

REDUCING DISTRACTIBILITY IN HEALTHY OLDER ADULTS

BY

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LIST OF ABBREVIATIONS

ACC:	Anterior cingulate cortex
AMPA receptor:	α -amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid receptor; an ionotropic glutamate receptor
APT-II:	Attention process training, version II
ANOVA:	Analysis of variance
BA:	Brodmann's area
BDNF:	Brain-derived neurotrophic factor
BOLD:	Blood-oxygen level dependent
BPM:	Biological parametric mapping
CBF:	Cerebral blood flow
CDF:	Cumulative distribution function
CES-D:	Center for epidemiological studies depression scale
CSF:	Cerebrospinal fluid
DMN:	Default mode network
EPI:	Echo-planar imaging
fMRI:	Functional magnetic resonance imaging
FWE:	Family-wise error rate
GLM:	General linear model
GM:	Gray matter
HSQ-12:	Twelve-item health survey questionnaire
HVLT:	Hopkins verbal learning test
IFC:	Inferior frontal cortex
LCD:	Liquid crystal display

MFC:	Medial frontal cortex
MMSE:	Mini-mental state examination
MNI:	Montreal neurological institute
NMDA receptor:	<i>N</i> -methyl <i>D</i> -aspartate receptor; an ionotropic glutamate receptor
PASL:	Pulsed arterial spin labeling
PFC:	Prefrontal cortex
POMS:	Profile of mood states
Q2TIPS-FAIR:	Quantitative imaging of perfusion using a single subtraction with thin slice periodic saturation with a flow-sensitive alternating inversion recovery
ROI:	Region of interest
RT:	Response time
SDMT:	Symbol digit modalities test
SPM:	Statistical parametric mapping
TWIN:	Time window of integration
VBM:	Voxel-based morphometry
WM:	White matter

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REDUCING DISTRACTIBILITY IN HEALTHY OLDER ADULTS

Dissertation under the direction of Paul J. Laurienti, M.D., Ph.D., Associate Professor of Radiology

ABSTRACT

In addition to age-related changes in individual sensory systems, older adults also experience changes in how information from multiple sensory modalities is combined. In particular, older adults exhibit increased multisensory integration, showing larger gains than younger adults when information in one sensory modality is accompanied by matching information in a different modality. Although these enhanced integration capabilities can be beneficial in certain situations, older adults are also more distracted by irrelevant or incongruent sensory stimuli than younger adults. The overarching purpose of this thesis was to investigate the source of age-related increases in multisensory integration and to evaluate the effects of a cognitive training intervention designed to reduce distractibility in older adults.

Based on evidence that older adults show impairments on some measures of attention, we hypothesized that age-related enhancements in multisensory integration were due to deficits in older adults' ability to focus attention on a single sensory modality. In contrast to our expectations, older adults were able to effectively engage modality specific selective attention to limit multisensory integration on a cued audiovisual discrimination paradigm. These results suggested that top-down mechanisms of modality-specific attention are intact in older adults, and that increased distractibility may be the result of increases in baseline sensory processing.

To counteract age-related increases in distractibility we developed a novel cognitive training program aimed at reducing older-adults' susceptibility to irrelevant

sensory information. A randomized controlled trial demonstrated that this intervention successfully reduced cross-modal distraction and multisensory integration in healthy older adults. Modest training-related improvements were also noted in dual-task performance, processing speed, and working memory, functions not explicitly targeted by the intervention program.

Additionally, the intervention also resulted in increased resting cerebral blood flow to the prefrontal cortex, a region known to demonstrate age-related hypoperfusion and to participate in attention, inhibition, and other executive functions. Although these perfusion changes were not accompanied by clear alterations in brain structure or functional activity, they were modestly correlated with behavioral improvements, suggesting that resting blood flow may be a sensitive marker for evaluating the effects of cognitive training interventions.

CHAPTER I

INTRODUCTION

Jennifer L. Mozolic and Paul J. Laurienti

This chapter is comprised of edited sections from the following two manuscripts: “Modality-specific selective attention attenuates multisensory integration” by Jennifer L. Mozolic, Chritina E. Hugenschmidt, Ann M. Peiffer, and Paul J. Laurienti, published in 2008 in *Experimental Brain Research*, volume 184, pages 39-52; and “Multisensory integration and aging” by Jennifer L. Mozolic, Chritina E. Hugenschmidt, Ann M. Peiffer, and Paul J. Laurienti, a chapter in review for inclusion in the book, Frontiers in the Neural Bases of Multisensory Processes, edited by Mark Wallace, Micah Murray, Sid Simon and Miguel Nicolelis. Included sections have been edited to provide a concise introduction to the present thesis.

