farah, 2009; Hackman et al., 2010; Raizada & Kishiyama, 2010).

Effects of childhood language exposure on the inferior frontal gyrus

Early language exposure is, on average, greatly diminished in children from low SES backgrounds. Twenty years ago, it was shown that the average number of hours of 1-on-1 picture book reading experienced by children prior to kindergarten entry was 25 for low SES children and between 1000 and 1700 for middle SES children (Adams, 1990). Subsequently, Hart and Risley showed that children from low SES backgrounds have heard on average 30 million fewer words by the age of three than children from more privileged families (Hart & Risley, 2003). Exposure to child-directed speech strongly predicted vocabulary at age three, and academic outcomes through the third grade. It is also important to highlight – even though the consequences are not yet well understood – that by the age of 4, children from low SES backgrounds have received on average 26,000 verbal encouragements and 57,000 discouragements, as compared with 166,000 encouragements and 26,000 discouragements for children from higher SES backgrounds.

Given these extreme differences in language exposure, it is perhaps not surprising that SES influences a critical brain region supporting language. Raizada and colleagues found a correlation between SES and the degree of hemispheric specialization in left inferior frontal gyrus (IFG) during a rhyming task in 5-year-old children (Raizada, Richards, Meltzoff, & Kuhl, 2008). The higher the SES of the child, the greater the difference in level of fMRI activation in left IFG (i.e. Broca's area) compared to right IFG. In other words, higher SES correlated with higher left-lateralization of language processing. The degree of left-lateralization of language has been found in several studies to be an indicator of the maturation of language-processing areas of the brain (Amunts, Schleicher, Ditterich, & Zilles, 2003; Lu et al., 2007).

Attention and working memory

There is behavioral evidence that children from low SES backgrounds score lower than children from middle and high SES backgrounds on attentional tasks (Mezzacappa, 2004). This research has been conducted with Posner's Attention Network Test (ANT), which measures three forms of attention: alerting, orienting, and executive attention (Berger, Jones, Rothbart, & Posner, 2000). Children from lower SES performed worse than their peers on the alerting and executive attention components of the ANT.

This behavioral difference in attention has since been investigated with EEG. D'Angiulli and colleagues found that children from a low SES group did not show

the same event-related potential (ERP) waveform difference between attended and unattended tones as a high SES group (D'Angiulli, Herdman, Stapells, & Hertzman, 2008). In this task, children listened to two audio streams, one in each ear. These streams differed in frequency, and children were instructed to attend to only one of the streams, pressing a button each time they heard a tone that was longer in duration than other tones in that stream. The two groups showed differential patterns of theta activity related to target tones in the irrelevant stream. Interestingly, the groups did not differ either in accuracy or response times, suggesting that neural measures were more sensitive than the behavioral measures. According to this interpretation, behavioral differences should be evident on a more challenging version of the task.

Orienting to novel stimuli is an important first step in learning. A novelty-orienting ERP response is characterized as a negative-going deflection over frontocentral electrode sites beginning around 200 ms after presentation of a novel stimulus (N2). Surprisingly, the results of a small study suggest that SES may affect even this rapid orienting process. Kishiyama, Knight, and colleagues investigated the prefrontal novelty response in children aged 7-12 from high and low SES backgrounds (Kishiyama, Boyce, Jimenez, Perry, & Knight, 2009). They found a reduced ERP response to novel pictures in children from low SES backgrounds. This finding mirrored the finding from a similar task in adult patients with PFC damage (Barcelo, Suwazono, & Knight, 2000; Knight, 1984; Yago, Duarte, Wong, Barcelo, & Knight, 2004). However, caution should be used in comparing adult patients with neurologically unimpaired children. Many of the most important questions will require multi-year longitudinal studies. What, if any, are the behavioral consequences of a blunted orienting response? Do the SES-related ERP differences observed in children persist into adulthood? Finally, can positive interventions counteract the early effects of socioeconomic disadvantage?

There is some evidence that when children grow up with prolonged and unaddressed disadvantage, this can have long-lasting consequences on cognitive functioning. For example, Evans and Schamberg (2009) showed that spatial working memory performance in adults is correlated with duration of poverty during childhood. This relationship between childhood SES and later working memory performance appears to be mediated by stress levels during childhood (Evans & Schamberg, 2009).

The influence of SES on PFC development is a sensitive topic of research, and as such should be broached with care. However, it is only by directly investigating these issues that we can improve our understanding of the environmental factors that influence cognitive and brain development. New research is starting to indicate that positive interventions might be able to level the playing field of social disadvantage. Currently, the vast majority of low SES children never receive such assistance. Additional neuroscientific research on the effects of low SES and poverty could influence public policy for the better, for

example through the work of such groups as the Forum on Early Child Development and the affiliated National Council on the Developing Child.

Positive environmental influences on prefrontal development

Intensive cognitive training studies in adults are beginning to reveal training-related changes in prefrontal structure and function (Braver, Paxton, Locke, & Barch, 2009; Erickson et al., 2007; Klingberg, 2010; Miotto et al., 2006). Further, there is strong evidence that physical exercise confers beneficial effects on PFC-dependent cognitive function in both adults and children (Hillman, Erickson, & Kramer, 2008). Here, we briefly review the animal literature on environmental enrichment. Then, we discuss extant intervention research involving children from deprived backgrounds.

Animal model: Environmental enrichment paradigm

Donald Hebb and his students showed more than 60 years ago that rats housed in a complex environment outperformed rats housed in a standard laboratory environment on several tests of rodent cognition (Markham & Greenough, 2004). Several groups, including those of Mark Rosenzweig and William Greenough, subsequently used this environmental enrichment paradigm to study how housing conditions could affect brain structure. In these studies, rats were assigned to one of several housing conditions at weaning. In the standard condition, three animals were kept in a standard laboratory cage, and provided with food and water. In the enriched condition, a group of 10-12 animals was kept in a large cage containing a variety of stimulus objects, which were changed daily. As Markham and Greenough note (Markham & Greenough, 2004), the term enriched is a misnomer, because this condition was not enriched relative to a natural habitat, but rather to the standard laboratory environment or to an impoverished (or isolated) condition, in which a single animal was housed in a standard sized cage.

A landmark study by Mark Rosenzweig and colleagues showed that rats raised in the EC had heavier brains than those raised in the IC (Rosenzweig, Krech, Bennett, & Diamond, 1962). Up to that point, brain weight had been considered a very stable trait – not one that was subject to environmental influences. Subsequent neuroanatomical research revealed that these differences in brain weight were caused by differences in cortical thickness. Animals exposed to the EC environment developed slightly but significantly thicker cerebral cortices than their SC or IC littermates (M. C. Diamond, Lindner, & Raymond, 1967). More detailed neuroanatomical measurements of pyramidal neurons in the occipital cortex revealed changes in size of cell bodies, number of dendritic spines, dendritic branching, and size of synaptic contacts (Rosenzweig, Breedlove, & Leiman, 2002). Subsequent research has provided evidence for environmental influences on the structure of PFC, in addition to other cortical regions. These studies have found changes in spine density in medial PFC (Kolb, Gorny,

Soderpalm, & Robinson, 2003) as well as in dendritic length in OFC (Bock, Murmu, Ferdman, Leshem, & Braun, 2008). Consistent with this research in animals, recent research in humans suggests that intensive training of attention, working memory, and other PFC-dependent cognitive functions may indeed lead to structural changes in the PFC.

Intervening after severe psychosocial deprivation

We will focus on research on interventions for these children to ask whether the impairments caused by institutionalization are reversible. Encouraging evidence has come from the Bucharest Early Intervention Program (BEIP), a study of a foster care intervention for institutionalized children in Bucharest, Romania. In this study, children were randomly assigned to either remain in the institution, or were placed into a foster care intervention. Random assignment removed the confound present in other studies that children who are most physically or mentally fit are most likely to be adopted.

Behaviorally, the BEIP has shown that children who were raised in a foster home rather than the orphanage have greatly improved emotional function (Ghera et al., 2009), language (Windsor, Glaze, & Koga, 2007), general cognitive abilities (C. A. Nelson, 3rd et al., 2007), and spatial working memory (Bos, Fox, Zeanah, & Nelson III, 2009). Importantly, improvements were greatest when children were removed from orphanages before the age of two.

The BEIP has shown that foster care normalized the abnormal pattern of EEG activity observed in institutionalized children, leading to an increase in alpha-band oscillatory activity and decreased short-distance EEG coherence (Marshall, Reeb, Fox, Nelson, & Zeanah, 2008), which likely reflect an increase in cross-talk between distant brain regions. Consistent with the behavioral results of the BEIP, the effects of intervention on EEG activity were most pronounced in children who were placed in foster care before the age of two. Future research with combined EEG/fMRI is needed to localize definitively the source of the changes in the EEG signal.

Nelson and colleagues have attributed improvements observed in the BEIP to activity-dependent mechanisms of plasticity engaged when children are placed in a cognitively stimulating environment (C. A. Nelson, 3rd et al., 2007). They have emphasized that sensitive periods may be modifiable given the right circumstances, and that extending the window for intervention may improve the prognosis for children recovering from early deprivation. This line of research has wide-reaching policy implications for countries deciding how to best care for abandoned, orphaned, or maltreated children. The BEIP has demonstrated that foster care leads to more positive developmental outcomes than institutionalization.

Programs for children from low SES families

The two best examples of randomized interventions with long-term longitudinal follow-up data are the Abecedarian Program (Barnett & Masse, 2007; Campbell, Pungello, Miller-Johnson, Burchinal, & Ramey, 2001), and the Perry Preschool Program (Belfield, Nores, Barnett, & Schweinhart, 2006; P. Muennig, L. Schweinhart, H. Montie, & M. Neidell, 2009). Both programs concentrated on low-SES, predominantly ethnic minority children. The Perry program enrolled 64 children at ages three and four, and consisted of intensive daily sessions lasting two and a half hours each, and also a weekly 90-minute home visit to build parental involvement. These sessions lasted for thirty weeks each year, for four years. Longitudinal follow-up is ongoing, with the most recent paper describing the participants 37 years later (P. Muennig, L. Schweinhart, J. Montie, & M. Neidell, 2009). The Abecedarian program was larger and was even more intensive, involving full-day care, five days per week, 50 weeks per year. The children started at an average age of 4.4 years, and remained in the program until age 8. Longitudinal follow-up continued until age 21.

Even decades later, the combination of a rigorous randomized-control design, intensive intervention, and long-term follow-up provided by these two programs remains unique. All three of these ingredients are essential for increasing our understanding of the long-term causal role of early childhood intervention, but they are also the very aspects which are the most difficult to implement. The Perry and Abecedarian programs targeted a broad range of cognitive skills, and so it is not possible to determine which components of these programs have been most effective, or why. However, there also exist several low-SES-targeted interventions focused on strengthening PFC-dependent skills. One influential study showed that executive functions were enhanced by a program that taxed cognitive control throughout the pre-school curriculum (A. Diamond, Barnett, Thomas, & Munro, 2007). Many of these children came from underprivileged backgrounds. This program consisted of instructional strategies that encouraged cognitive control throughout the day, rather than expensive computer programs.

Introduction to thesis research

While these studies have demonstrated plasticity in some cognitive skills, it is still widely believed that training cannot alter other abilities. In particular, many consider fluid reasoning – the ability to solve novel problems – to be set in stone. Reasoning is a skill that is central to theories of intelligence: most intelligence tests contain a measure of reasoning. Figure 1.1 shows three examples of questions that tax reasoning ability.

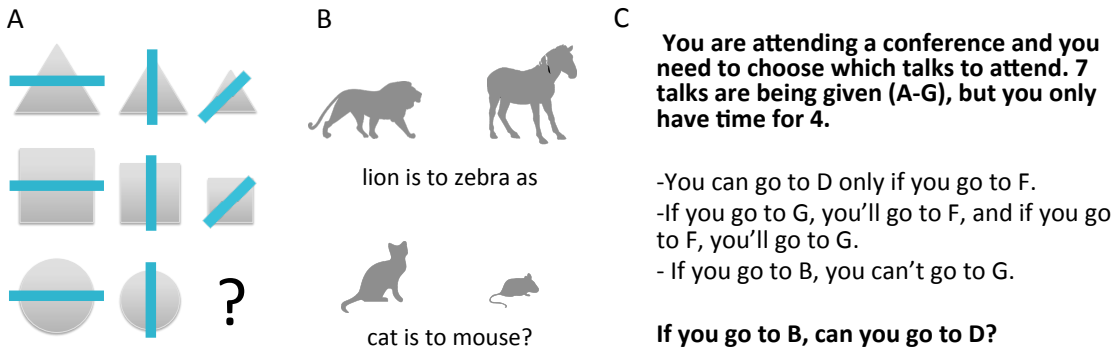

Figure 1.1. Reasoning questions. A. A matrix reasoning question. To solve the question, one must integrate changes in shape type, shape size, and line orientation. The correct answer is a small circle with a diagonal line. B. An analogy question. To determine whether the analogy is valid, one needs to extract the relationship between lion and zebra and determine whether it matches the relationship between cat and mouse. The correct answer is "yes." C. A question modeled after the Logic Games section of the LSAT. To answer the question, one has to integrate the given verbal rules. The correct answer is "no."

Because reasoning ability is highly predictive of academic outcomes, the view that it is fixed has broad implications for education policy. If it is not possible to improve reasoning with training, then there is little hope for the academic success of children who have been exposed to negative environmental influences. This view also calls into question the fairness of standardized tests for school admission that measure reasoning ability, as it would not be possible to improve one's score through effort and practice. However, there is good evidence reasoning ability is improved by schooling (for review, see Nisbett, 2009). Additionally, people who prepare for standardized tests of reasoning can improve dramatically. In other words, there is good real-world evidence that experience alters reasoning ability.

Further, it seems unlikely that reasoning ability would be less plastic than the neural circuitry that supports it. Reasoning ability relies heavily on lateral PFC, which, as described above, can be altered by experience (Prado, Chadha, & Booth, 2011; Krawczyk, 2012; Duncan et al. 2000). Rostrolateral prefrontal cortex (RLPFC) has been implicated in the process of relational integration, which is necessary for the types of reasoning questions shown in Figure 1.1 (Wendelken, Chung, & Bunge, 2011; Wendelken, O'Hare, Whitaker, Ferrer, & Bunge, 2011). RLPFC is one of the last regions to develop during childhood (Giedd et al., 1999) and has undergone the greatest expansion over the course of evolution (Semendeferi et al., 2001), perhaps reflecting the complexity and abstraction of its functions.

The overarching goal of this thesis research was to demonstrate malleability in reasoning ability, and to investigate changes in brain structure and function that accompany reasoning training.

In the study presented in Chapter 2, we designed and assessed an intervention to improve reasoning in children from low SES backgrounds. We chose novel, engaging games that would "cross-train" brain regions that have shown to be critical for reasoning: anterior prefrontal cortex and posterior parietal cortex. We also designed an intervention to target cognitive speed, an important but distinct skill. Both interventions were implemented at a school with a history of poor statewide test scores. After just 8 weeks, both interventions led to an improvement in the targeted skill of over 30%. In the reasoning group, this gain corresponded to roughly 10 points in performance IQ.

In the study presented in Chapters 3 and 4, we wanted to test whether reasoning could be improved in young adults. We studied the behavioral and neural effects of preparation for the Law School Admissions Test (LSAT), an exam with strong reasoning demands (see Figure 1.1C), because it was a real-life instance of adults learning a novel, relevant cognitive skill.

In Chapter 3, we sought to test the hypothesis that patterns of intrinsic functional connectivity in brain networks supporting reasoning can change as a function of training. In the trained group, but not in a well-matched control group, we observed strengthened coupling at rest between frontal, parietal, and striatal regions previously implicated in reasoning, as well as weakened coupling between these regions and motor cortex. It is one thing to show that training can alter patterns of task-related functional connectivity (a result that could reflect changes in the way participants are performing the task), and quite another to show that it can alter the so-called 'intrinsic' architecture of the brain. In terms of evidence for neural plasticity, this latter measure sets a much higher bar.

In Chapter 4, we tested whether structural connectivity, as measured by diffusion in white matter, also changes with training. In trained participants but not controls, we observed decreased radial diffusivity (RD) in white matter connecting frontal cortices, and decreased mean diffusivity (MD) within frontal and parietal lobe white matter. While the cellular underpinnings are unknown, these results provide evidence of experience-dependent white matter changes that may not be limited to myelination. Taken together, results from this study provide evidence for neural plasticity in large-scale networks supporting reasoning.

Finally, in Chapter 5, I will discuss the many open questions left to be answered by future studies of brain plasticity in humans.

Chapter 2
Reasoning training in children from low socioeconomic backgrounds

Fluid reasoning (FR) represents the capacity to think logically and solve problems in novel situations (Cattell, 1987; Horn & Cattell, 1967). Cattell proposed the Investment Hypothesis, whereby FR serves as a scaffold that allows a child to acquire other cognitive skills and knowledge (Cattell, 1987). Indeed, FR is a strong predictor of performance in school, at university, and in cognitively demanding occupations (Floyd, Evans, & McGrew, 2003; Fuchs et al., 2006; Gottfredson, 1997). Although FR is typically thought of as a stable characteristic of an individual, several lines of research have called into question this long-held assumption (Flynn, 2007; Gray & Thompson, 2004; Nisbett, 2009).