In the United States and many other developed nations, adults over the age of 65 have become the most rapidly growing sector of the population. By 2030, the number of Americans age 65 or over is projected to increase from 35 million to 72 million, and will represent nearly 20% of the total US population (He et al., 2005). This demographic shift reflects the success of public health interventions; however, we must continue to respond to challenges created by this achievement by minimizing chronic illness, injury, disability, and health-care costs for the elderly, as well as by promoting healthy aging and improved quality of life. Aging causes significant changes in a number of sensory and cognitive processes, as well as alterations in the structure and function of the brain. In particular, age-related changes in how information from multiple sensory modalities is processed and integrated can impair normal, healthy functioning by causing communication disturbances (Helfer, 1998; Murphy et al., 2006), memory deficits (Stine et al., 1990; Sreenivasan and Jha, 2007), and balance impairments that can increase the likelihood of falls (Hu and Woollacott, 1994a; Borger et al., 1999; Redfern et al., 2001).

The fundamental purpose of this thesis is to investigate the underlying source of age-related changes in multisensory integration and distractibility and to evaluate an intervention designed to reduce older adults' susceptibility to distraction. In order to provide a contextual framework for the thesis, this introductory chapter will first review the normal mechanisms of multisensory integration and attention. Next, some potential causes of age differences in multisensory integration will be considered, underscoring age-related changes in attention and distractibility as plausible mechanisms for modifying sensory processing in older adults. Finally, background information on the use of behavioral interventions for improving cognition in older adults will be introduced.

1.1 Multisensory Integration

Our perception of the environment depends on the combination of information from various sensory systems. Intuitively we know that pairing matching information from multiple sensory modalities can be helpful; if someone is speaking quietly, it is easier to understand what they are saying if you can see their lips moving in addition to hearing their voice. This is borne out in the laboratory, where numerous studies in animals and humans have demonstrated the utility of multimodal stimuli in improving subjects' detection, discrimination, and localization abilities, a phenomenon known as multisensory integration (Hershenson, 1962; Morrell, 1968; Stein et al., 1989; Burnett et al., 2004; Laurienti et al., 2004). These multisensory benefits are generated by positive interactions between individual sensory inputs that can increase neuronal firing rates beyond the simple summation of unisensory inputs (Meredith and Stein, 1983, 1986b; Stein et al., 1989). In contrast to the behavioral and neural benefits that can be gained from the positive interaction of sensory stimuli, there are also situations in which the presence of stimuli in two sensory modalities can impair behavioral performance and decrease neuronal firing rates (Meredith and Stein, 1986b; Stein et al., 1989). Multiple sub-cortical and cortical areas are involved in multisensory integration, including the superior colliculus (Meredith and Stein, 1983, 1986b), anterior cingulate cortex (Laurienti et al., 2003), superior temporal sulcus (Calvert et al., 2000; Stevenson and James, 2009), and other cortical association areas (Wallace et al., 1992).

Several different factors that fall into two broad categories help to determine the degree of interaction between sensory inputs. In the first category are stimulus characteristics such as timing and spatial location that contribute to “bottom-up”

modulation of multisensory integration. For example, stimuli from two different sensory modalities that are temporally synchronized and/or spatially coincident are much more likely to be integrated together than stimuli that occur at disparate times or locations (Meredith and Stein, 1986a; Teder-Salejarvi et al., 2005). Another bottom-up factor governing multisensory integration is known as the principle of inverse effectiveness. According to this principle, decreasing the effectiveness of individual sensory stimuli typically increases the magnitude of multisensory enhancements (Meredith and Stein, 1983, 1986b). In other words, when a unisensory stimulus is presented just above threshold level, the gains produced by bimodal stimuli are larger than when the individual stimuli are highly salient. Importantly, each of these bottom-up mechanisms ensures that the appropriate stimuli from different sensory modalities will be combined to enhance sensory processing in the most effective manner.