Given that FR ability is relevant for scholastic achievement, and that it is likely to be influenced by environmental factors (Flynn, 2007; Nisbett, 2009), we hypothesized that this cognitive skill would be a good target for a cognitive intervention in children from socioeconomically disadvantaged backgrounds. It has been shown that several cognitive skills that support reasoning, including working memory (WM) (Evans & Schamberg, 2009), attention (Mezzacappa, 2004), and language (Noble, McCandliss, & Farah, 2007) are compromised by low socioeconomic status (SES), and that academic outcomes are consistently worse for low SES children than for their middle class peers (Bradley, Convyn, Burchinal, McAdoo, & Coll, 2001; McLoyd, 1998).

In the present study, we conducted a cognitive intervention in students of ages 7 to10 at a school with a history of low statewide test scores and a high percentage of economically disadvantaged students. We chose to focus on this age range because the strongest influences of FR on later achievement have been observed among children of ages 5 to 10 (Ferrer & McArdle, 2004; Ferrer et al., 2007).

Over the years, interventions aimed at improving FR have had mixed results (Sternberg, 2008). Several studies have provided evidence that training of working memory, a cognitive function that is strongly related to FR (Engle, Tuholski, Laughlin, & Conway, 1999; Fry & Hale, 1996), leads to moderate improvements in FR (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Klingberg et al., 2005; Olesen, Westerberg, & Klingberg, 2004; Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009). Further, Holmes and colleagues have shown that training-related gains in WM, even in the absence of corresponding gains in FR, can lead to improvements in academic outcomes (Holmes, Gathercole, & Dunning, 2009). On the other hand, Owen and colleagues (Owen et al., 2010) have found in a large sample of adults that multiple days of playing a set of computerized cognitive tasks online, including FR tasks, does not transfer to a measure of speeded verbal reasoning.

We predicted that a training program targeting children, featuring a variety of computerized and non-computerized reasoning games in a classroom setting, could lead to larger gains in FR than those observed in previous studies. We sought to work with children from low SES backgrounds, since we reasoned that these children would be most likely to benefit from environmental enrichment (Gray, Chabris, & Braver, 2003; Raizada, 2009).

Many prior cognitive intervention studies have included for comparison a group of individuals who did not participate in the training (a passive control group) or a group whose training did not get progressively difficult over time (an active control group with non-adaptive training); other studies simply did not include a control group. Here, we sought to compare the effects of two well-matched training programs that emphasized different cognitive functions – FR and processing speed (PS) – each of which is a critical component of cognition (Gottfredson, 1997; Kail, 1991). Both training programs included a variety of engaging, commercially available games that increased in difficulty as participants improved. Unlike prior studies, in which researchers sought to show a larger improvement in cognitive test scores for the intervention group than the control group upon re-testing, we predicted a double-dissociation in the magnitude of the effects of our two training programs on FR and PS.

Our FR intervention was informed by research on the neural basis and development of this capacity (Ferrer, O'Hare, & Bunge, 2009). Many tests of FR require *relational integration*, or the ability to jointly consider distinct relationships between stimuli (Halford, Wilson, & Phillips, 1998). Such tests include, but are not limited to, Raven's Progressive Matrices, Tower of London, transitive inference problems, and propositional analogies. Although these tests differ from one another in many ways, they engage common brain regions – lateral prefrontal and posterior parietal cortices – in addition to task-specific regions (Bunge & Wendelken, 2009; Glascher et al.; Gray et al., 2003; Jung & Haier, 2007). In adults, rostrolateral PFC (rlPFC) plays a specific role in FR: it is primarily engaged on trials that require relational integration (Christoff & Gabrieli, 2002; Christoff et al., 2001; Wendelken & Bunge, 2009). Using several of these tests, it has been shown that children aged 7-12 engage the appropriate set of brain regions while performing reasoning tasks, but that they exhibit an immature, non-selective activation profile in rostrolateral prefrontal cortex (Crone et al., 2009; Ferrer et al., 2009; Wright, Matlen, Baym, Ferrer, & Bunge, 2007).

Given the commonalities and differences in brain activation observed across these various FR tasks, we hypothesized that 'cross-training' on various tasks that require relational integration would lead to maximal gains in FR. Importantly, because fluid intelligence characterizes the ability to tackle novel problems, we ensured that children were continually challenged with new tasks.

We designed a speed intervention that emphasized rapid visual detection and rapid motor responses during performance of a variety of games with simple rules. With this training program, we sought to tax PS, or "the ability to fluently perform cognitive tasks automatically, especially when under pressure to maintain focused attention and concentration" (McGrew, 1998). This skill is considered a central factor in cognitive development. Indeed, Kail and Salthouse (Kail & Salthouse, 1994) have argued that changes in PS over the lifespan underlie many of the observed changes in cognitive performance. Further, Bavelier and colleagues have shown that playing action video games results in improved PS across a variety of perceptual and attentional tasks (for review, see Dye, 2009). We sought to create a speed training program that would include as large a variety of games as the reasoning training program.

PS is thought to contribute to FR only weakly, and indirectly, through its influence on WM (Kail, 2007; Kail & Ferrer, 2007). Thus, while we anticipated that speed training might lead to slight gains in FR, we predicted that gains resulting from direct FR training would be much larger. In contrast, since FR training did not emphasize rapid responding, we predicted that reasoning training would result in minimal or no change in cognitive speed.

In summary, we sought to test whether children who participated in one of two 8-week cognitive training programs would exhibit selective improvements in the targeted cognitive processes. Importantly, both groups participated in active interventions focused on foundational cognitive skills. Given that motivation is critical for learning, we selected commercially available games that were designed to be entertaining. Further, recognizing the importance of social interaction in learning (Gelman, 2009), children in both groups had extensive and equal interactions with the researchers and with other children throughout the program.

Methods

School Selection

Our intervention was conducted within an after-school program at an elementary school in Oakland, California. This school was selected based on its low statewide test scores, which place it in the bottom 20% of California schools. 36% of students at this school are English language learners. In 2008, over 60% of students failed to achieve proficiency in English, and around 40% failed to achieve proficiency in Math on the California Standards Test. 72% of students at this school qualify as economically disadvantaged and receive free or reduced price lunch.

Participants

Children aged 7-10 with no history of neurological or psychiatric illness were recruited from this after-school program with approval from the Institutional Review Board at University of California, Berkeley. Children whose parents spoke languages other than English speakers were included in the study, given the relatively high proportion of these students in the after-school program. However, all potential study participants spoke English fluently. Informed consent was attained from parents in their native language (Spanish or English), and an information letter was given to children. Participants were randomly assigned to either the reasoning training program or the speed program, which were offered on alternate days of the week (Mondays and Wednesdays or Tuesdays and Thursdays). Data are reported for 17 children (10 boys and 7 girls, with a mean age of 8y 6m) who participated in reasoning training, and 11 children (8 boys and 3 girls, with a mean age of 8y 6m) who participated in speed training. No significant differences were found between groups in demographic measures (see Table 2.1). Demographic data for individual children can be found in Appendix A.

Training Group	**Gender**	**Age**		**Education of Primary Caregiver**		**Training Days Attended**		**WASI Vocabulary Raw (Normed)**	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Reasoning	10 M, 7 F	8.58	0.68	10.33	1.50	12.71	2.37	28.2 (48)	6.66 (9.58)
Speed	8 M, 3F	8.52	0.67	10.50	3.07	12.00	2.05	28.2 (46.2)	8.64 (7.01)

Table 2.1: Demographic Information. No significant differences were found in demographic variables between groups.

The study took place over the course of two semesters, with each child participating in a single 8-week training program. During the first semester, 12 children aged 7-10 participated in reasoning training and 10 children in speed training. The three 10-year-olds in the study (2 in the reasoning group and 1 in the speed group) displayed little interest in playing games with the younger children, and were not fully engaged in the program. As it was evident early in training that the emergent group dynamics were not conducive to learning for the older children, it was decided that the 10-year-olds would be excluded from final data analysis, and that enrollment during the second semester would be restricted to children aged 7-9. Additionally, two children from the speed group

were excluded from data analysis based on pre- or post-training assessment scores 2 standard deviations from the means for all children in the study. During the second semester, 7 additional children participated in reasoning training and 4 in speed training. In total, data are presented for 17 children in the reasoning group and 11 children in the speed group. In Appendix A, we provide data for all study participants.

Cognitive assessments

Assessments of cognitive ability were conducted both before and after 8 weeks of training. Standard cognitive measures of PS, FR, and WM were administered by researchers who were not involved in the training program. During the first semester of the training program, assessments were administered in a quiet corner of the training classroom. Since children were assessed on the days they attended training (either Mondays and Wednesdays or Tuesdays and Thursdays), the researchers conducting the assessments during the first semester could deduce each child's training group. During the second semester, assessments were administered in a separate room by a researcher who was blind to the group assignments.

To assess FR, we chose the Test of Nonverbal Intelligence (TONI-3), a matrix reasoning test with two equivalent versions. We administered these versions in a counterbalanced manner between participants, thereby guarding against the possibility that participants would remember the correct answer for a question upon re-testing.

We examined the effects of cognitive training on two different PS measures (Feldmann, 2004): Cross Out from Woodcock-Johnson-Revised and Coding B from Wechsler Intelligence Scale for Children IV. Cross Out is a timed test in which one must rapidly identify and put a line through each instance of a specific symbol in a row of similar symbols. A row is counted as correct if a child correctly identifies all five instances of the target symbol in that row. The raw score on this assessment is the total number of rows completed correctly in three minutes. Unlike Cross Out, Coding requires a mental transformation; it is a timed test in which one must rapidly translate digits into symbols by identifying the corresponding symbol for a digit provided in a legend. The total number of digits translated in two minutes serves as the raw score.

Although we did not attempt to train working memory *per se* in either training program, we sought to determine whether playing the reasoning and/or speed games would result in gains in this core cognitive function. We measured working memory with simple span measures of phonological and visuospatial working memory, namely the Digit and Spatial Span tests from the Wechsler Memory Scale. Both span tasks require participants to recall encoded stimuli in the same order in which they were presented (Forward span), and in the reverse order

(Backward span). Two trials are presented for each number of stimuli. The raw score represents the number of correct trials. The Forward tests measure the ability to maintain information online, whereas the Backward tests measure the ability to both maintain and manipulate information online. Digit Span and Spatial Span scores are computed as the sum of the Forward and Backward scores for each test.

Training

Each program was offered for 75 minutes per day, two days per week for 8 weeks. 60 minutes of the 75-minute sessions were dedicated to training, the remaining 15 minutes were used to take attendance, explain games, and provide breaks. Attendance ranged from 8 days to 16 days per child, and mean attendance did not differ significantly between groups (12.7 days for the reasoning group and 12 days for the speed group, p=.42). During the first semester, all children began training on the same day. During the second semester, start dates were staggered over the first three weeks of training. This modification made it feasible for the researchers performing assessments to be blind to the group assignments.

The games included in the reasoning and speed training programs are listed in Table 2.3 (for additional information about games and child-researcher interactions, see Supplemental Text A1). As noted previously, we sought to provide children with a variety of new reasoning games over the course of training. We sought to include a similarly varied set of games in the speed training so that it would be a well-matched control program. Both programs incorporated a mix of commercially available computerized and non-computerized games, as well as a mix of games that were played individually or in small groups. Games selected for reasoning training demanded the joint consideration of several task rules, relations, or steps required to solve a problem. Games selected for speed training involved rapid visual processing and rapid motor responding based on simple task rules.

Each day, children spent 15 minutes at each of 4 stations: computer games, Nintendo DS games, group non-computerized games, and individual non-computerized games. The remaining time was spent as short breaks between stations. This format kept children on task and engaged for a full hour during each training session. Two researchers managed the non-computerized game stations (one per station), and one researcher managed both computerized game stations. Researchers ensured that children stayed on task and motivated by providing hints and increasing the difficulty of games when appropriate.

Reasoning Games			
Game	***Company***	***Format***	***Players***
Set	SET Enterprises	NC	Group
Qwirkle	MindWare	NC	Group
Rush Hour	ThinkFun	NC	Indiv.
Tangoes	REX Games	NC	Indiv.
Chocolate Fix	ThinkFun	NC	Indiv.
Azada	Big Fish Games	C	Indiv.
Azada II	Big Fish Games	C	Indiv.
Big Brain Academy (Think Games)	Nintendo (Edutainment)	DS	Indiv.
Picross	Nintendo (Jupiter Multimedia)	DS	Indiv.
Professor Brainium's Games (Mind Bender)	Nintendo (BOLD games)	DS	Indiv.
Neves	Atlus Co. (Yuke's USA)	DS	Indiv.
Pipe Mania	Empire Interactive (Razorwork Studios)	DS	Indiv.
Speed of Processing Games			
Game	***Company***	***Format***	***Group/Indiv.***
Spoons	n/a	NC	Group
Pictureka	Hasbro Games	NC	Group
Speed	n/a	NC	Group
Blink	Mattel	NC	Group
Perfection	MiltonBradley	NC	Indiv.
Feeding Frenzy	Oberon Media (Sprout Games)	C	Indiv.
Super Cow	Big Fish Games (Nevosoft)	C	Indiv.
Bricks of Atlantis	Arcade Lab	C	Indiv.
Nervous Brickdown	Eidos Interactive (Arkedo Studio)	DS	Indiv.
Super Monkey Ball	Sega	DS	Indiv.
Mario Kart	Nintendo	DS	Indiv.
Ratatouille	THQ (Helixe)	DS	Indiv.

Table 3: Training Games. For computerized and DS games, the company format is as follows: Publisher (Developer). All C games are available for purchase and download at bigfishgames.com. Computerized: C; Non-computerized: NC; Nintendo DS: DS; Indiv.: Individual.

Results

Both training programs led to significant improvements in the trained cognitive ability, as measured by standard cognitive assessments. After reasoning training, children were able to solve an average of 4.5 more matrix reasoning problems on the Test of Nonverbal Intelligence (TONI-3) (t=4.36, df=16, P<.001; one-tailed p-value reported here and for all subsequent t-tests). This change corresponds to an effect size (Cohen's d) of 1.51 (Figure 2.1a, Table 2.2). Before training, children in the reasoning group had an average score of 96.3 points on the TONI, which is normed with a mean of 100 and a standard deviation is 15. After training, they had an average score of 106.2 points. This gain of 9.9 points brought the reasoning ability of the group from below average for their age (as indicated by the dotted line in Fig. 1a) to just above average. Gains on the TONI were not significant for children in the speed group (1.7 problems; 3.5 points; t=1.27, df=10, P=.10).

Assessment	Reasoning Training Group (n=17)						Speed Training Group (n=11)					
	Pre-training		Post-training				Pre-training		Post-training			
	Mean	SD	Mean	SD	*p*	*d*	Mean	SD	Mean	SD	*p*	*d*
TONI	15.7	2.6	20.2	3.5	<0.001*	1.51	17.4	4.1	19.1	5.3	0.1	0.38
Coding	36.5	4.9	37.8	8.5	0.2	0.19	34.3	7.5	42.6	7.8	<0.001*	1.15
Cross Out	14.8	2.7	16.5	3.7	0.002*	0.56	15.4	4.1	18.8	3.5	<0.001*	0.92
Digit Span-Forward	7.4	2.0	7.8	1.8	0.19	0.22	7.1	2.4	6.9	2.2	0.38	-0.04
Digit Span-Backwards	4.1	1.5	4.5	1.6	0.09	0.28	4.1	1.6	5.2	2.1	0.08	0.70
Spatial Span-Forward	6.0	1.7	7.1	1.8	0.01	0.65	7.0	1.7	6.6	1.6	0.26	-0.25
Spatial Span-Backwards	4.5	1.9	5.4	2.2	0.07	0.41	4.3	2.4	4.5	1.9	0.36	0.10

Table 2.2: Pre- and Post-training Assessment Scores**.** Significant paired one-tail t-tests are bolded. Spatial span was not collected for one subject in the speed group, so post-training data is reported for 10 subjects. Bold p-values are significant at p<.05 uncorrected. Asterisks indicate p-values that survived false discovery rate (FDR) corrected for multiple comparisons (α of .05 adjusted for 14 independent tests: p<0.004).

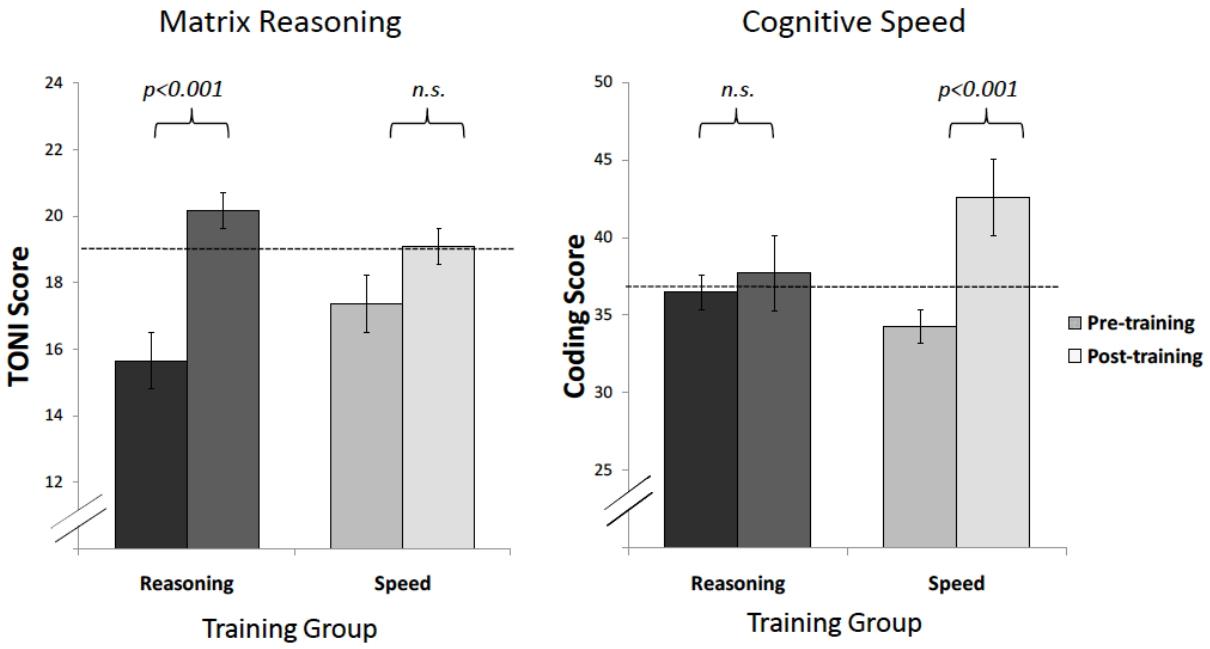

Figure 2.1. Raw TONI and Coding Scores Pre- and Post- Training. Training led to improvement specifically on the trained skill. Dotted lines represent the performance of an average 8.5 year old child. Error bars represent standard error. Reasoning group: N=17; Speed group: N=11.