A second category of factors that can influence multisensory integration is comprised of “top-down” cognitive mechanisms like semantic knowledge (Calvert et al., 1999; Laurienti et al., 2004; Vatakis and Spence, 2007; Doehrmann and Naumer, 2008) and attentional control (Bertelson and Radeau, 1981; McDonald et al., 2003; Alsius et al., 2005; Talsma et al., 2007; Mozolic et al., 2008a). Studies in humans have demonstrated that multisensory stimuli representing contextually congruent or matching information (e.g., a red circle and a verbalization of the word red) can enhance performance in a discrimination task, while stimuli that convey incongruent or non-matching information (e.g. a red circle and a verbalization of the word green) impair performance (Laurienti et al., 2004). In this case, the semantic content or meaning of the stimulus influences multisensory integration, despite the fact that stimulus features such as timing, location,

contrast, and volume remain constant. Experiments using cues to direct participants' attention also show that paying attention to both the auditory and visual modality promotes multisensory integration, while focusing attention on a single sensory modality attenuates these gains (Mozolic et al., 2008a). That is, participants show robust response time benefits during audiovisual conditions relative to unisensory auditory or visual conditions when they are cued to attend to both sensory modalities. When participants are instructed to pay attention only to the auditory or the visual modality, they are not speeded during multisensory conditions. Here, all stimulus features and semantic content were held constant, yet the extent to which multisensory integration occurred was determined solely by attention.

1.2 Attention

Attention is a critical top-down control mechanism that allows us to process relevant stimuli while ignoring extraneous and potentially distracting information (Posner and Driver, 1992). From both personal experience and laboratory data, we know that selectively focusing on one location improves the speed and accuracy with which we can respond to stimuli that appear in that location (Downing, 1988; Posner and Petersen, 1990). Single cell recordings in monkeys have demonstrated that selective attention to a particular location in space works to bias processing such that neuronal responses to visual stimuli occurring in the attended location are enhanced compared to responses to the same stimuli in unattended spatial locations (Spitzer et al., 1988; Motter, 1993; Kastner and Ungerleider, 2000). Neuroimaging data also demonstrate that spatial attention increases the magnitude of activation in cortical regions that process stimuli in

the attended location (Heinze et al., 1994; Kastner et al., 1998; Mangun et al., 1998). Attention can also influence the behavioral and neural processing of auditory and tactile stimuli, as focusing attention on a location in space can enhance perception of stimuli that occur in that location, regardless of stimulus modality (Spence et al., 1998; Johnen et al., 2001; Macaluso et al., 2002; McDonald et al., 2003).

In addition to spatial location, attention can also be directed to specific stimulus features (Corbetta et al., 1990; Moore and Egeth, 1998) or sensory modalities (Woodruff et al., 1996; Macaluso et al., 2002; Mozolic et al., 2008b). The behavioral effects of modality-specific selective attention have been observed when participants are instructed to attend to a single sensory modality (auditory, visual, or tactile) before performing speeded detection and discrimination tasks (Spence and Driver, 1997; Spence et al., 2001). Participants generally respond quicker and more accurately when the target appears in the expected modality than when the target appears in the unexpected modality, but these benefits are typically very small. In contrast with spatial attention, which produces robust benefits for stimuli at the attended location, the more consistent effect produced by modality-specific attention is a reduction in the efficiency of processing stimuli in the unattended modality (Spence et al., 2001). This decrease in processing efficiency is basically the process of ignoring a stimulus, and is reflected in accuracy and response times (RT) costs for targets in the unattended modality. The neural effects of modality-specific attention can also be observed in imaging experiments where modest increases in activation for attended sensory modality are accompanied by robust decreases in activity in cortical regions that process the unattended sensory

modality (Macaluso et al., 2002; Loose et al., 2003; Johnson and Zatorre, 2006; Mozolic et al., 2008b).

1.3 Age-related changes in multisensory integration

As we age, there are significant changes in all sensory systems and a variety of cognitive functions. Visual acuity normally decreases and hearing thresholds generally increase (Kalina, 1997; Liu and Yan, 2007), while performance levels on tasks of motor speed, executive function, and memory typically decline (Rapp and Heindel, 1994; Birren and Fisher, 1995; Rhodes, 2004). There are also widespread changes in the aging brain, including reductions in gray and white matter volume (Good et al., 2001; Hugenschmidt et al., 2008; Salat et al., 2009), alterations in neurotransmitter systems (Muir, 1997; Backman et al., 2006), regional hypoperfusion (Martin et al., 1991; Bertsch et al., 2009), and modified patterns of functional activity during cognitive tasks (Cabeza et al., 2004; Grady, 2008). Given the extent of age-related alterations in sensation, perception, and cognition, as well as in the anatomy and physiology of the brain, it is not surprising that multisensory integration also changes with age.