In contrast, children in the speed training group improved significantly on a measure of cognitive speed, Coding (t=5.35, df=10, P<.001), whereas children in the reasoning group did not (t=0.88, df=16, P=.20) (Figure 2.1b, Table 2.3). Children in the speed group were able to complete an average of 8.3 more items on this measure, which corresponds to an effect size of 1.15. Training brought this group from slightly below average for their age (as indicated by the dotted line in Fig. 1b), to above average. Both groups improved on Cross Out (Table 2.3), but the improvement was greater for the speed group (t=1.76, df=26, P=.04).

To test for a double dissociation in training outcomes, we compared the percent change in raw scores on each measure for each group (Figure 2.2). The training group by outcome interaction was significant (F(1,26)=13.03, P<.001), showing that training led to selective improvements in the targeted skill. Reasoning training tended to show larger improvements on the TONI than did speed training (t=1.63, df=26, P=.058), and speed training resulted in larger improvements in Coding than did reasoning training (t=3.44, df=26, P=.001).

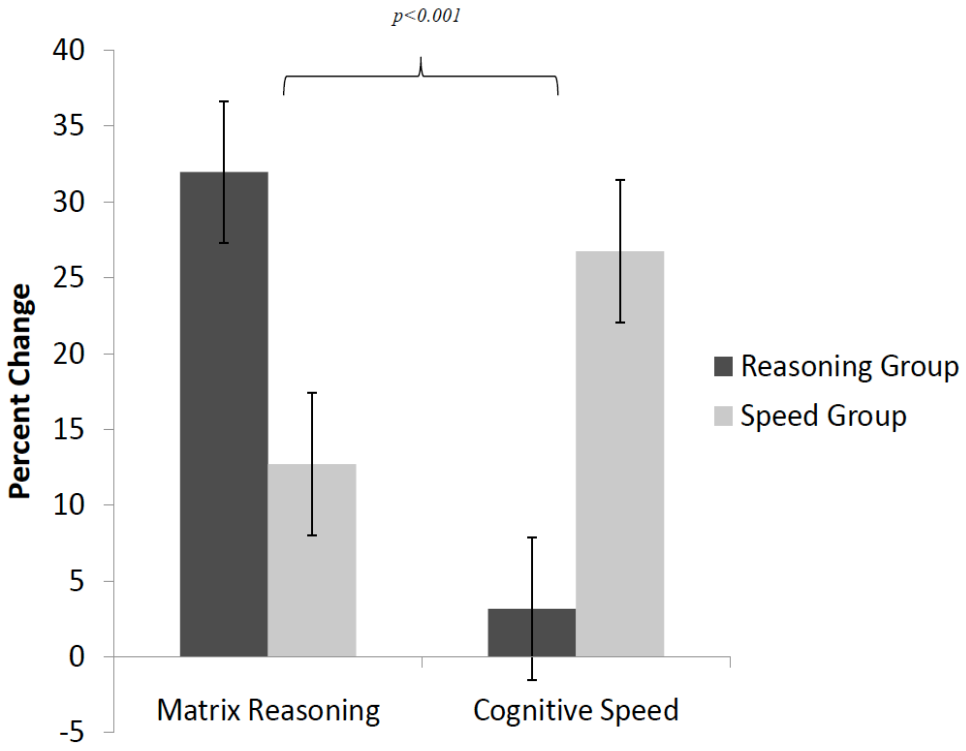

Figure 2.2. Double-Dissociation in Training Outcomes. Improvements in the two primary outcome measures show a significant training improvement by training condition interaction. Error bars represent standard error of the ANOVA. Reasoning group: N=17; Speed group: N=11.

Several groups have found that intensive practice of a working memory task results in moderate improvements in FR (Jaeggi et al., 2008; Klingberg et al., 2005; Olesen, Macoveanu, Tegner, & Klingberg, 2006; Thorell et al., 2009). As such, we sought to test whether children in the reasoning group improved on WM. Because both the FR and PS games required children to keep relevant information in mind, and because they placed an emphasis on visuospatial processing, we hypothesized that children in either or both groups might exhibit gains in WM, particularly on the Spatial Span measure.

Indeed, children in the reasoning group exhibited a moderate improvement on Forward Spatial Span (t=2.51, df=16, P=.01; Cohen's d=.65) (Table 2.2, Figure 2.3). After training, children in the reasoning group remembered an average of 5.5 locations on the Forward Span task, as compared with 5 locations before training. The reasoning group also showed a trend-level improvement on Backward Spatial Span (t=1.57, df=16, P=.07), and therefore the effect of FR training on Total Spatial Span was significant (t=2.94, df=16, P=.005). The gain in Total Spatial Span was greater than the gain in the speed group (t=2.31, df=26, P=.01), who did not improve significantly on any of the Spatial Span measures. In contrast with the Spatial Span results, neither group exhibited a significant effect

of training on Forward or Backward Digit Span. However, there was a trend towards higher Backward Digit Span after PS training (t=1.54, df=10, P=.08).

Given that the reason group improved on Spatial Span, we sought to determine whether their gains in reasoning could be explained by underlying gains in spatial WM. In fact, our data do not support this hypothesis. Gains on these working memory span measures were not correlated with gains in FR in the reasoning group (Forward Spatial Span: R^2=.05, P=.37; Backward Spatial Span: R^2=.06, P=.36), or in both groups combined (Forward Spatial Span: R^2=.02, P=.46; Backward Spatial Span: R^2=.11, P=0.09). In other words, participants who improved the most on TONI were not necessarily the same individuals who improved substantially on the spatial working memory span task. It is an open question whether reasoning training would have resulted in improvements on more demanding measures of working memory, such as the complex span tasks of Engle and colleagues (Engle et al., 1999).

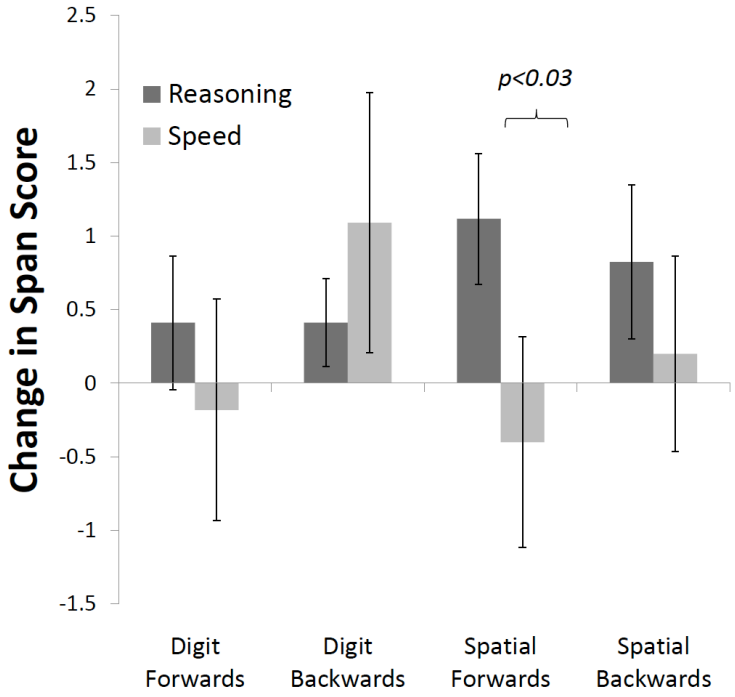

Figure 3: Improvements in Working Memory with Training. Neither group showed a significant improvement in Forward or Backward Digit Span. The reasoning training group showed a significant improvement in Forward Spatial Span. Error bars represent standard error. Reasoning group: N=17; Speed group: N=11 for Digit Span, N=10 for Spatial Span

Next, we sought to test whether initial FR and PS scores and/or days of training predicted training outcomes. We found a significant negative correlation between pre-training TONI scores and TONI improvement (R^2=.33, P=.02). We did not find a correlation between pre-training Coding and Coding improvement (R^2=.09, P=.37). In summary, children who began the intervention with the lowest FR

scores showed the largest gains in FR after reasoning training. Initial PS scores did not predict gains in PS after speed training. Gains were also not correlated with training days attended – either when each group considered separately (FR: R^2=.02, p=.62; PS: R^2=.08, p=.71), or when percent change in the targeted skill was considered for both groups (R^2=.01, p=.69).

Discussion

We found that a mere 8 weeks of playing commercially available games can lead to large improvements on standard cognitive tests of FR and PS in children. To our knowledge, this study provides the first clear evidence of a double dissociation in cognitive gains between two training programs in children, and the strongest effect of training on FR. Both programs targeted general cognitive skills that are central to cognitive development (Fry & Hale, 1996; Kail, 2007) and that have the potential for widespread influences.

Particularly surprising is the finding that FR training resulted in an average gain in Performance IQ of almost 10 points, with 4 of the 17 children showing gains of over 20 points. This large effect underscores the point that FR is modifiable by environmental influences, contrary to claims that it is a relatively fixed ability (Cattell, 1987). Indeed, the very existence and widespread use of IQ tests rests on the assumption that tests of FR measure an individual's innate capacity to learn. These and other findings (Diamond, Barnett, Thomas, & Munro, 2007; Jaeggi et al., 2008; Klingberg et al., 2005; Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005) indicate that cognitive training *can* influence FR, even if it does not always do so (Owen et al., 2010). This collective evidence suggests that prior experience does impact test performance – even on FR tests, which were designed to be 'culture fair' (Cattell, 1987).

In addition to the large effect on FR, reasoning training also had a moderate effect on Spatial Span (Cohen's *d*=.65). Calculated in the same way, Klingberg and colleagues' spatial WM training research has yielded effect sizes on Spatial Span ranging from .86 in children with ADHD (Klingberg et al., 2005) to .89 in preschool children (Thorell et al., 2009). The absolute amount of improvement in our study (2 points in Spatial Span) was similar to that found by Klingberg and colleagues. Thus, our results indicate that – just as engaging in progressively more challenging spatial working memory problems results in improved spatial WM, so too does playing a variety of engaging reasoning games that rely on visuospatial processing.

Our results may appear to contradict recent findings by Owen and colleagues (Owen et al., 2010), who have shown recently that computerized training games targeting FR and WM do not transfer to gains on other tasks. However, several factors make it difficult to compare results across studies, including differences in the study populations (children from low SES backgrounds versus typical adults),

training settings (a classroom setting versus unsupervised training at home), and outcome measures (a standard visuospatial reasoning test vs. a speeded verbal reasoning test).

Speed training led to roughly a 30% improvement on Coding. To our knowledge, this is the first study that has found large training gains in PS in children. While these gains did not transfer to gains in WM, as one might predict based on Fry and Hale's Developmental Cascade Model (Fry & Hale, 1996), the trend observed for Digit Span Backwards suggests that a significant effect might emerge with a larger sample size – and/or with complex span measures of WM (Conway, Kane, & Engle, 2003). Additionally, the speed group showed a trend towards improvement on the TONI. However, this gain is difficult to interpret without a passive control group, as we cannot determine whether this gain is larger than would be expected from test-retest effects.

Potential caveats and future directions

Although our findings are very encouraging, some issues deserve attention. Due to the intensive nature of our training programs, our sample size was fairly small. With a larger sample size, it would be possible to assess the influence of each of the following factors on training outcomes: training-related variables (e.g., days attended, semester of enrollment), demographic variables (age, gender, socioeconomic status), and cognitive functioning prior to training.

Additionally, because we administered assessments in an after-school setting, we had limited time to assess each child. Therefore, we had to choose tests of PS, WM and FR that could be administered quickly, and we were not able to administer as many tests of each skill as would have been ideal. It is unclear whether reasoning or speed training would have transferred to gains on complex span measures of WM, like those designed by Engle and colleagues (Conway et al., 2003).

We chose not to compare gains to a passive control group (i.e. a group of children who only took pre- and post- assessments) because we wanted every child who signed up to be assigned to an active training program. We were concerned that the children whose parents would sign them up for this option could be different from the other two groups in ways that are difficult to quantify (e.g. parental involvement and attitudes towards research and/or educational opportunities). Without a passive control group, we were limited in our ability to interpret the trend towards improvement on the TONI in the speed group, and the gain on Cross Out in speed group.

Training in a social environment has many benefits, but it does not lend itself to tight experimental control over instruction and task progression. It was not possible to standardize feedback from researchers and from other children. We

have matched the two training programs in terms of researcher interactions to the best of our ability, but there is no question that training programs aimed at different cognitive skills would involve different teaching strategies. Further, we do not have the data to address the question of which games (e.g. computerized vs. non-computerized, or group vs. individual) had the greatest impact on cognitive skills. We hypothesize that no single game drove the effects that we observed, but instead that the variety of games helped to train FR and PS from multiple angles, while sustaining the children's interest.

Additional research is also needed to address the following critical questions. How long do these training effects last? Even if training effects fade without continued practice, the finding that these skills are malleable is important. Gains in physical fitness would not be expected to be maintained without practice, but this does not mean that exercise is not beneficial. Can training-related gains in cognitive skills lead to improved academic outcomes? The encouraging results of these and other recent cognitive training studies warrant the pursuit of larger-scale research that includes academic outcome measures.

The central message of this paper is hopeful. Even though there is increasing evidence that cognitive skills are compromised in low SES children (Kishiyama, Boyce, Jimenez, Perry, & Knight, 2009; Noble et al., 2007; Stevens, Lauinger, & Neville, 2009), there is also increasing evidence that cognitive skills are amenable to training (Raizada, 2009). Notably, our work and others' shows that cognitive training need not be expensive. Simple instructional strategies and inexpensive commercially available games can be used to train core cognitive processes in children who stand to benefit most.

In future research, we will investigate the effects of FR and PS training on brain structure and/or function in children. We hypothesize that FR training would lead to repeated co-activation of parietal and lateral prefrontal regions that support the processing and integration of visuospatial relations. This repeated co-activation could, in turn, lead to activity-dependent changes in these regions, such as myelination and dendritic branching. Research presented in the following two chapters uses neuroimaging methods to provide insight into these potential mechanisms for training-related gains in cognitive skills. This research focuses on training in adults, so the neural effects likely differ both quantitatively and qualitatively from what would be observed in a training study of children.

Chapter 3
Reasoning training in adults alters brain connectivity at rest

Correlations in spontaneous fluctuations of blood-oxygenation level dependent (BOLD) fMRI signal at rest are thought to reflect the prior history of co-activation of brain regions (Dosenbach et al., 2007; Fair et al., 2009; Seeley et al., 2007). These networks have frequently been interpreted as state traits: stable markers of an individual's neural functioning (Fox & Raichle, 2007; Shehzad et al., 2009). Rs-fMRI networks can be identified in various states of consciousness in adults (Boly et al., 2008), as well as in children (Fair et al., 2008; Fair et al., 2009) and non-human primates (Vincent et al., 2007). However, if these networks do indeed reflect a prior history of co-activation, then they should be influenced by experience. While there is ample evidence of experience-dependent plasticity at the cellular level (Fu & Zuo, 2011), there is very little evidence of plasticity in large-scale functional networks in humans. The timing of the changeability of rs-fMRI networks is unknown, but it is reasonable to suppose that large-scale experience-dependent structural changes are accompanied by, or even preceded by, changes in patterns of functional activity. In other words, examining experience-dependent changes in resting-state connectivity may provide a window into network plasticity in humans that could complement evidence from structural imaging studies.

The aim of the present study is to investigate changes in resting-state connectivity associated with intensive training on relational reasoning, or the ability to compare and combine mental representations (see Hummel & Holyoak, 2005 and Halford, Wilson, & Phillips, 1998). A number of brain regions have been shown to be engaged during reasoning, including frontal regions (rostrolateral prefrontal cortex (RLPFC), middle frontal gyrus (MFG), inferior frontal gyrus (IFG), precentral gyrus), parietal regions (superior parietal lobule, angular gyrus, supramarginal gyrus, posterior parietal, precuneus), and striatum (caudate nucleus and putamen)(Duncan et al., 2000; Ferrer, O'Hare, & Bunge, 2009; Krawczyk, 2010; Melrose, Poulin, & Stern, 2007; Prado, Chadha, & Booth, 2011). Among these regions, we consider that some are integral in relational processing, whereas others support task performance through their more general roles in working memory, cognitive control, and/or motor control. On the basis of a number of fMRI studies, our laboratory has proposed that structured relations between stimuli are maintained in working memory by lateral parietal cortex along with domain-specific regions and then compared or integrated by RLPFC (Wendelken, Chung, & Bunge, 2011; Wendelken, O'Hare, Whitaker, Ferrer, & Bunge, 2011). Broadly consistent with this hypothesis, RLPFC and lateral parietal cortex exhibit strong temporal correlations both during reasoning (Wendelken & Bunge, 2010; Wendelken, Chung, et al., 2011) and at rest (Mars et al., 2011; Nelson et al., 2010).

Here, we sought first and foremost to test the hypothesis that intensive experience with relational reasoning tasks over the course of several months would lead to tighter coupling between lateral parietal cortex and RLPFC, particularly in the left hemisphere. Additionally, we sought to explore whether reasoning training would alter patterns of connectivity among the broader set of brain regions that are commonly engaged during performance of reasoning tasks. These changes could reflect increased efficiency in processing visual stimuli, monitoring and manipulating information in working memory, and/or selecting and executing a response.

Rather than design an artificial laboratory-based reasoning training paradigm, we studied the effects of preparation for the Law School Admissions Test (LSAT), a standardized test that places strong demands on relational reasoning. We selected this program in part because students were highly motivated to adhere to the training regime since LSAT scores play an almost determinative role in law school acceptance. We predicted that this high level of motivation would maximize the chances of observing experience-dependent neural changes because motivation (Bergan, Ro, Ro, & Knudsen, 2005) and increased dopamine levels (Bao, Chan, & Merzenich, 2001) are associated with enhanced neural plasticity in adult animals. Another benefit of this training paradigm was its ecological validity. Many people prepare for the LSAT every year; during the 2010-2011 academic year alone, 155,000 adults took this exam.

We recruited students (n = 25) who had signed up for an intensive LSAT preparation course. This course provided 100 hours of class time, 70 of which were dedicated to instruction on reasoning questions. We also recruited a group of pre-law participants who did not study for the LSAT between testing sessions (n = 24). All participants took part in scanning sessions approximately 90 days apart that included an rs-fMRI scan. Because the stress of studying for an important test has been associated with changes in fronto-parietal connectivity (Liston, McEwen, & Casey, 2009), we collected a questionnaire measure of perceived stress at both time points. Further, because sleep deprivation can also alter prefrontal function (Walker & Stickgold, 2006), we asked all participants to report on their sleep habits at both visits.

Methods

Participants

Research was approved by the Committee for the Protection of Human Subjects at the University of California at Berkeley. Twenty-five adults (14 females) took part in the training group, and twenty-four adults (14 females) took part in the age- and IQ-matched pre-law control group (Table 3.1).

Participants in the training group were recruited through an e-mail announcement and an in-class announcement to students in Blueprint Test Preparation courses. Participants in the control group were recruited through e-mails to pre-law organizations on campus and online postings. Participants had no history of psychiatric or neurological disorder. All participants were fluent in English. Because our predictions for training-related changes did not vary by handedness, we enrolled both right- and left- handed participants. In the training group, three participants were left-handed, and in the control group, two participants were left-handed.

Training Paradigm

The Blueprint Test Preparation course was selected as the training paradigm because it provided more classroom time than other local programs: 100 hours distributed across the three components of the LSAT (35 hours for Logic Games, 35 hours for Logical Reasoning, and 30 hours for Reading Comprehension). "Logic Game" questions require test takers to integrate a series of rules in order to sequence or group a set of items. "Logical Reasoning" questions ask them to determine the logical flaw in an argument, identify an assumption, or choose a statement that would strengthen or weaken an argument. The remaining 30 hours of class time were dedicated to "Reading Comprehension" questions that require test takers to interpret short passages of text. A recent LSAT exam can be found at http://www.lsac.org/jd/pdfs/SamplePTJune.pdf.

For the Logic Games section, students were taught to break down problems into the essential information and to use diagrams to represent and integrate rules. For the Logical Reasoning section, students were taught basic logic principles (such as *modus ponens* and *modus tollens*), as well as how to avoid common logical fallacies. Students attempted problems at home and then instructors worked through the problems in class, answering any questions students might have. Special attention was paid to keeping motivation levels high by making the content fun through relatable examples.

Blueprint course instructors administered four practice tests spread evenly throughout the course. LSAT practice test scores were either provided by the participants or by the test preparation course with the consent of the participants. We compared the scores on each of the LSAT sections for the first and last practice test as an index of change from time 1 to time 2.

Behavioral Measures

During the first testing session, we administered the Matrix Reasoning and Vocabulary subtests of the Wechsler Adult Scale of Intelligence (WASI) (Wechsler, 1999), to match the groups on IQ, as well as the Young Adult Self Report (Achenbach, 1990; 1997) to screen out participants who scored in the

clinical range. During both testing sessions, we administered the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983) and asked participants to report their sleeping habits over the previous week. These measures were used to ensure the groups did not differ, and to ensure that our results could not be accounted for by changes in stress levels or amount of sleep. Two participants – one from the trained group and one from the control group – were excluded from the study based on these measures because they exhibited a dramatic change in stress levels and amount of sleep from time 1 to time 2 (more than 3 SD from the mean of all participants).

Image Acquisition

MRI scanning was performed on a Siemens 3T Trio at the Brain Imaging Center at the University of California at Berkeley. Participants underwent a series of anatomical scans, two fMRI tasks (for details, see (Bishop, Fossella, Croucher, & Duncan, 2008; Wendelken & Bunge, 2010)), and an rs-fMRI scan; in this first study, we report only data from the resting-state scan. The order of scans was fixed across participants and time-points, to ensure that any differences between groups or timepoints could not be accounted for by order effects. During the six-minute rs-fMRI scan, participants were asked to relax and remain awake while gradient-echo EPI data were acquired (TR = 2000ms, TE = 25ms, 33 axial slices, 2.0 x 1.8 x 3.0 mm voxels, no interslice gap, flip angle = 90°, field of view = 230mm).

Preprocessing

FMRI data were pre-processed and analyzed with FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl)(Smith et al., 2004; Woolrich et al., 2009). The following pre-processing steps were carried out at the single subject level: slice-timing correction; motion correction using MCFLIRT(Jenkinson, Bannister, Brady, & Smith, 2002); non-brain removal using BET(Smith et al., 2002); spatial smoothing using a Gaussian kernel of FWHM 5 mm; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s). Registration to high-resolution structural and standard space images was carried out using FLIRT(Jenkinson et al., 2002; Jenkinson & Smith, 2001). Additionally, high-resolution structural images were segmented using FAST(Zhang, Brady, & Smith, 2001) to obtain masks of white matter and cerebrospinal fluid (CSF), which were then registered to the functional images. Timecourses were extracted from these masks and from outside of the brain and used as covariates of no interest, along with their temporal derivatives.

Anatomical regions of interest were created from the unthresholded Harvard-Oxford cortical and subcortical atlases distributed with FSL(Desikan et al., 2006) (http://www.cma.mgh.harvard.edu/fsl_atlas.html). We included bilateral frontal

(RLPFC, MFG, IFG *pars opercularis*, precentral gyrus), striatum (caudate and putamen), and parietal (superior parietal, angular gyrus, supramarginal gyrus, posterior parietal cortex) regions. We created the RLPFC region by excluding the medial portion of the frontopolar cortex atlas region ($X < \pm 14$). We refer to the superior lateral occipital cortex region as posterior parietal cortex because it encompasses a large portion of parietal cortex (see Fig. 3a, left hemisphere). Regions were registered into native subject space. Average timecourses were extracted for each region from the residuals of a GLM that included the covariates of no interest described above.

Statistical analyses

Pairwise correlations were computed and Fischer-transformed to produce normally distributed values. Within each group, paired t-tests were conducted for each pair of regions to test for an effect of time point on correlation strength (n = 25 in the trained group, n = 24 in the control group, two-tailed). To correct for the 231 comparisons, the Benjamini-Hochberg false discovery rate (FDR)(Benjamini & Hochberg, 1995) procedure was employed with an α-level of $P < .05$, revealing 18 significant changes in the trained group and none in the control group.

To show the magnitude and direction of the correlation changes in the trained group, we created correlation change matrices for each hemisphere and for cross-hemisphere connections. Correlation changes were colored by the number of standard deviations from the mean change, calculated across all correlation pairs and both groups (M = .003, SD = .06). Significant changes were marked with an asterisk. To visualize the spatial distribution of correlation changes, we calculated the number of significant increased and decreased connections for each region. Each pairwise correlation change was counted twice, once for each region in the pair, for a total of 36 changes. Cortical regions are projected onto the brain surface using CARET (Computerized Anatomical Reconstruction and Editing Toolkit 5, http://www.nitrc.org/projects/caret)(Van Essen et al., 2001), and subcortical regions are shown on slices.

Results

Demographics and behavioral results

The trained group and the control group were well-matched in terms of age, gender, IQ, and the number of days between scan sessions (Table 3.1). Additionally, the groups were matched on stress levels and amount of sleep, and neither group exhibited a change in either of these variables from time 1 to time 2 (Table 3.1). Because head motion has been shown to alter resting-state connectivity patterns (Van Dijk, Sabuncu, & Buckner, 2012), we confirmed that absolute head displacement did not change between time points for either group (Ps > .3) or differ between groups at either time point (Ps > .5).

	Trained N=25	**Control** N=24
Age	22.15 (1.88)	21.44 (1.99)
WASI Matrix	29.04 (2.49)	29.67 (1.74)
WASI Vocabulary	66.04 (5.79)	66.92 (3.66)
Days between scans	90.48 (16.32)	92.04 (23.18)
Perceived Stress		
Time 1	21.86 (5.04)	20.63 (8.29)
Time 2	21.88 (6.19)	21.96 (9.01)
Hours of Sleep		
Time 1	7.52 (0.81)	7.59 (0.91)
Time 2	7.35 (0.99)	7.37 (1.13)

Table 3.1: Participant information. Means and standard deviations are reported for the variables that the trained group and control group were matched on (*P*s >.2). Raw scores are reported for the WASI subscales.

The participants in the trained group for whom practice test scores were available (n = 21) improved significantly on the LSAT (P < .001, df = 20, t = 6.7) (Fig. 1). For a subset of participants (n = 18), scores for each of the subtests were available. These scores revealed significant improvements on the two reasoning components of test, Logic Games (P = .001, df = 20, t = 3.56) and Logical Reasoning (P < .001, df = 20, t = 6.08). By contrast, there was no change in Reading Comprehension scores, although participants spent 30 classroom hours preparing for this section of the exam (P = .41, df = 17, t = .84). The gains on the reasoning subtests were significantly greater than the change in Reading Comprehension (LG: P = .004, df = 17, t = 2.92; LR: P = .003, df = 17, t =3.16). The improvement in LSAT total score corresponds roughly, depending on the year, to an improvement from the 44th percentile to the 73rd percentile. For a student with the mean grade point average of the trained group (3.4), a change from 149 to 157 would vastly widen the pool of law schools to which he or she had a realistic chance of acceptance (http://www.bc.edu/offices/careers/gradschool/law/lawlocator.html).

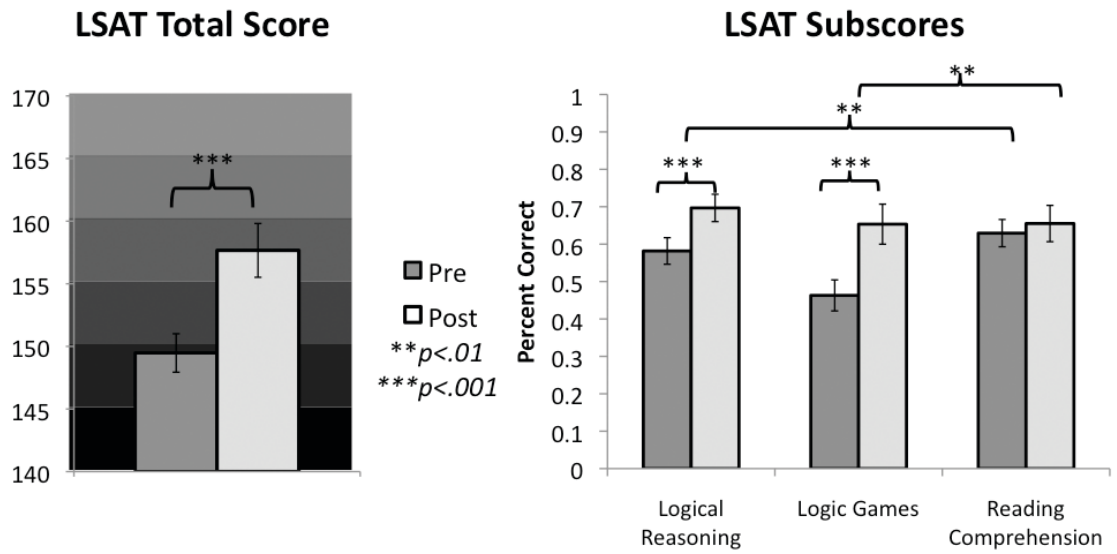

Figure 3.1: Changes in LSAT performance
a. Improvement on overall LSAT scores between the first and the last practice test (*n* = 21). Each horizontal gray band represents a score range for which likelihood of admission can be estimated. b. Change in each subscale of the LSAT (*n* = 18). Error bars represent standard error of the mean.

Rs-fMRI analyses

We sought to provide a comprehensive view of training-related changes in functional connectivity between brain regions involved in reasoning. Thus, we looked to a meta-analysis of 28 neuroimaging studies of reasoning ability (Prado et al., 2011) to generate a list of brain regions most often recruited during performance of reasoning tasks (Fig. 2A). Based on this list, we extracted timecourses from structural definitions of 11 regions in each hemisphere, and calculated pairwise correlations between regions. We tested whether any of the 231 pairwise correlations changed between time 1 and time 2 for each group (two-tailed paired t-tests). The distribution of significance values (*P*-values) for each group is shown in Figure 3.2B. While the distribution of the *P*-values for the control group tracked closely with the distribution expected by chance (blue line), the distribution for the trained group included many more low *P*-values. Fifty correlation pairs had a *P*-value of less than .05 in the trained group, compared to 17 in the control group; 11.5 would be expected by chance. Further, for the trained group, 18 correlation pairs survived a false discovery rate (FDR) correction for multiple comparisons, shown in green, while no pairs survived this correction in the control group. We interpreted this striking difference between groups as evidence of widespread training-related changes in connectivity, and sought to characterize the directionality and spatial distribution of these changes.

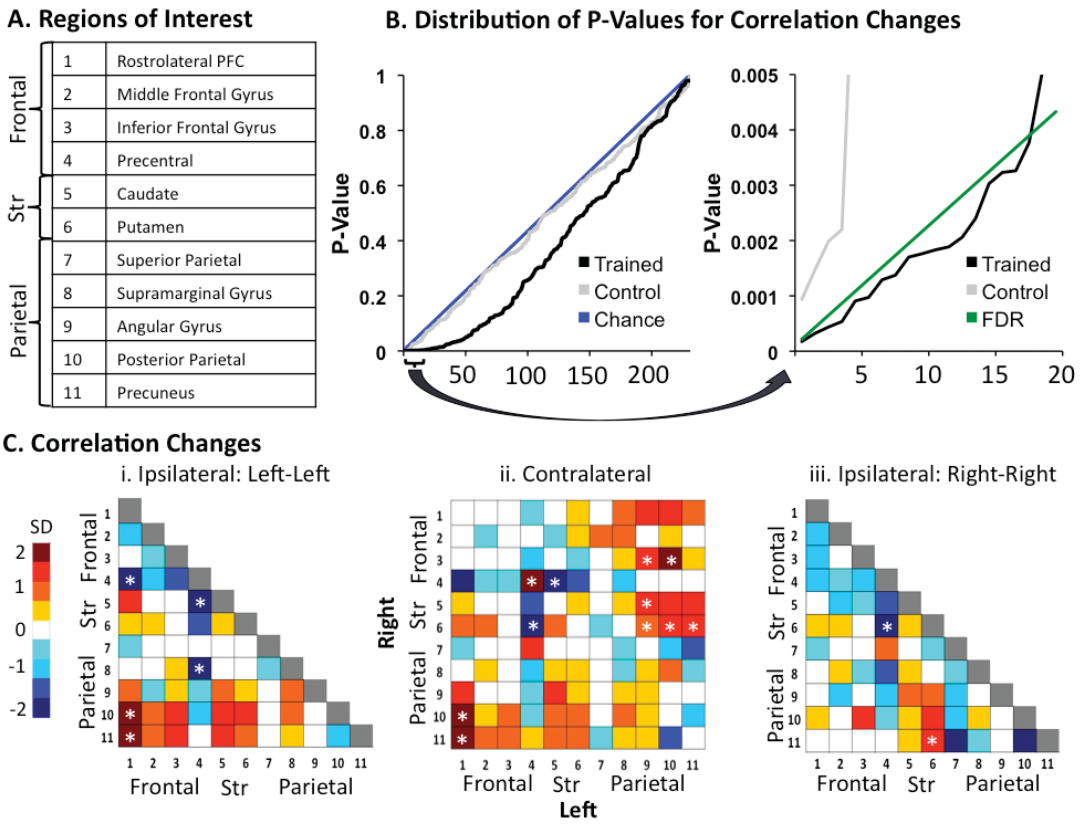

Figure 3.2: Changes in pairwise correlations for ROIs
a. List of regions implicated in reasoning. b. *P*-values for t-tests between time points for 231 pairwise correlations, ordered from lowest to highest. The distribution for the trained group is in black, and the control group is in gray. The distribution expected by chance is marked by a blue line. The portion of the *P*-value distribution that is less than *P* = .005 for the trained group is magnified on the right. The FDR correction is marked by a green line, which crosses the *P*-value distribution of the trained group at the 19th pair, indicating that the top 18 correlation changes were significant. c. Magnitudes of change for all 231 pairwise correlations. Correlations are colored by standard deviations from the mean, calculated across all pairs and both groups. Region numbers refer to part a. (Str= Striatum). White asterisks denote significant changes. i. Connections within the left hemisphere. ii. Connections between the left and right hemispheres. iii. Connections within the right hemisphere.