Several early studies provided mixed results on the differences between multisensory processing in older and younger adults (Stine et al., 1990; Helfer, 1998; Strupp et al., 1999; Cienkowski and Carney, 2002; Sommers et al., 2005). For example, Stine and colleagues (1990) reported that although younger adults' memory for news events was better after audiovisual presentation than after auditory information alone, older adults did not show improvement during the multisensory conditions. In contrast, Cienkowski and Carney (2002) demonstrated that audiovisual integration on a

multisensory illusion called the McGurk effect (McGurk and MacDonald, 1976) was similar for older and younger adults, and that in some conditions, older adults were even more likely to report the fusion of visual and auditory information than their young counterparts. Similarly, in a study examining the contribution of somatosensory input to participants' perception of visuospatial orientation, Strupp et al. (1999) reported an age-related increase in the integration of somatosensory information into the multisensory representation of body orientation.

Despite providing a good indication that multisensory processing is somehow altered in aging, the results of these studies are somewhat difficult to interpret due to their use of complex cognitive tasks and illusions, and to the variability in analysis methods. Several newer studies that have attempted to address these factors more clearly demonstrate that multisensory integration is enhanced in older adults (Laurienti et al., 2006; Peiffer et al., 2007; Diederich et al., 2008).

On a two-choice audiovisual discrimination task, Laurienti and colleagues (2006) showed that (RT) benefits for multisensory versus unisensory targets were larger for older adults than for younger adults. That is, older adults' responses during audiovisual conditions were speeded more than younger adults', when compared to their respective responses during unisensory conditions. Multisensory gains in older adults remained significantly larger than those observed in younger adults, even after controlling for the presence of two targets in the multisensory condition (redundant target effect; (Miller, 1982, 1986) (Laurienti et al., 2006)).

Using similar analysis methods, Peiffer et al. (2007) also reported increased multisensory gains in older adults. On a simple response time task, where average

unisensory response times were equivalent in younger and older adults, older adults actually responded *faster* than younger adults on multisensory trials due to their enhanced multisensory integration (Peiffer et al., 2007). Diederich and colleagues (2008) have also shown that older adults exhibit greater speeding of responses to multisensory targets than younger adults on a saccadic response time task. The analysis methods used in this experiment indicate a slowing of peripheral sensory processing, as well as a wider time window over which integration of auditory and visual stimuli can occur (Diederich et al., 2008).

Together, these experiments highlight several possible explanations that could help to answer a critical question about multisensory processing in aging: why do older adults exhibit greater integration of multisensory stimuli than younger adults? Below, several potential sources of age-related multisensory enhancement are reviewed, emphasizing the need for additional studies to develop a more comprehensive model of multisensory integration in older adults.

1.3.1 General cognitive slowing

It is well-documented that older-adults exhibit a general slowing of sensorimotor and cognitive processing that impacts their performance on nearly all tasks (Cerella, 1985; Birren and Fisher, 1995; Salthouse, 2000). This general cognitive slowing is very mild on easy tasks, but is exacerbated on more demanding tasks that require more cognitive processing.

To rule out general cognitive slowing as an explanation for age-related multisensory enhancements, Peiffer et al. (2007) employed a very simple audiovisual

detection task. The effects of general cognitive slowing are minimized on such tasks where response times on unisensory trials are the same for younger and older adults (Yordanova et al., 2004). In this experiment there were no differences between old and young RTs on unisensory visual or auditory trials; however older adults exhibited significantly more integration than younger adults and faster responses on multisensory trials (Peiffer et al., 2007). These results support the notion that there are specific age-related differences in multisensory processing that can not be explained by general cognitive slowing.

1.3.2 Inverse effectiveness

In addition to non-specific slowing of cognitive processes evident in aging, older adults also demonstrate functional declines in all sensory systems, as outlined briefly above. These functional declines are due both to age-related changes in the peripheral sensory organs, such as rigidity in the lens, loss of hair cells, and changes in cutaneous receptors and the olfactory epithelium (Kovács, 2004; Liu and Yan, 2007; Shaffer and Harrison, 2007; Charman, 2008), and to age-related alterations in how the central nervous system processes sensory information (Schmolesky et al., 2000; Cerf-Ducastel and Murphy, 2003; Ostroff et al., 2003; Quiton et al., 2007).