We first looked at the magnitude of all correlation changes for the trained group (Fig. 3.3C). We created correlation change matrices with brain regions ordered from anterior to posterior along each axis, following the order in Figure 3.2A. Significant changes are marked with an asterisk. Within the left hemisphere, increased connections were observed between prefrontal (regions 1-3) and parietal (regions 9-11) cortices (Fig. 3.2Ci, bottom left). A similar pattern of increased fronto-parietal connectivity was seen between hemispheres (Fig. 3.2Cii, bottom left and upper right). Within each hemisphere, and between hemispheres, we found increased connectivity between parietal cortices and the striatum (regions 5 and 6), as well as decreased connectivity between precentral gyrus (region 4) and most other regions (Fig. 3.2C i-iii).

We then examined the spatial distribution of the 18 correlation pairs that survived the FDR correction. Detailed statistics for these pairs are shown in Table 3.2 (statistics for pairs reaching significance at the $P < .05$ level are shown in Supplemental Table B.1). For each region, we counted the number of increased and decreased connections (Fig. 3.3). Left RLPFC and right putamen exhibited the greatest number of increased connections, followed by left angular gyrus and left posterior parietal cortex. By contrast, left precentral gyrus exhibited the greatest number of decreased connections.

Region 1	Region 2	Change	Trained Time 1	Trained Time 2	Trained T-Test	ANOVA
L Precentral	L Caudate	-	0.00	-0.16	0.0002	0.09
L Precentral	L Supramarg	-*	0.31	0.16	0.0003	0.009
L Caudate	R Precentral	-	-0.06	-0.20	0.0004	0.36
L RLPFC	R Precuneus	+	-0.28	-0.09	0.0005	0.01
L Precentral	R Precentral	+	0.85	1.04	0.0009	0.03
L Ang	R Caudate	+	-0.02	0.09	0.001	0.07
L RLPFC	R Post Par	+	-0.37	-0.19	0.001	0.23
L Ang	R Putamen	+	-0.05	0.03	0.001	0.17
L Post Par	R Putamen	+	-0.19	-0.07	0.002	0.02
L Post Par	R IFG	+	-0.16	-0.02	0.002	0.002
L Precuneus	R Putamen	+	-0.16	-0.06	0.002	0.01
R Putamen	R Precuneus	+	-0.16	-0.05	0.002	0.02
R Precentral	R Putamen	-	0.07	-0.09	0.002	0.11
L Ang	R IFG	+	0.01	0.13	0.002	0.04
L RLPFC	L Precuneus	+	-0.09	0.08	0.003	0.05
L Precentral	R Putamen	-	0.05	-0.10	0.003	0.09
L RLPFC	L Post Par	+	-0.09	0.10	0.003	0.44
L RLPFC	L Precentral	-	-0.02	-0.18	0.004	0.08

Table 3.2: Correlations showing an effect of training.
18 out of 231 pairs of region showed an effect of training ($P < .05$, FDR corrected). Table is ordered from lowest to highest *P*-value for the t-test for the trained group. The only correlation that was significantly different between groups at time 1 is denoted with a †. The correlation value for the controls was .17 compared to a value of .31 for the trained group ($P = .04$). The right-most two columns show results from a group X time ANOVA.

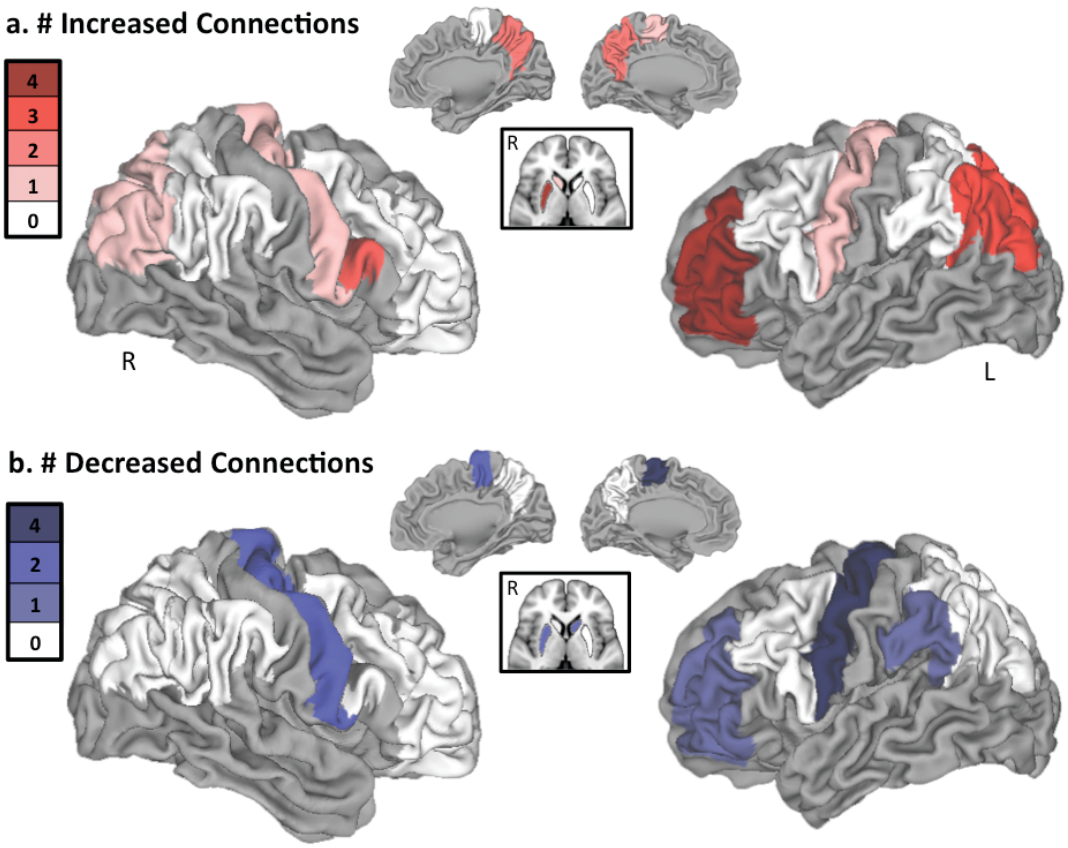

Figure 3.3: Number of changed connections per region
Regions were taken from the Harvard-Oxford Atlas and rendered on a CARET brain. a. Number of significant increased connections for each region. b. Number of significant decreased connections for each region. No region showed 3 decreased connections.

Discussion

Broadly, we sought to test the hypothesis that engaging in novel, complex cognitive tasks would strengthen connectivity within the reasoning network at rest. Indeed, the present findings show that connectivity between brain areas implicated in cognition is experience-dependent and can be modified by intensive training. More specifically, we predicted that relational reasoning training would strengthen connectivity between RLPFC, a region implicated in relational integration, and parietal regions thought to support processing of individual relations. We found that left RLPFC showed the greatest number of correlation increases, specifically with posterior and medial parietal regions. The fronto-parietal changes were significant within the left hemisphere and between hemispheres. In addition to the increase in fronto-parietal coupling, we observed an increase in connectivity between parietal cortex and the striatum. These changes were significant only between hemispheres, although a similar trend was observed within the left hemisphere as well. While not predicted in advance,

the increase in parieto-striatal connectivity is consistent with the known role of the striatum in reasoning (Melrose et al., 2007; Prado et al., 2011), as well as in learning across both cognitive and motor domains, based on its strong dopaminergic inputs (Ashby, Turner, & Horvitz, 2010).

In contrast with the fronto-parietal connectivity increases, the decreases in precentral gyrus connectivity were unexpected. Independent component analyses of resting-state data have shown that this region tends to segregate into a somatomotor network rather than participating in the fronto-parietal network (Beckmann, DeLuca, Devlin, & Smith, 2005). However, we have found previously that RLPFC is correlated with bilateral motor regions during reasoning task performance (Wendelken & Bunge, 2010; Wendelken, Chung, et al., 2011), suggesting that RLPFC interacts with precentral gyri when a motor response is required. Repeatedly working through lengthy, complex problems without generating immediate motor responses may have led to the observed decoupling between precentral gyri and the lateral fronto-parietal network.

Many rs-fMRI studies exclude weak correlations and ignore negative correlations, because they are difficult to interpret. Here, we sought to measure training-related changes in correlation strength between regions of interest, regardless of initial value. Many of the largest changes were observed for pairs that were weakly correlated or negatively correlated prior to training. For example, we observed increased connectivity between RLPFC and parietal regions that were not strongly correlated with it at time 1. One possible explanation for these results is that our measures are less sensitive to changes in correlation for pairs that were already strongly correlated prior to training. A second possibility is that training led to a more widespread area of cortex recruited into the reasoning network, along the lines of the use-dependent cortical expansion observed in laboratory animals (Buonomano & Merzenich, 1998).

A potential caveat is that the resting-state data were acquired during the same scan session as task data. Indeed, other studies have shown that these networks can be altered over the short-term by preceding the rs-fMRI scan with a task (Harrison et al., 2008; Stevens, Buckner, & Schacter, 2010; Waites, Stanislavsky, Abbott, & Jackson, 2005). However, since the order of scans was fixed across groups and time points, it is unlikely that the tasks influenced resting-state data in a systematic way that was specific to the trained group. Further, the tasks performed during scanning bore little resemblance to the types of problems students practiced during the LSAT training. Thus, the most parsimonious explanation for the observed changes in functional connectivity is that 3 months of cognitive training altered the strength of coordinated activity within and across large-scale brain networks.

While it is possible only to speculate about the cellular processes underlying changes in functional connectivity in humans, structural MRI data could shed light on which mechanisms may be at work. Changes in cortical thickness could indicate a change in dendritic volume, while changes in fractional anisotropy, as measured with diffusion tensor imaging, could indicate a change in myelination or coherence of axons (Zatorre, Fields, & Johansen-Berg). Importantly, however, functional connectivity changes may occur preceding measurable changes in brain structure (Taubert, Lohmann, Margulies, Villringer, & Ragert), or even in the absence of gross structural changes.

Not only do the observed changes in resting-state connectivity speak to the functional roles of the regions involved, but they also challenge the notion that resting-state networks supporting higher cognition are stable in adulthood. These results build on evidence of training-induced resting-state changes in other domains, including motor learning (Taubert et al.), processing speed (Takeuchi et al.), and meditation (Xue, Tang, & Posner). Additionally, there is some evidence that working memory training may also alter resting-state connectivity (Jolles, van Buchem, Crone, & Rombouts, 2011). Demonstrating neural plasticity in the network that supports reasoning – a skill that is central to theories of intelligence (Gray & Thompson, 2004) – is particularly significant because it runs counter to the widespread assumption, among researchers as well as the general public, that intelligence is a fixed ability.

The results of the current study have broad societal relevance. Millions of young adults prepare intensively for the LSAT and other standardized exams. To correctly interpret the significance of these test scores, it is important to know whether these exams measure individuals' cognitive *potential,* or whether they more accurately reflect their cognitive *history* – i.e., the prior level of engagement of specific brain networks.

Finally, understanding plasticity in cognitive skills in healthy adults is critical as more and more people extend their formal education into the third and fourth decades of their lives. More broadly, throughout the lifespan, individuals encounter profound shifts in their environments that necessitate categorical changes in cognition. Neural plasticity at the synaptic level, and indeed at the level of large-scale networks, enables our brains to rise to meet novel cognitive demands. However, changes in brain connectivity associated with a brief change in cognitive activity are unlikely to last indefinitely, just as a student who has just prepared intensively for the LSAT is unlikely to perform as well on the exam after many months have elapsed. To maintain a high level of reasoning ability, we hypothesize, it is important to regularly tax the underlying brain circuitry.

Chapter 4
Reasoning training in adults alters white matter microstructure

Advances in neuroimaging techniques have led to important progress in understanding how brain regions are structurally and functionally connected in the human brain. Much of this knowledge has been obtained from cross-sectional studies, which provide only a snapshot of an individual's brain at a single point in time. As a result, we have only just begun to understand how learning and experience shape brain connectivity. In this chapter, we provide evidence for experience-dependent changes in white matter microstructure among young adults participating in intensive cognitive training.

White matter microstructure can be investigated *in vivo* using diffusion-weighted imaging (DWI). DWI relies on the biophysical principal that, as water diffuses, it follows the path of least resistance. Water diffusing in any given white matter voxel encounters axons (which contain dense cytoskeletons, are bounded by cellular membranes, and are surrounded by myelin) and glial cells. Research in animals has shown that water preferentially moves along axons rather than through the myelin sheath (for review see Beaulieu, 2002; Assaf and Pasternak, 2008). Activity-dependent increases in myelination could, therefore, reduce diffusion through the myelin sheath. However, changes in unmyelinated axons, and the number and/or size of glia, could also alter diffusion.

Diffusion tensor imaging (DTI) analysis fits a tensor to DWI to extract measures of axial diffusion (axial diffusion (AD or λ_1)), the preferential direction of water diffusion, and radial diffusion (RD or λ_{23}), the average of the two directions perpendicular to AD. AD has been related to diffusion along an axon, whereas RD is linked to diffusion through the myelin sheath (Beaulieu, 2002). Fractional anisotropy (FA) is a scaled ratio of AD to RD (Basser, 1995; Pierpaoli and Basser, 1996). High FA indicates strong directionality of water diffusion, i.e., high white matter coherence. Mean diffusivity (MD) is the average of diffusion parameters in all three orthogonal directions. Low MD reflects a high density of cells and/or extracellular material that impedes the diffusion of water through brain tissue. Because these diffusion measures (AD, RD, FA, and MD) have been shown to relate to different aspects of white matter composition (Song et al., 2002; 2003), some DTI studies of neuroplasticity have investigated the measures separately, though many have focused specifically on FA.

Neuroplasticity in humans has been studied through two main approaches. A first approach has been to compare experts to novices, with the assumption that any brain differences between the groups can be attributed to the extensive training experts have received over the course of their lives. This work has yielded mixed results in terms of the direction of observed differences in DTI measures. For example, when comparing musicians to non-musicians, both increased and decreased FA in the corticospinal tract have been observed (Imfeld et al., 2009).

Additionally, when comparing fighter pilots – who demonstrate enhanced cognitive control relative to the general population – with controls, lower RD in white matter underlying parietal cortex and higher RD in white matter near medial frontal cortex were observed (Roberts et al., 2010). In such studies, it is not possible to disambiguate the effects of experience from an innate predisposition to pursue a particular type of training.

A second approach to studying neuroplasticity in humans involves direct experimental control over individuals' experience. To date, there have been very few published studies on training-related plasticity in white matter microstructure in healthy adults. One study showed that working memory training increased FA in left parietal and frontal white matter, as well as white matter under somatomotor cortices (Takeuchi et al., 2010). However, this study did not include a control group, so effects of maturation in the study's young participants cannot be ruled out. A second study showed that juggling training increased FA in white matter near right posterior parietal cortex, potentially related to enhanced use of visual areas important for detecting motion (Scholz et al., 2009). A third study showed decreased FA in bilateral frontal lobes, and increased mean diffusivity (MD) in right parietal lobe and cerebellum following practice with a balancing task (Taubert et al. 2010). Finally, a fourth study showed that meditation training leads to increased FA in medial anterior corona radiata (Tang et al., 2010). Further analysis of this data set revealed that the majority of voxels exhibiting increased FA showed both decreased RD and AD (Tang et al, 2012).

In the present study, we investigated white matter changes associated with intensive training on relational reasoning, the ability to compare and combine mental representations. The reasoning training paradigm consisted of a course aimed at improving scores on the Law School Admissions Test (LSAT). The LSAT has three parts: Logic Games, Logical Reasoning, and Reading Comprehension. Both of the logic sections heavily tax relational reasoning. Because this exam plays an almost determinative role in law school acceptance, we reasoned that students would be highly motivated to prepare for it.

Numerous studies have implicated a bilateral fronto-parietal network in reasoning (see Krawczyk, 2012; Hampshire et al., 2011; Prado et al., 2011 for review), several of which have suggested that rostrolateral prefrontal cortex (RLPFC) is specifically involved in relational integration (Wendelken and Bunge, 2010; Hampshire et al., 2011; Wendelken et al., 2011a; Wendelken et al., 2011b). Based on these findings, we predicted changes in white matter connecting frontal and parietal cortices both within and between hemispheres. We were specifically interested in changes in the trained group that were significantly greater than those measured for an age- and IQ-matched control group. In other words, we considered changes in the trained group that could not be accounted for by typical development in young adults over 3 months to be the strongest evidence for experience-dependent plasticity.

Methods

Participants

Twenty-five adults (14 females) took part in the training group, and twenty-five adults (14 females) took part in the age- and IQ-matched pre-law control group. The training group was recruited through e-mail and classroom announcements to students in Blueprint Test Preparation courses. The control group was recruited through e-mails to pre-law organizations and online postings. Recruitment and experimental procedures were approved by the Committee for the Protection of Human Subjects at the University of California at Berkeley. Participants had no history of psychiatric or neurological disorder, and were fluent in English. Three participants in the trained group and two participants in the control group were left-handed.

Two participants – one from each group – were excluded from the study because they exhibited dramatic changes in stress levels and amount of sleep from time 1 to time 2 (more than 3 SD from the mean of all participants). Additionally, two participants from the control group were excluded because more than 5% of their brain volumes contained movement-related artifacts. Finally, we tested for outliers in average whole-brain diffusion measures at time 1, time 2, and in change between time points, and excluded one participant in the trained group for showing a decrease in MD and RD that was greater than 2 standard deviations lower than the mean across both groups. Thus, our final dataset included DTI data at two time points for 23 trained individuals and 22 controls (Table 1).

Behavioral Data

During the first testing session, we administered the Young Adult Self Report (Achenbach, 1990; 1997) to screen out participants who scored in the clinical range. We also administered two scales from the Wechsler Adult Scale of Intelligence (WASI) (Wechsler, 1999), Matrix Reasoning and Vocabulary, to match the groups on IQ (see Table 4.1). During both testing sessions, we administered the Perceived Stress Scale (Cohen et al., 1983) and asked participants to report their sleep schedules for the preceding two weeks. Reported stress levels and hours of sleep did not differ between groups at either time point (*Ps* > .4), and neither group changed significantly between time points (*Ps* > .2).

	Trained *N* = 23	Control *N* = 22
Age	21.39 (1.42)	21.44 (2.15)
WASI Matrix	29.75 (2.10)	29.37 (1.74)
WASI Vocabulary	66.33 (5.76)	67.10 (3.67)
Days between scans	89.17 (15.61)	90.91 (22.87)
Perceived Stress Time 1 Time 2	 21.67 (7.71) 21.16 (7.07)	 20.24 (7.32) 22.11 (9.13)
Hours of Sleep Time 1 Time 2	7.50 (0.88) 7.33 (1.08)	7.57 (0.96) 7.34 (1.14)

Table 4.1: Demographic and behavioral measures for study participants. Means and standard deviations are reported. None of the measures differed significantly between groups ($P > .2$).

Training Paradigm

We selected the Blueprint Test Preparation course as the training paradigm because it provided more classroom time than other local programs: 100 hours distributed across the three components of the LSAT (35 hours for Logic Games, 35 hours for Logical Reasoning, and 30 hours for Reading Comprehension). "Logic Game" questions require test takers to integrate a series of rules in order to sequence or group a set of items. "Logical Reasoning" questions ask them to determine the logical flaw in an argument, identify an assumption, or choose a statement that would strengthen or weaken an argument. The remaining 30 hours of class time were dedicated to "Reading Comprehension" questions that require test-takers to interpret short passages of text.

For the Logic Games section, students were taught to break down problems into the essential information and to use diagrams to represent and integrate rules. For the Logical Reasoning section, students were taught basic logic principles (such as *modus ponens* and *modus tollens*), as well as how to avoid common logical fallacies. Students attempted problems at home and then instructors worked through the problems in class, answering any questions students might have. Special attention was paid to keeping motivation levels high by making the content fun through relatable examples.

Four LSAT practice tests were administered throughout the course. Practice test scores were provided either by the participants or (with participants' consent) by

the test preparation company. We compared the scores on each of the LSAT sections for the first and fourth practice test as an index of change from time 1 to time 2.

Voxel-based Morphometry Analysis

To rule out the possibility that gray matter changes associated with training could be misinterpreted as changes in DTI parameters, we performed voxel-based morphometry analyses on the structural data from the trained group using the Functional MRI of the Brain Softward Library (FSL) (Ashburner, 2000; Good, 2001; Smith, 2004). Structural images were skull-stripped using the Brain Extraction Tool (BET) (Smith 2002), and tissue-type segmentation was carried out using FMRIB's Automated Segmentation Tool (FAST4) (Zhang 2001). Gray-matter partial volume images were then aligned to standard space using FSL's Linear Image Registration Tool (FLIRT) (Jenkinson, 2001; 2002), followed by nonlinear registration using FSL's Nonlinear Image Registration Tool (FNIRT) (Andersson 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert 1999). The resulting images were averaged to create a study-specific template, to which the native grey matter images were then non-linearly re-registered. The registered partial volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm. Finally, a voxel-wise paired t-test GLM comparing pre-training to post-training data was applied using Randomise (Nichols and Holmes, 2002) with 5000 permutations, correcting for multiple comparisons at $P < .05$.

DTI Data Acquisition and Preprocessing

Data were acquired on a 3 Tesla Siemens Trio TIM MR scanner using a 12-channel head coil with a maximum gradient strength of 40 mT/m. Structural and functional scans were collected in a fixed sequence across subjects and across time points. DTI data were acquired using echo-planar imaging (EPI; TR = 7900 ms; TE = 102 ms; 2.2 mm^3 isotropic voxels; 55 axial slices). Parallel acquisition (GRAPPA) was used with at an acceleration factor of 2. Seven non-diffusion-weighted directions and 64 diffusion-weighted directions were acquired with a b-value of 2000 s/mm^2, uniformly distributed across 64 gradient directions.

Analyses were performed using tools from FDT (Functional MRI of the Brain (FMRIB) Diffusion Toolbox, part of FSL 4.1; Smith et al., 2002; Woolrich et al., 2009). Brain volumes were skull-stripped using BET (Smith, 2002). A 12-parameter affine registration to the b = 0 weighted volume was applied to correct for head motion and eddy current distortions introduced by the gradient coils, and the gradient directions were rotated accordingly. A diffusion tensor model was

fitted to the data in a voxel-wise fashion to generate whole-brain maps of AD, RD, FA, and MD.

The first volume of our DTI acquisition had no diffusion weighting and was used to align the DTI scans at both time points to each other using a 12 parameter affine transformation and skull images to constrain the registration scaling using FLIRT (Jenkinson 2001, 2002). Both images were resampled into a space halfway between the two. This transformation was then applied to the FA maps and the aligned maps averaged to generate a subject-specific mid-space template. We subsequently non-linearly aligned these template FA maps into standard space using FNIRT (Andersson et al., 2007a;b). Whole-brain MD, AD, and RD maps were aligned to standard space through application of the same two-step transform (linearly into subject-template space, then non-linearly into standard space).

A white matter mask was created from each subject's high resolution T1-weighted scan, after brain extraction, using FAST (Zhang, Brady, & Smith, 2001). This mask was transformed into the subject's DTI space by applying the inverse of the affine registration of the non-diffusion weighted volume to the high resolution image. Both the registration and calculations of the inverse transform used FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002). Once in DTI space, the white matter masks were registered to subject-template space and combined (through multiplication) to create a subject-specific definition of white matter voxels.

DTI Analyses

We performed voxel-wise statistical analysis using TBSS (Tract-Based Spatial Statistics, Smith et al., 2006). After FA maps were aligned to standard space, the mean FA image was generated and thinned to produce a mean FA skeleton that represented the centers of all tracts common to the group. Each subject's aligned FA, AD, RD, and MD data were then projected onto this skeleton by finding the nearest maximum FA value for the individual. This projection step aims to remove the effect of cross-subject spatial variability that remains after the non-linear registration. Skeletonized difference images (time 2 - time 1) were created for each subject, and the resulting data were fed into an unpaired t-test to compare the trained group to the control group. Voxel-wise cross-subject permutation-based nonparametric statistics were performed using Randomise (Nichols and Holmes, 2002) with 5000 permutations and threshold-free cluster enhancement to correct for multiple comparisons at $P < .05$ (Smith and Nichols, 2009). We used the same statistical approach to test for pre-training differences between groups (unpaired t-test of time 1 data).

To better characterize the anatomy of white matter showing an effect of training, we examined a recently developed tensor index used to identify regions of crossing fibers (Douaud et al., 2011): the mode of anisotropy (Ennis & Kindlmann, 2006). Regions with a positive mode have linear anisotropy, and are likely to be part of a highly directional tract. In contrast, regions with a low or negative mode can be described as having planar anisotropy, and are more likely to contain crossing fibers. We extracted mode of anisotropy values from voxels that were significant in the whole-brain analyses, as well as mode values across the entire white matter skeleton. Specifically, we extracted values from the average of all time 1 and time 2 mode maps after they had been registered into the standard space by following the same two-step registration process as described above. Histograms with a bin width of 0.01 were created using fslstats, an FSL tool (Smith, 2004). We used a Mann-Whitney *U*-test to investigate differences in the distributions of mode values within each of the results regions and the white matter skeleton.

We tested for correlations between LSAT improvement, as measured by the difference between the first and fourth practice test, and diffusion changes at the whole brain level following the approach described above. We then tested for brain-behavior correlations in the anatomical regions defined by the Johns Hopkins University White Matter Label Atlas (Mori, 2005). While we predicted correlations in frontoparietal white matter, we decided to perform an exploratory analysis because we considered that brain-behavior relationships might be most prominent in tracts less centrally involved in reasoning. Therefore, we tested all 48 labels and corrected all statistics for multiple comparisons using a randomization-based family-wise error correction (Nichols and Hayasaka, 2003)

White matter labels were nonlinearly registered to subject-template space (halfway between time 1 and time 2 for each subject, described above) using the inverse of the transform previously used to register subject data to standard space. Then, the average value of all voxels which lay within each ROI and the subject-specific white matter mask was extracted separately from each map. A difference measure was calculated by subtracting the average value for time 1 from the average value for time 2.

We also applied this process to calculate the average difference values for FA, AD, RD and MD in the voxels that reached significance in the whole brain analyses (see inset in Figure 4.1).

Results

Behavioral improvement

For participants for whom all 4 practice test scores were available (n = 16), training was associated with a gain of 9 points on the LSAT ($P < .001$, $df = 15$, $t = 6.59$). Subtest data was available for 13 participants. These participants

improved significantly on the two reasoning components of the test, Logic Games ($P < .01$, $df = 12$, $t = 3.21$) and Logical Reasoning ($P < .001$, $df = 12$, $t = 4.91$). They also improved slightly on Reading Comprehension ($P = .03$, $df = 12$, $t = 2.45$). LSAT improvement was significantly correlated with the reasoning subtest scores (LG: $R = .85$, $P = .0002$; LR: $R = .68$, P = .01), but not with RC ($R = .5$, $P = .08$), suggesting that changes in LSAT scores were driven by reasoning gains.

Changes in diffusion measures

The trained and control groups did not differ at time 1 on any of the diffusion measures (FA, RD, AD, and MD). The groups also did not differ on grey or white matter volume at either time 1 or time 2. Further, we did not observe a significant effect of training on grey/white matter classification within the trained group.

Whole-brain voxel-wise statistical analyses revealed significant decreases in RD and MD (but not in FA or AD) from time 1 to time 2 for the trained group compared to the control group, as described below. RD decreases were observed in white matter connecting frontal cortices (genu, anterior body of the corpus callosum, anterior corona radiata), and in descending white matter, including superior corona radiata, anterior internal capsule, and ventral brainstem (Figure 4.1, green). Training-related decreases in MD were generally more lateral, and closer to cortex, with the exception of decreases through anterior callosum (Figure 4.1, blue). MD decreases were particularly notable in white matter underlying left frontal cortex, including left RLPFC (see Figure 4.1, Z = 0), and right parietal cortex (Figure 4.1, Z = 30, X = 35).

When we extracted all four diffusion measures (FA, AD, RD, and MD) for the trained group from the voxels showing significant changes in RD (Figure 4.1, inset, left) and MD (Figure 4.1, inset, right), different patterns emerged. On average, voxels showing a decrease in RD also showed an increase in FA, which was likely not significant at the whole-brain level because of a slight concomitant decrease in AD. In contrast, voxels showing a significant decrease in MD showed roughly equal decreases in AD and RD, and therefore, no trend towards a change in FA.

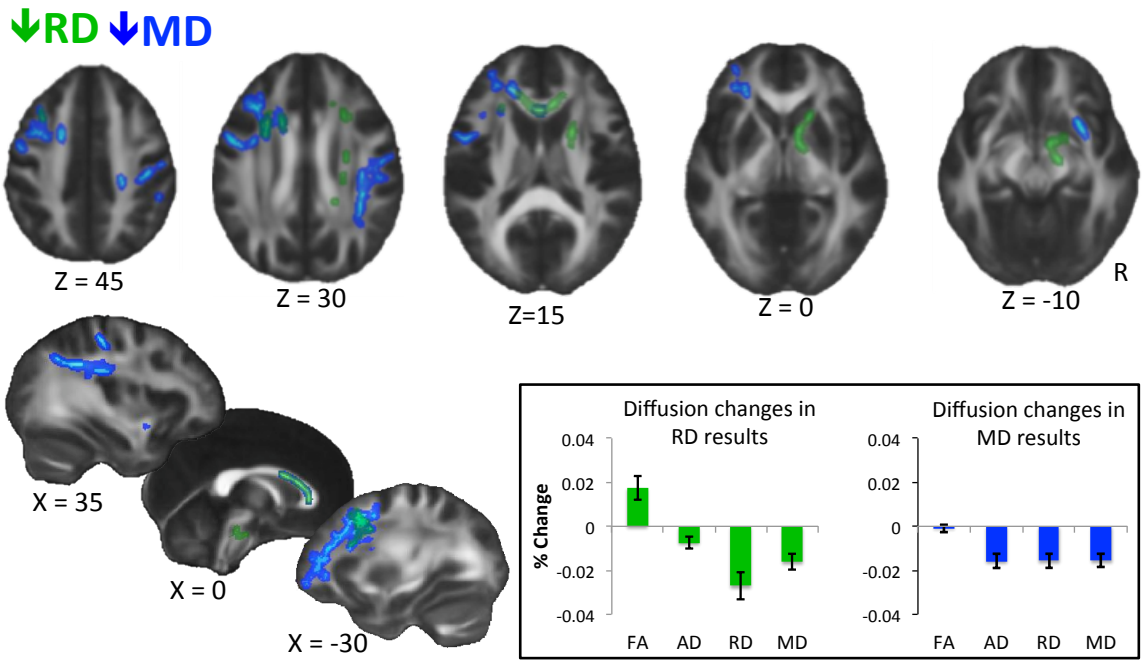

Figure 4.1: Results of whole-brain voxel-wise statistics. Decreases in RD are shown in green, and decreases in MD are shown in blue. Statistics were performed on skeletonized images, and results were filled for visualization purposes. Results are thresholded at $P < .05$, corrected for multiple comparisons with threshold-free cluster enhancement (Smith and Nichols, 2009). Inset shows percent change in diffusion measures extracted from voxels showing a significant decrease in RD (left) and MD (right) for the trained group only. Error bars represent standard error of the mean. No statistics are performed as they would be biased because values are extracted from voxels showing a significant change in diffusion at the whole brain level. The graph is meant to show qualitative differences in diffusion parameters between RD and MD results.

Locations of RD and MD changes according to the JHU White Matter Label Atlas are shown in Tables 2 and 3, respectively. While 85% of the voxels showing a decrease in RD were classified by the JHU atlas, only 35% of the voxels showing a decrease in MD fell into a white matter label, likely because this atlas classifies primarily deep white matter and not white matter nearer to cortex. Importantly, because TBSS analyses test voxels along a white matter skeleton, we tested only voxels that were solidly in white matter, and not those contaminated by gray matter.

White Matter Label	Number of voxels
Anterior limb of internal capsule, R	526
Genu of corpus callosum	332
Superior corona radiata, R	254
Body of corpus callosum	178
Cerebral peduncle, R	178
Anterior corona radiata, R	172
Superior corona radiata, L	170
Anterior corona radiata, L	136
Corticospinal tract, R	133
Posterior limb of internal capsule, R	75
Superior cerebellar peduncle, R	68
Superior fronto-occipital fasciculus, R	67
Middle cerebellar peduncle	54
Posterior corona radiata, R	41
Pontine crossing tract	37
Splenium of corpus callosum	37
Medial lemniscus, R	13
Superior longitudinal fasciculus, R	5
External capsule, R	2
Total labeled voxels	2478
Total voxels	2912

Table 4.2: Locations of voxels showing RD decreases. Voxels are 1 mm^3. L = left, R= right.

White Matter Label	Number of voxels
Anterior corona radiata, L	468
Superior corona radiata, L	299
Superior longitudinal fasciculus, R	266
Genu of corpus callosum	253
Body of corpus callosum	224
Superior longitudinal fasciculus, L	100
External capsule, R	99
Superior corona radiata, R	37
Uncinate fasciculus, R	13
Anterior limb of internal capsule, L	3
Superior fronto-occipital fasciculus, L	1
Total labeled voxels	1763
Total voxels	4989

Table 4.3: Locations of voxels showing MD decreases. Voxels are 1 mm^3. L = left, R= right.

In addition to an apparent difference in spatial distribution, we were interested to know whether the distribution of mode of anisotropy, a proxy measure for the presence of crossing fibers, differed between voxels showing a significant decrease in RD and MD. Figure 2 shows histograms of mode values for voxels showing changes in RD (green) and MD (blue). Mode values for the entire white matter skeleton are shown for comparison (black). Voxels showing a decrease in RD have a median mode (*Mdn* = 0.70) that is significantly greater than the median mode of the white matter skeleton (*Mdn* = 0.48, *Mann-Whitney U* = 1.19 x 10^8, *df* = 121805, *P* = 1.35 x 10^{-186}), providing evidence that RD changes occurred in highly directional tracts. In contrast, voxels showing a decrease in MD have a median mode slightly lower than the whole white matter skeleton (*Mdn* = 0.44, *U* = 2.78 x10^8, *df* = 123882, *P* = 2.93 x 10^{-21}), suggesting that MD

changes were more likely to occur in regions with crossing fibers. The peak in mode values above 0.9 comes principally from voxels in the anterior callosum. Importantly, only 5% of RD results and 6% of MD results have a negative mode, so excluding these voxels from the analysis because they were not fit well by the standard linear tensor would not appreciably alter the results.