This reduced sensitivity or acuity in the individual sensory systems is another potential explanation for increased multisensory benefits for older adults, due to the principle of inverse effectiveness which says that decreasing the effectiveness of individual sensory stimuli increases the magnitude of multisensory enhancements (Meredith and Stein, 1983, 1986b). For example, Hairston and colleagues (2003)

demonstrated that young participants with normal vision were able to localize unimodal visual and bimodal audiovisual targets equally well; however, when participants' vision was artificially degraded using myopia-inducing lenses, their localization abilities were significantly enhanced during audiovisual conditions relative to performance on visual targets alone.

The evidence for inverse effectiveness as a source of enhanced multisensory integration in older adults is not yet clear. In the study performed by Peiffer and colleagues (2007; mentioned above), response times on unisensory trials were similar for younger and older adults, yet the older adults still showed larger multisensory gains than the younger group. This finding suggests that other mechanisms beyond inverse effectiveness may be required to explain the age-related enhancements. The paradigm used in this study, however, matched performance between populations using super-threshold stimuli and did not specifically investigate the consequence of degrading stimulus effectiveness.

Results from a study conducted by Cienkowski and Carney (2002) provide some clues on the effects of hearing loss on age-related integration enhancements. This experiment tested three groups of participants on the McGurk illusion (McGurk and MacDonald, 1976): (1) young adults with normal hearing, (2) older adults with mild, but age-appropriate hearing loss, and (3) a control group of young adults with hearing thresholds artificially shifted to match the older adults. Both the older adults and the threshold-shifted controls were more likely integrate the visual and auditory information than young, normal hearing participants in some experimental conditions (Cienkowski and Carney, 2002); however, the level of integration experienced by each group across

various experimental conditions did not have a clear inverse relationship with successful unisensory target identification. Clearly, more studies that carefully modulate signal intensities and compare the multisensory gains in younger and older adults will be needed to further characterize the role of inverse effectiveness in age-related multisensory enhancements.

1.3.3 Larger time window of integration

A common finding across many studies that compare distributions of response times in younger and older adults is that older adults' responses are both slower and more variable, creating distributions that are broader and shifted to the right in older adults relative to young (Hale et al., 1988; Morse, 1993; Hultsch et al., 2002). Multisensory enhancements have also been demonstrated to occur over a wider distribution of response times for older adults (Laurienti et al., 2006; Peiffer et al., 2007; Diederich et al., 2008).

Recently, Diederich and colleagues (2008) studied the temporal characteristics of integration in older and younger adults using a time-window-of-integration (TWIN) model. This model is able to distinguish the relative contributions of early, peripheral sensory processes and subsequent, central integration processes to multisensory enhancements (Colonius and Diederich, 2004; Diederich et al., 2008). Using a focused attention task where saccadic reaction time to a visual target was measured with and without an accessory auditory stimulus, the authors reported that older adults' responses were slower, more variable, and showed greater multisensory enhancements than younger adults' responses (Diederich et al., 2008). Additionally, the TWIN model analysis indicated that peripheral slowing in older adults resulted in a broader temporal window of

multisensory integration. Despite this longer period for potential interaction between stimuli, increased response time and variability in older adults actually reduced the *probability* that processing of both the auditory and visual stimulus would occur within this time window. While these results replicated findings of enhanced integration magnitude in older adults, the data also suggest that a longer time window for cross-modal interactions can only partially compensate for an age-related reduction in the probability that multisensory integration will occur (Diederich et al., 2008). Thus, a wider time window of integration in older adults is primarily the result of slower and more variable peripheral sensory processing, and can not explain why, when integration does occur, its magnitude is larger in older adults.

1.3.4 Deficits in attentional control

As discussed above, in addition to stimulus properties such as timing, location, and intensity that can affect multisensory integration, there are also top-down cognitive factors that can modulate cross-modal interactions (Laurienti et al., 2004; Alsius et al., 2005; Talsma and Woldorff, 2005; Talsma et al., 2007; Mozolic et al., 2008a). In young, healthy adults, dividing attention across multiple sensory modalities appears to be critical for multisensory integration, while restricting attention to a single sensory modality can abolish behavioral and neural enhancements associated with multisensory stimuli (Alsius et al., 2005; Talsma and Woldorff, 2005; Talsma et al., 2007; Mozolic et al., 2008a).

Many studies have demonstrated that older adults have deficits in attention and are more distracted by stimuli within and across sensory modalities (Dywan et al., 1998; Alain and Woods, 1999; West and Alain, 2000; Milham et al., 2002; Andres et al., 2006;

Poliakoff et al., 2006; Yang and Hasher, 2007; Healey et al., 2008). For example, Andres and colleagues (2006) reported that older adults were more distracted by irrelevant sounds than younger adults on an auditory-visual oddball paradigm. It would seem possible then, that increased multisensory integration in older adults could result from a deficit in top-down attentional control that allows more cross-modal information to be processed.

This apparently simple account of age-related increases in distractibility is complicated by the fact that there is also strong evidence suggesting that older adults can, in fact, successfully engage selective attention on a variety of tasks (Groth and Allen, 2000; Verhaeghen and Cerella, 2002; Madden et al., 2004; Townsend et al., 2006; Ballesteros et al., 2008; Hugenschmidt et al., in press). For example, Hugenschmidt and colleagues (in press) reported that older adults exhibited the same pattern of costs and benefits during modality-specific attention as younger adults during two audiovisual tasks. These results suggest that older adults may not have any attentional deficits under these task conditions. However, it is still not clear what role age-related changes in attention and distractibility play in modulating multisensory integration in older adults. An experiment explicitly designed to address this question will be presented in Chapter 2 of this thesis.

1.4 Cognitive training in older adults

In addition to investigating the mechanisms of age-related alterations in multisensory processing and cross-modal attention, this thesis will also assess the merits of a novel cognitive training intervention designed to limit older adults' susceptibility to

cross-modal distraction and reduce integration of extraneous sensory information. Although clinicians and researchers have been designing and implementing cognitive interventions for several decades, the studies presented here are, to our knowledge, the first reports on the use of a multisensory attention training program targeting cross-modal distraction in healthy older adults.

The majority of cognitive interventions have traditionally focused on improving memory through training on mnemonic strategies, encoding skills, and retrieval practice (Yesavage, 1985; Verhaeghen et al., 1992; Neely and Backman, 1995; Jennings et al., 2005; Dunlosky et al., 2007). For example, Jennings et al. (2005) reported that healthy older adults exhibit improvements in episodic memory, as well as working memory and processing speed, after several sessions of recollection training. Several memory training paradigms have also shown promise for improving memory or slowing the rate of decline in older adults with mild cognitive impairment and Alzheimer's disease (Rapp et al., 2002; Belleville et al., 2006; Troyer et al., 2008; Kurz et al., 2009; Yu et al., 2009).

A number of other studies have also combined training across multiple domains to enhance memory (Oswald et al., 1996; Gunther et al., 2003; Mahncke et al., 2006; Winocur et al., 2007), or have targeted other cognitive processes for improvement (Ball et al., 2002; Angelakis et al., 2007; Bugos et al., 2007; Levine et al., 2007). In the largest randomized controlled trial to date, Ball et al. (2002) examined outcomes for over 2,800 older adults assigned to one of four different protocols: speed of processing training, episodic memory training, reasoning training, or a no-contact control group. Initial results from this trial indicated that each of the interventions improved the targeted abilities (Ball et al., 2002), and a 5-year follow-up study suggested not only that all

participants maintained improvements in the trained domains, but also that those involved in reasoning training had significantly less difficulty with instrumental activities of daily living like housework and shopping (Willis et al., 2006). Functions such as balance and postural control have also been shown to be sensitive to integrative training programs (Hu and Woollacott, 1994a, 1994b; Li et al., 2005; Westlake and Culham, 2007; Maki et al., 2008). Additionally, a number of studies demonstrate that cardiovascular or aerobic fitness training can improve cognitive function in older adults (Kramer et al., 1999; Colcombe et al., 2004; Angevaren et al., 2008).

Many training programs designed specifically to target attentional control were initially designed to rehabilitate patients with traumatic brain injury (Sohlberg and Mateer, 1987; Niemann et al., 1990; Park and Ingles, 2001). For example, Attention Process Training, a multifaceted program emphasizing sustained, focused, selective, and divided attention was demonstrated to successfully improve measures of attention and executive control in patients with acquired brain injury (Sohlberg and Mateer, 1987; Sohlberg et al., 2000). This program was also adapted for use in patients with schizophrenia (Lopez-Luengo and Vazquez, 2003) and attention deficit hyperactivity disorder (Sohlberg and Mateer, 2001). Another line of research has focused on improving visual processing speed and attention in healthy older adults (Ball et al., 1993; Owsley, 1994; Roenker et al., 2003; Lunsman et al., 2008). Studies suggest that expanding older adults' useful field of view can improve performance on instrumental activity of daily living and promote driving safety (Roenker et al., 2003; Edwards et al., 2005; Ball et al., 2007). Additionally, dual-task performance, a function that requires

considerable attentional control, has also been shown to be amenable to training in healthy older adults (Bherer et al., 2005, 2008).