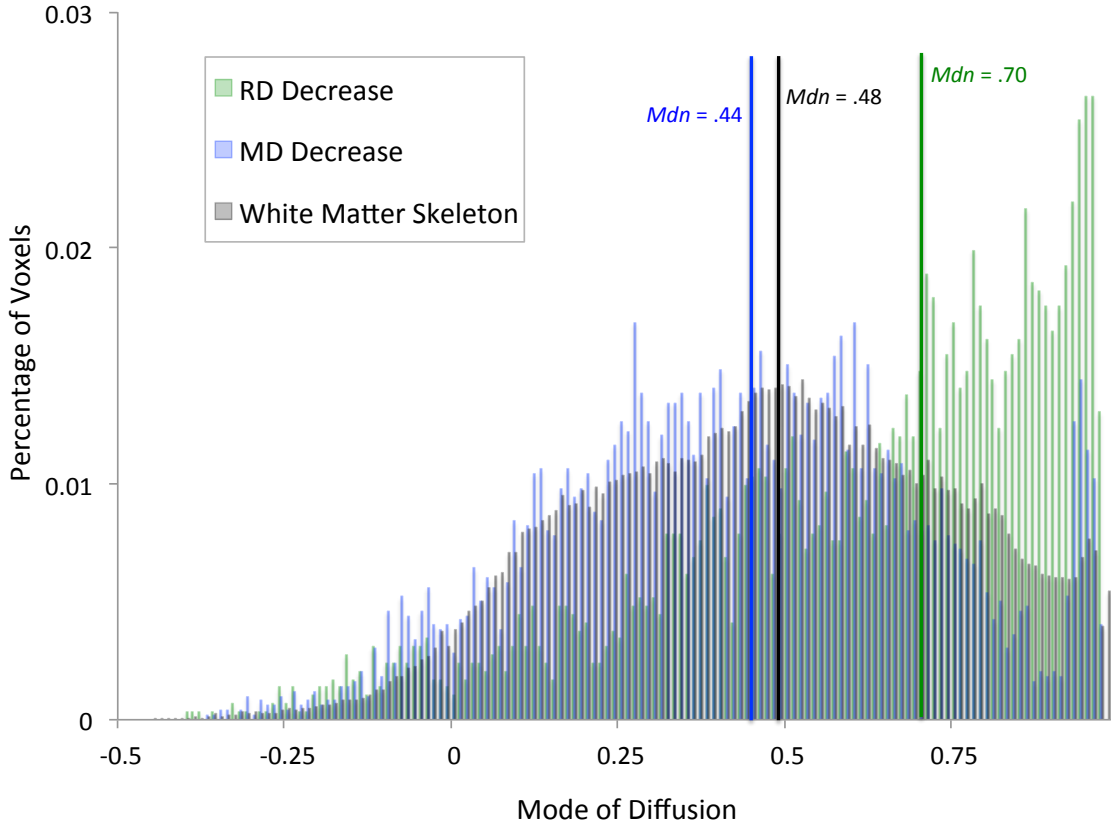

Figure 4.2: Distribution of diffusion mode for whole-brain results. Histograms showing percentage of voxels with a given mode value were calculated for voxels that exhibited a significant training effect at the whole-brain level in RD (green) or MD (blue). For comparison, a histogram of mode values for the entire white matter skeleton is shown (black). Median mode for each set of voxels is marked by a vertical line (RD: green, MD: blue, white matter skeleton: black).

Diffusion-behavior correlations

We tested for significant correlations between behavioral improvement and diffusion changes at the whole-brain level, but did not find significant results ($P >$ 0.05 after correcting for multiple comparisons). We then tested for correlations between diffusion and LSAT improvement within ROIs defined from the JHU White Matter Atlas. This analysis revealed a significant negative correlation between change in MD and change in LSAT score in the retrolenticular part of the right internal capsule (Figure 3, Spearman's rho = -.667, P(uncorrected) = .005). This correlation was significant after a randomization -based family-wise

error correction for 48 comparisons (Nichols and Hayasaka, 2003), as we tested each of the regions in the JHU White Matter Label Atlas (*P*(corrected) = .02).

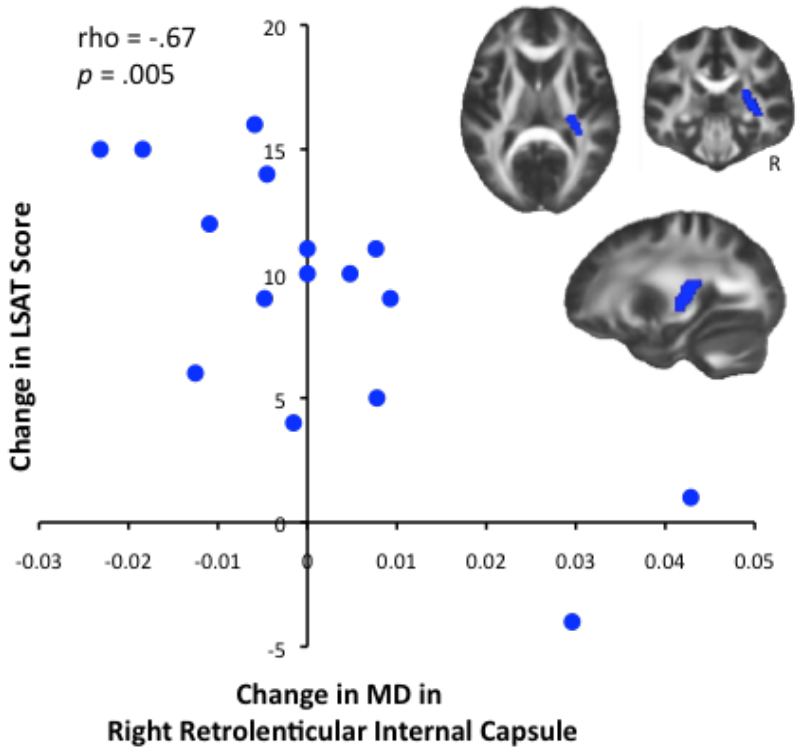

Figure 4.3: Correlation between LSAT improvement and MD decrease. LSAT change and MD change were significantly negatively correlated (Spearman's rho = -.667, *P*(uncorrected) = .005, *P*(corrected) = .02) in the right retrolenticular part of the internal capsule, an anatomical ROI defined from the JHU Label Atlas. Slices shown are: X = 27, Y = -29, Z = 10.

Discussion

In this study, we sought to test whether three months of reasoning training altered white matter microstructure. While we found no changes in white matter volume, we observed training-related changes in diffusion parameters within white matter. Indeed, our results show that reasoning training led to decreased RD in white matter connecting frontal cortices, and decreased in MD in white matter underlying left frontal and right parietal cortices. These experience-dependent changes fall into tracts that would be predicted by prior work showing that reasoning relies on an interhemispheric frontoparietal network (for review, see Prado, 2011). Our findings are also consistent with the view that reasoning is largely left-hemisphere dominent (e.g. Krawczyk, 2012), but that homologous cortex in the right hemisphere can be recruited as needed to support complex

reasoning. Perhaps learning to reason more efficiently involves recruiting compensatory neural circuitry more consistently.

Relationships between diffusion changes and LSAT changes were not particularly robust, perhaps because neuroplastic changes were driven by experience shared across individuals. We found an unpredicted negative correlation between change in MD and improvement on the LSAT in the retrolenticular part of the right internal capsule (white matter that interconnects posterior cortices and thalamus) as well as corticopontine fibers originating in the right parietal lobe (Nolte, 2009). Future research with a larger sample size will be needed to determine whether these brain-behavior correlations are replicable, and whether there are any additional statistically significant relationships between diffusion change and reasoning improvement.

The results featured here meet a more conservative criterion than several prior training studies, in that changes in the trained group needed to surpass changes in the control group to be considered significant. The participants in our study were, on average, in their early twenties, and developmental changes in white matter are known to occur during this age range (Lebel et al., 2008). Additionally, both groups consisted largely of university students, and their academic experiences over the course of three months alone could have altered their white matter microstructure. Thus, changes that were significantly greater in the trained group than in a well-matched control group provide strong evidence for experience-dependent plasticity, and not simply maturational changes.

An active control group is often preferable to a passive control group in training studies, because it controls for general factors like beliefs about how much one is learning or improving on a task. For this study, however, selecting an appropriate active control group for this study would have been difficult as most adults would not choose to spend 100 hours over 3 months training on a skill that is not directly relevant to their life goals. Had we administered an artificial active control training program in the lab, differences between groups in neuroanatomical changes could have been confounded by differences in levels of motivation and attention. Alternatively, if our control group had consisted of individuals enrolled in a different professional training course, such as the Medical College Admissions Test (MCAT), we might have encountered initial group differences based on differences in interests, coursework, and experiences that would predispose students to seek admission to one professional program over another.

In this paper, we have examined changes in four measures of diffusion. On the one hand, this broad approach introduces a multiple comparison problem that would not exist if we had simply investigated changes in a single measure. On the other hand, if we had only looked at one measure, we would have painted a limited picture of white matter plasticity. Further, we did not have strong reason to

believe that one index of white matter microstructure was more important or more likely to change with training than the others.

It is important to recognize that a tract defined by an atlas does not necessarily reflect an individual's anatomical tract. Rather, it reflects where tracts lie on average across individuals. At the current resolution, it is not possible to determine whether any given voxel contains axons connecting, for example, bilateral motor cortices or frontal and parietal cortices. Advances in diffusion imaging, such as diffusion spectral imaging (DSI), may make it possible to better classify the principal direction(s) of each voxel that shows a quantified change in diffusion. However, these sequences have yet to be used in the context of research on neuroplasticity. As the required scan time for advanced diffusion imaging pulse sequences decreases, and as scanners employ stronger gradients, it should become feasible to include more sensitive measures of white matter microstructure in studies of neuroplasticity that involve multiple structural and functional brain scans.

Even with advances in imaging methodology that make it possible to determine the direction of diffusion precisely, the study of white matter plasticity in humans will still be limited by the scale at which we can observe neuroanatomical changes. The cellular basis for training-induced changes in diffusion in humans is and will remain unclear, at least for the foreseeable future, though it is possible to speculate about potential mechanisms based on plasticity observed in animals (see Zatorre et al., 2012 for review).

Studies in animals have shown that both decreased RD and increased FA are related to increased myelination (Blumenfeld-Katzir et al.; Vorisek and Sykova, 1997; Zhang et al., 2009). It is possible, then, that the experience-dependent decreases in RD (and increases in FA) that we observed were driven by myelination, especially because they tended to be in highly directional, heavily myelinated tracts. However, it is important to note that while myelin does affect diffusion (Mottershead et al, 2003; Concha et al, 2010), unmyelinated axon membranes do as well (Partridge et al 2004), and myelin volume and axon counts are very highly correlated (Schmierer et al., 2007; Concha et al., 2010). Therefore, the extent to which axonal cell membranes also constrain diffusion is unclear.

Decreased MD, on the other hand, has been related to proliferation and/or growth of astrocytes (Blumenfeld et al., 2006). A reduction in MD could additionally or alternatively reflect the myelination of axons traveling in multiple directions. It is therefore intriguing that we observed decreased MD near cortex, and also in white matter that was not highly directional and therefore could contain crossing fibers. Hopefully, future research linking changes in cell structure and function to plasticity in large-scale networks will further our understanding of how experience shapes the anatomy of the human brain.

Chapter 5
Summary and Future Directions

The research presented in this thesis demonstrates that reasoning ability is modifiable in children and young adults. In children from low socioeconomic backgrounds, playing games that tax relational integration led to large gains in reasoning ability. The games we used were inexpensive and widely available, making the training program easy to implement more broadly. Since the publication of this study, schools all over the world have implemented some version of our training paradigm. Future replications of our results are critical before we would advocate for the inclusion of a similar program in school curricula. Our initial study was underpowered, included too few cognitive assessments, and suffered from the problem that testers in the first semester of the study were not blind to group assignment.

In adults, preparing for the LSAT led to improvement on the reasoning subscales of the test, showing that it is indeed possible to learn to reason. We observed changes in functional and structural connectivity suggesting that reasoning training led to increased integration between left and right frontoparietal networks. We found strengthened functional connectivity between contralateral frontal and parietal cortices. Because contralateral frontal and parietal cortices are not monosynaptically connected, a change in functional connectivity between them was likely mediated by a change in connectivity between frontal or parietal homologues. Indeed, when we looked to structural connectivity data, we found decreased radial diffusion in anterior callosum, which contains fronto-frontal tracts. Decreased radial diffusion could have been driven by activity-dependent myelination. We also found decreased mean diffusion in white matter underlying left frontal and right parietal cortices, which could have been driven by changes in local white matter architecture, such as myelination of disparate axons or increased size of number of glia. One intriguing interpretation of these findings is that training involved the repeated recruitment of compensatory mechanisms that rely on communication between homologues.

Interestingly, training also strengthened striatoparietal connectivity. In the functional data, this was evident from increased correlations between striatum and parietal cortex. In the structural data, we observed decreased radial diffusion in the internal capsule, which contains corticostriatal connections. These finding are consistent with the striatum's role in learning through its dopaminergic inputs. In other words, perhaps learning to reason relies on mechanisms similar to those important for other types of cognitive and motor learning.

These results have broad societal relevance. Millions of young adults prepare intensively for the LSAT and other standardized exams. To correctly interpret the significance of these test scores, it is important to know whether these exams measure individuals' cognitive *potential,* or whether they more accurately reflect

their cognitive *history* – i.e., the prior level of engagement of specific brain networks.

There are still many open questions regarding how training alters brain development and function.

Does reasoning training transfer to academic gains?

Reasoning and academic performance are correlated: children who do well on reasoning tests tend to do well in school, and adults with high LSAT scores tend to excel in law school. However, it is unclear whether reasoning gains will lead to better performance in school. On the one hand, it is possible that some general third factor, such as neural "integrity", drives the correlation between reasoning and academic abilities. If this is the case, then training reasoning would have limited benefits. However, it is also possible that better reasoning skills directly transfer to better performance in the classroom. Learning to reason about spatial relationships might improve math skills. Learning to reason by analogy might help students connect new information to existing knowledge frameworks. Intuitively, it seems that if students are better able to detect relationships between concepts and integrate information, they will learn more effectively.

How long do training gains last?

It is possible that training-related gains in PFC function fade as quickly as they are instilled. Maintaining cognitive gains might require regular practice. Such a finding would not invalidate the cognitive intervention; it is generally agreed that physical exercise is important for bodily health, even though one must exercise regularly to enjoy its benefits over the long term. Evidence that short-term apparent fade-out can be followed many years later by meaningful gains comes from the Perry Preschool and Abecedarian programs: children appeared to lose their gains within 1 or 2 years after the interventions ended, but decades later their rates of high school graduation and college enrollment were markedly higher than those of the control group (Knudsen, Heckman, Cameron, & Shonkoff, 2006). Perhaps, reasoning training has the potential to alter the course of development by boosting skills necessary for learning and problem solving (Blair & Diamond, 2008).

How does training interact with development?

The behavioral and neural effects of training likely differ between children and adults. It is not known when during development the neural network supporting reasoning is most receptive to training. Younger brains are generally more plastic, so training might be more effective in childhood, but training gains might also fade more quickly. Also, because reasoning relies heavily on skills including attention, processing speed, and working memory, reasoning training may have

limited efficacy in children who have not adequately developed these lower-level skills. Importantly, there is currently no evidence to suggest that reasoning training is *not* effective at any point in the lifespan.

How do individual differences in genetics and environmental factors alter the efficacy of training?

Individuals might differ in the extent to which their brains can be shaped by experience. For example, Bruce Ellis and W. Thomas Boyce have described "dandelion" and "orchid" children (Ellis and Boyce, 2008). Dandelions thrive regardless of the environmental circumstances that surround them. Orchids, in contrast, are highly susceptible to both negative and positive environmental factors. Orchids might develop mental illnesses or struggle in school if they grow up in suboptimal environments, but ideal environments allow them to flourish. Orchids might be more responsive to cognitive training than dandelions, but they might also be more likely to need it. This analogy is meant to illustrate the two ends of a continuum of potential for plasticity. This continuum is likely created by individual differences in both genetics, with some genotypes associated with greater plasticity and others with greater stability, and environment. Stress, for example, might limit plasticity. It might be adaptive for the brain to refrain from energy-intensive long-term remodeling projects in the face of an acute threat.

Research that addresses these questions will provide theoretical insights for our understanding of individual differences in cognitive abilities. Additionally, it will provide practical insights, improving our ability to intervene to improve cognitive skills. Because this research has important implications for policy, it must be carried out and reported with great care.