Despite a wealth of knowledge on the behavioral results of various training regimens, much less is known about how different interventions impact the brain's physical structure and its functional characteristics at rest and during cognitively demanding tasks. Existing evidence suggests that both physical exercise training (Colcombe et al., 2006) and skill learning (Boyke et al., 2008) can alter brain tissue volumes in older adults. However, there is virtually no information on changes in resting metabolism or blood flow after training, despite new data demonstrating that cognitive training can modify task-related neural activity (Nyberg et al., 2003; Erickson et al., 2007; Scalf et al., 2007; Dahlin et al., 2008). Although brain regions such as the striatum (Dahlin et al., 2008), the prefrontal cortex (Erickson et al., 2007; Scalf et al., 2007), and the parietal cortex (Nyberg et al., 2003) have been implicated in behavioral improvements in task performance after training, there is some debate about the role of relative increases and decreases in neural activity in supporting functional outcomes (Erickson et al., 2007).

1.5 Thesis outline

To address existing gaps in the research on cross-modal interactions in aging, this thesis will first present a study designed to determine how modality-specific attention modulates multisensory integration in older adults (Chapter 2). The next chapter will focus on the design, implementation, and acute behavioral effects of a cognitive training program targeting multimodal distraction in healthy older adults (Chapter 3). Subsequent

chapters will assess the impact of this intervention on brain structure and cerebral blood flow at rest (Chapter 4) and patterns of neural activity associated with cognitive tasks (Chapter 5). A final chapter will summarize the results from this series of experiments, provide a brief report on follow-up data collected on a sub-set of participants, and discuss the implications of our findings for continued research on the mechanisms of cognitive training and healthy aging (Chapter 6).

REFERENCES

- Alain, C. and Woods, D. L. (1999). Age-related changes in processing auditory stimuli during visual attention: evidence for deficits in inhibitory control and sensory memory. *Psychol Aging* **14**(3): 507-19.
- Alsius, A., Navarra, J., Campbell, R. and Soto-Faraco, S. (2005). Audiovisual integration of speech falters under high attention demands. *Curr.Biol.* **15**(9): 839-43.
- Andres, P., Parmentier, F. B. and Escera, C. (2006). The effect of age on involuntary capture of attention by irrelevant sounds: a test of the frontal hypothesis of aging. *Neuropsychologia* **44**(12): 2564-8.
- Angelakis, E., Stathopoulou, S., Frymiare, J. L., Green, D. L., Lubar, J. F., et al. (2007). EEG neurofeedback: a brief overview and an example of peak alpha frequency training for cognitive enhancement in the elderly. *Clin Neuropsychol* **21**(1): 110-29.
- Angevaren, M., Aufdemkampe, G., Verhaar, H. J., Aleman, A. and Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev*(2): CD005381.
- Backman, L., Nyberg, L., Lindenberger, U., Li, S. C. and Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: current status and future prospects. *Neurosci Biobehav Rev* **30**(6): 791-807.
- Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., et al. (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. *Jama* **288**(18): 2271-81.
- Ball, K., Edwards, J. D. and Ross, L. A. (2007). The impact of speed of processing training on cognitive and everyday functions. *J Gerontol B Psychol Sci Soc Sci* **62 Spec No 1**: 19-31.
- Ball, K., Owsley, C., Sloane, M. E., Roenker, D. L. and Bruni, J. R. (1993). Visual attention problems as a predictor of vehicle crashes in older drivers. *Invest Ophthalmol Vis Sci* **34**(11): 3110-23.
- Ballesteros, S., Reales, J. M., Mayas, J. and Heller, M. A. (2008). Selective attention modulates visual and haptic repetition priming: effects in aging and Alzheimer's disease. *Exp Brain Res* **189**(4): 473-83.
- Belleville, S., Gilbert, B., Fontaine, F., Gagnon, L., Menard, E., et al. (2006). Improvement of episodic memory in persons with mild cognitive impairment and healthy older adults: evidence from a cognitive intervention program. *Dement Geriatr Cogn Disord* **22**(5-6): 486-99.
- Bertelson, P. and Radeau, M. (1981). Cross-modal bias and perceptual fusion with auditory-visual spatial discordance. *Percept Psychophys* **29**(6): 578-84.
- Bertsch, K., Hagemann, D., Hermes, M., Walter, C., Khan, R., et al. (2009). Resting cerebral blood flow, attention, and aging. *Brain Res.*
- Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., et al. (2005). Training effects on dual-task performance: are there age-related differences in plasticity of attentional control? *Psychol Aging* **20**(4): 695-709.
- Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., et al. (2008). Transfer effects in task-set cost and dual-task cost after dual-task training in older