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Appendices

A. Supplemental material for chapter 2

Subject Number	Age	Gender	Education of Primary Caregiver	WASI Vocabulary Raw	Training Days Attended	Semester
R1	8.50	M	12	22	13	Fall
R2	6.92	M	8	20	13	Fall
R3	8.50	F	12	21	13	Fall
R4	8.75	M	12	38	13	Fall
R5	8.50	M	8	28	16	Fall
R6	8.92	F	8	27	14	Fall
R7	8.92	F	N/R	27	14	Fall
R8	9.00	M	N/R	32	13	Fall
R9	7.17	M	10	17	16	Fall
R10	8.83	M	10	30	16	Fall
R11	8.67	F	10	30	8	Spring
R12	9.67	F	12	31	13	Spring
R13	8.42	M	10	23	12	Spring
R14	8.83	F	11	30	12	Spring
R15	8.08	F	12	18	8	Spring
R16	9.08	M	10	37	12	Spring
R17	9.08	M	10	34	10	Spring
R1exc (excluded for age)	10.00	M	7	16	13	Fall
R2exc (excluded for age)	10.67	M	4	31	16	Fall
Mean (n=17)	**8.58**	**10 M/ 7 F**	**10.33**	**27.35**	**12.71**	**10 Fall/ 7 Spring**
Mean (n=19)	**8.76**	**12 M/ 7 F**	**9.76**	**26.95**	**12.89**	**12 Fall/ 7 Spring**

Table A1: Demographic Information for the Reasoning Training Group

Subject Number	Age	Gender	Education of Primary Caregiver	WASI Vocabulary Raw	Training Days Attended	Semester
S1	7.75	M	12	30	10	Fall
S2	8.50	F	12	22	11	Fall
S3	8.50	M	N/R	29	15	Fall
S4	7.83	M	13	30	12	Fall
S5	8.00	M	9	14	13	Fall
S6	9.08	M	N/R	35	13	Fall
S7	7.83	M	12	19	15	Fall
S8	9.67	F	13	45	12	Spring
S9	8.33	F	N/R	22	8	Spring
S10	8.75	M	9	29	11	Spring
S11	9.50	M	4	35	12	Spring
S1exc (behavioral outlier)	8.67	M	6	31	13	Fall
S2exc (excluded for age)	10.75	F	3	23	13	Fall
S3exc (behavioral outlier)	9.00	F	7	33	13	Fall
Mean (n=11)	8.52	8 M/ 3 F	10.50	28.18	12.00	7 Fall/ 4 Spring
Mean (n=14)	8.73	9 M/ 5 F	9.09	28.36	12.21	10 Fall/ 4 Spring

Table A2: Demographic Information for the Speed Training Group

	Reasoning Group					
	TONI		Speed			
			Coding		Crossout	
Subject Number	Pre	Post	Pre	Post	Pre	Post
R1	13	14	36	25	10	11
R2	12	17	25	21	11	12
R3	15	23	42	48	18	20
R4	13	25	35	44	16	18
R5	17	15	43	45	19	23
R6	17	18	42	42	18	17
R7	14	18	39	39	11	11
R8	15	26	33	43	18	19
R9	13	24	28	28	16	18
R10	17	24	35	30	12	12
R11	17	19	35	38	15	15
R12	16	20	38	44	14	18
R13	15	17	41	49	16	14
R14	21	19	40	41	13	16
R15	13	20	35	43	15	22
R16	18	22	40	33	15	20
R17	20	22	33	29	14	15
R1exc	24	19	43	47	15	18
R2exc	18	12	38	42	17	16
Mean (n=17)	15.65	20.18	36.47	37.76	14.76	16.53
Mean (n=19)	16.21	19.68	36.89	38.47	14.89	16.58

Table A3: Reasoning and Speed Raw Scores for the Reasoning Training Group

	Speed Group					
	TONI		Speed			
			Coding		Crossout	
S1	17	12	30	39	16	20
S2	12	18	19	29	9	12
S3	19	21	38	42	18	19
S4	20	18	36	39	23	25
S5	18	12	31	45	17	18
S6	19	24	45	54	12	19
S7	12	19	44	49	19	22
S8	21	27	37	50	15	21
S9	25	27	38	39	14	15
S10	13	17	32	50	10	19
S11	15	15	27	33	16	17
S1exc	13	29	42	42	17	21
S2exc	24	13	41	53	15	17
S3exc	34	19	38	36	9	16
Mean (n=11)	17.36	19.09	34.27	42.64	15.36	18.82
Mean (n=14)	18.71	19.36	35.57	42.86	15.00	18.64

Table A4: Reasoning and Speed Raw Scores for the Speed Training Group

Reasoning Training Group								
	Digit Forward		Digit Backward		Spatial Forward		Spatial Backward	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
R1	9	10	1	4	3	7	2	6
R2	4	5	2	2	6	10	2	2
R3	9	9	5	8	7	10	8	7
R4	6	5	5	5	5	6	4	4
R5	9	10	2	3	9	8	6	7
R6	7	6	3	4	6	8	6	6
R7	9	7	4	5	5	5	4	7
R8	9	8	4	5	8	9	4	10
R9	6	9	4	4	6	5	2	6
R10	5	5	4	4	5	8	6	5
R11	8	9	7	8	6	6	5	4
R12	7	8	5	4	6	6	4	2
R13	6	6	4	4	4	4	4	4
R14	4	10	6	5	10	8	8	8
R15	8	8	4	3	5	7	4	4
R16	10	9	5	4	6	9	6	6
R17	10	9	4	4	5	5	2	3
Mean (n=17)	7.41	7.82	4.06	4.47	6.00	7.12	4.53	5.35

Speed Training Group								
	Digit Forward		Digit Backward		Spatial Forward		Spatial Backward	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
S1	6	7	5	4	7	6	2	2
S2	3	3	3	3	9	9	0	2
S3	8	8	4	7	7	6	7	5
S4	5	5	2	5	5	7	5	4
S5	6	6	4	3	5	5	3	3
S6	11	10	6	9	9	9	8	6
S7	10	6	2	8	6	7	4	5
S8	5	9	6	6	9	4	3	6
S9	7	6	6	5				
S10	9	10	5	4	8	7	6	8
S11	8	6	2	3	5	6	5	4
Mean (n=11)	7.09	6.91	4.09	5.18	7.00	6.60	4.30	4.50

Table A5: Working Memory Scores

Text A1: Training Information

Reasoning Training Games

Individual Games

Rush Hour: This game gives cue cards that arrange cars in a specific pattern on the board. The player then has to manipulate the cars forwards and backwards or up and down (depending on how the car is placed) to move a specific car out of the board through an exit. To complete a puzzle efficiently, it is necessary to plan several moves in advance.

Chocolate Fix: The game consists of 9 plastic chocolate pieces of 3 different shapes and 3 different colors. Children need to place these pieces according to a set of rules given by a cue card. For example, one clue might show that the top row must all pink pieces and the left column must be all square, so the child must integrate these clues to deduce that the upper left piece is a pink square.

Towers: This game is modeled after a classic test of planning skills known as the Tower of London or the Tower of Hanoi. This game consists of 3 posts and anywhere from 3 to 7 rings. Children use two rules (only one ring can be moved at a time, and larger rings cannot be placed on smaller rings) to move a stack of rings from one post to another.

Tangoes: The objective of this game is to recreate a two dimensional figure using seven smaller pieces. This game requires children need to change the scale of an object and map the location of the smaller components.

Group Games

Quirkle: This game comes with tiles of different shapes and colors. The goal for each turn is to align as many tiles as possible that match along one dimension (i.e. color, shape). As the game progresses, the existing grid of tiles becomes more complicated, and it becomes more difficult to place multiple pieces in a turn.

Set: The goal of this game is to find a “set” in which three cards are either the same of different on each of four dimensions: shape, number, pattern, and color. Twelve cards are laid out on the table, and children try to find the sets as quickly as possible. To find the sets, children must flexibly switch between searching for matches along each of the four dimensions.

Nintendo DS Games

Picross: In this game, children are shown a grid with numbers along the rows and columns. The goal is to fill in squares to create a picture. It is necessary to integrate the information provided for the columns and rows to determine which squares should be filled in.

Big Brain Academy: Children played the three games in the “Thinking” category of this Nintendo DS game: Heavier, Pathfinder, and Boneyard.

a) Heavier: One or more cartoons is presented on each side of a balance scale, and multiple balance scales are presented simultaneously. It is necessary to examine the relationships between cartoons within and across balance scales to determine which of the cartoons is heaviest. For example, if one balance scale shows that the pear is heavier than the apple, and another scale shows that the apple is heavier than the pineapple, then the player should indicate that the pear is the heaviest item.
b) Pathfinder: This game requires the player to draw a horizontal line to complete a path that allows an animal at the top of the screen to reach a specific animal at the bottom. Once the player has drawn a line, the animal moves along the specified path. It is necessary to plan ahead, following the turns that the animal will make to get to the destination, to ensure that the animal lands in the correct spot.
c) Boneyard: This game gives the player a series of directions to follow to move a dog to his bone. For example, the game would tell the player that the dog will move 2 squares up, 3 squares left and 1 square down, and the player must integrate this information to determine his final destination.

Brain Teasers: Mind Benders. Four slots are presented on the screen, and the player must place a colored ball in each slot. The player must deduce the correct series by integrating feedback in response to each guess about the appropriate color and position of a ball. Pipe Mania: In this game, the player must create a pipeline from a set of differently shaped pipe segments. To direct the flow of water from a start point to a specified end point, it is necessary to place and rotate each segment correctly, considering how the water will flow along the path.

Computer Games

Azada:

a) Chemicals is similar to Mind Benders, except that the player must place drops of colors on a paper in the correct sequence.
b) Towers is a computerized version of the wooden Towers game described above.
c) Sliders is a computerized analogue of Rush Hour, except that the items that need to be moved are wooden blocks rather than cars.

d) Runes is like Set with 3 features per item rather than 4.
e) Shapes is the computerized analogue of Tangoes and Neves.
f) Round and Round is a grid with several colored squares that need to be moved in a circular fashion so that they end up in boxes outlined in the matching color. Because the blocks can only be moved in a specific manner, it is necessary to plan a series of moves to get the objects to the correct locations.

Azada II:

a) Connections is a game with hexagonal tiles that have numbers that represent how many other tiles they need to touch. The goal of the game is to arrange the tiles on the board to meet these conditions.
b) Dominos is a game in which 2-part tiles must be arranged along a circle such that each tile matches its neighbor in one characteristic (color or shape).

Speed Training Games

Individual Games

Perfection is a game in which the player must place different shaped pieces in their matching holes within the shortest amount of time possible.

Group Games

Pictureka is a multiplayer visual search game. Cue cards instruct players to find certain objects on the board in a limited amount of time. The boards are periodically shuffled to prevent the player from learning the location of the items on the board. Blink is a two-player card game. Each player is dealt half of the card deck and is required to match the cards in their hands along several dimensions (color, number, shape) as quickly as possible to two starter cards that are placed in the center of the table. The first player to get rid of all their cards wins. Speed is a two-player card game in which two cards are placed on the table and each player starts with half of the deck. Each player can hold 5 cards at a time, and can pick up a new card each time they put a card down. The goal is to get rid of one's cards as quickly as possible by placing them on cards that are one higher or lower (e. g. a 3 can be placed on a 2 or a 4). Spoons is a multiplayer card game in which players aim to collect all 4 of a card (ex: all Queens). Each player is dealt 4 cards and spoons are placed in the middle of the table (one fewer than the number of players). Cards are then passed around in a circle one at a time. If a player needs a card, he or she picks up the card and discards one from his or her hand. When one player has all 4 of one type of card, he or she reaches for a spoon. Every other player then reaches for a spoon, and the player who doesn't get one sits out the next round.

Nintendo DS Games

Nervous Brickdown is a computerized brick buster game. The player must move a platform back and forth quickly to catch a bouncing ball that breaks a set of bricks. Super Monkey Ball is a game in which the player navigates through various courses, adjusting speed and turning so as not to fall off the course. Mario Kart and Diddy Kong Racing are games in which the player drives on a racecourse and must respond rapidly to curves in the road or potential roadblocks. The objective of this game is to cross the race line first by quickly responding to the various challenges within the game.

Computer Games

Feeding Frenzy is a game in which the player guides a fish to eat smaller fish without being eaten by bigger fish. The player needs to move rapidly to avoid bigger fish and other hazards while still eating all of the smaller fish and collecting other objects for extra points. Atlantis is similar to Nervous Brickdown. Super Cow is a sidescroller game in which the player is a cow who must navigate through a space as quickly as possible, responding to a variety of obstacles.

Child-researcher interactions during training

Researchers in both groups asked children to verbally describe why they were stuck when they asked for help, rather than providing hints (e.g. the next correct move). The exact instructions that children varied across games, but in both groups, researchers would ask children to describe the most difficult parts of the game, and the easiest. They would ask children to try to change the order of the steps they were taking, and to try the easier parts of the games first.

For example, while playing Chocolate Fix, if a child couldn't solve a problem, they would be asked to explain which clues they had used successfully, and which they could not place. We would ask them whether they could try the clues in a different order, and to distinguish between the moves they were sure about from the moves they had guessed. While children were playing Perfection, if a child couldn't place all of the pieces in the time limit, we would ask them which pieces were more difficult to place than others, and whether they should change the order in which they attempt to place the pieces.

B. Supplemental material for chapter 3

Region 1	Region 2	Trained T1	Trained T2	Trained T-Test	Control T-Test	ANOVA	
						F	*p*
L Precentral	L Caudate	0.00	-0.16	0.0002	0.39	3	0.09
L Precentral	L Supramarg	0.31	0.16	0.0003	0.66	7.51	0.009
L Caudate	R Precentral	-0.06	-0.20	0.0004	0.20	0.84	0.36
L RLPFC	R Precuneus	-0.28	-0.09	0.0005	0.23	5.86	0.01
L Precentral	R Precentral	0.85	1.04	0.0009	0.74	5.09	0.03
L Ang	R Caudate	-0.02	0.09	0.001	0.77	3.46	0.07
L RLPFC	R Post Par	-0.37	-0.19	0.001	0.04	1.49	0.23
L Ang	R Putamen	-0.05	0.03	0.001	0.92	1.94	0.17
L Post Par	R Putamen	-0.19	-0.07	0.002	0.90	5.42	0.02
L Post Par	R IFG	-0.16	-0.02	0.002	0.30	10.19	0.002
L Precuneus	R Putamen	-0.16	-0.06	0.002	0.34	7.09	0.01
R Putamen	R Precuneus	-0.16	-0.05	0.002	0.65	6.31	0.02
R Precentral	R Putamen	0.07	-0.09	0.002	0.51	2.62	0.11
L Ang	R IFG	0.01	0.13	0.002	0.94	4.56	0.04
L RLPFC	L Precuneus	-0.09	0.08	0.003	0.57	4.25	0.05
L Precentral	R Putamen	0.05	-0.10	0.003	0.55	3.09	0.09
L RLPFC	L Post Par	-0.09	0.10	0.003	0.10	0.61	0.44
L RLPFC	L Precentral	-0.02	-0.18	0.004	0.71	3.2	0.08
R Post Par	R Precuneus	0.59	0.46	0.005	0.17	1.01	0.32
R Precentral	R Caudate	-0.07	-0.18	0.005	0.36	0.86	0.36
L IFG	L Post Par	0.02	0.14	0.006	0.30	7.29	0.009
L Putamen	L Post Par	-0.18	-0.07	0.007	0.20	1.76	0.19
L Putamen	L Precuneus	-0.14	-0.05	0.008	0.81	3.63	0.06
R Sup Par	R Precuneus	0.12	-0.02	0.009	0.02	0	0.99
L Ang	R RLPFC	0.07	0.18	0.01	0.29	7.86	0.007
L IFG	L Precentral	0.21	0.12	0.01	0.95	2.58	0.11
L Caudate	L Post Par	-0.13	-0.02	0.01	0.03	0	0.98
R Precentral	R Supramarg	0.26	0.16	0.01	0.72	1.34	0.25
L Caudate	L Precuneus	-0.14	-0.02	0.01	0.26	1.56	0.22
L Caudate	L Ang	0.04	0.13	0.01	0.25	0.96	0.33
R Putamen	R Ang	-0.02	0.07	0.01	0.83	3.02	0.09
L Precuneus	R Caudate	-0.16	-0.04	0.01	0.75	2.83	0.09
L Caudate	R Ang	0.03	0.12	0.02	0.83	2.31	0.13
L Precentral	R IFG	0.08	0.00	0.02	0.35	4.25	0.04
L Post Par	R Precuneus	0.45	0.34	0.02	0.31	0.56	0.46
L Precentral	L Putamen	0.09	-0.02	0.02	0.62	1.86	0.18
L RLPFC	R Ang	0.08	0.19	0.02	0.79	3.73	0.05
L IFG	L Precuneus	-0.17	-0.06	0.03	0.34	5.64	0.02
L Supramarg	L Post Par	0.07	0.16	0.03	0.74	3.07	0.09
L Supramarg	R Precentral	0.14	0.05	0.03	0.99	1.84	0.18
R IFG	R Post Par	-0.05	0.05	0.03	0.31	5.45	0.02
L Precentral	R Supramarg	0.15	0.08	0.03	0.36	0.21	0.65

L Post Par	R RLPFC	-0.22	-0.09	0.03	0.35	0.87	0.36
R Caudate	R Ang	0.07	0.15	0.04	0.93	1.7	0.19
R IFG	R Precentral	0.16	0.07	0.04	0.60	2.9	0.1
L Post Par	R Caudate	-0.17	-0.07	0.04	0.05	0.01	0.91
L RLPFC	R Precentral	-0.12	-0.24	0.04	0.32	0.6	0.44
L Precentral	R Caudate	-0.05	-0.16	0.04	0.31	0.58	0.45
L Putamen	R Precuneus	-0.16	-0.10	0.04	0.89	1.69	0.2
L Precentral	R Sup Par	0.24	0.34	0.05	0.61	1.05	0.31

Table B2: Correlations showing an effect of training
50 out of 231 pairs of region showed an effect of training ($P < .05$, uncorrected). Table is ordered from lowest to highest *P*-value for the t-test for the trained group. The first 18 region pairs are presented in Table 3.2