- and younger adults: further evidence for cognitive plasticity in attentional control in late adulthood. *Exp Aging Res* **34**(3): 188-219.
- Birren, J. E. and Fisher, L. M. (1995). Aging and Speed of Behavior: Possible Consequences for Psychological Functioning. *Annual Review of Psychology* **46**(1): 329-353.
- Borger, L. L., Whitney, S. L., Redfern, M. S. and Furman, J. M. (1999). The influence of dynamic visual environments on postural sway in the elderly. *J Vestib Res* **9**(3): 197-205.
- Boyke, J., Driemeyer, J., Gaser, C., Buchel, C. and May, A. (2008). Training-induced brain structure changes in the elderly. *J Neurosci* **28**(28): 7031-5.
- Bugos, J. A., Perlstein, W. M., McCrae, C. S., Brophy, T. S. and Bedenbaugh, P. H. (2007). Individualized piano instruction enhances executive functioning and working memory in older adults. *Aging Ment Health* **11**(4): 464-71.
- Burnett, L. R., Stein, B. E., Chaponis, D. and Wallace, M. T. (2004). Superior colliculus lesions preferentially disrupt multisensory orientation. *Neuroscience* **124**(3): 535-47.
- Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., et al. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cereb Cortex* **14**(4): 364-75.
- Calvert, G. A., Brammer, M. J., Bullmore, E. T., Campbell, R., Iversen, S. D., et al. (1999). Response amplification in sensory-specific cortices during crossmodal binding. *Neuroreport* **10**(12): 2619-23.
- Calvert, G. A., Campbell, R. and Brammer, M. J. (2000). Evidence from functional magnetic resonance imaging of crossmodal binding in the human heteromodal cortex. *Curr Biol* **10**(11): 649-57.
- Cerella, J. (1985). Information processing rates in the elderly. *Psychol Bull* **98**(1): 67-83.
- Cerf-Ducastel, B. and Murphy, C. (2003). fMRI brain activation in response to odors is reduced in primary olfactory areas of elderly subjects. *Brain Res* **986**(1-2): 39-53.
- Charman, W. N. (2008). The eye in focus: accommodation and presbyopia. *Clinical and Experimental Optometry* **91**(3): 207-225.
- Cienkowski, K. M. and Carney, A. E. (2002). Auditory-visual speech perception and aging. *Ear Hear* **23**(5): 439-49.
- Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., et al. (2006). Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci* **61**(11): 1166-70.
- Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., et al. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A* **101**(9): 3316-21.
- Colonius, H. and Diederich, A. (2004). Multisensory interaction in saccadic reaction time: a time-window-of-integration model. *J Cogn Neurosci* **16**(6): 1000-9.
- Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L. and Petersen, S. E. (1990). Attentional modulation of neural processing of shape, color, and velocity in humans. *Science* **248**(4962): 1556-9.
- Dahlin, E., Neely, A. S., Larsson, A., Backman, L. and Nyberg, L. (2008). Transfer of learning after updating training mediated by the striatum. *Science* **320**(5882): 1510-2.

- Diederich, A., Colonius, H. and Schomburg, A. (2008). Assessing age-related multisensory enhancement with the time-window-of-integration model. *Neuropsychologia* **46**(10): 2556-62.
- Doehrmann, O. and Naumer, M. J. (2008). Semantics and the multisensory brain: How meaning modulates processes of audio-visual integration. *Brain Research* **1242**: 136.
- Downing, C. J. (1988). Expectancy and visual-spatial attention: effects on perceptual quality. *J Exp Psychol Hum Percept Perform* **14**(2): 188-202.
- Dunlosky, J., Cavallini, E., Roth, H., McGuire, C. L., Vecchi, T., et al. (2007). Do self-monitoring interventions improve older adult learning? *J Gerontol B Psychol Sci Soc Sci* **62 Spec No 1**: 70-6.
- Dywan, J., Segalowitz, S. J. and Webster, L. (1998). Source monitoring: ERP evidence for greater reactivity to nontarget information in older adults. *Brain Cogn* **36**(3): 390-430.
- Edwards, J. D., Wadley, V. G., Vance, D. E., Wood, K., Roenker, D. L., et al. (2005). The impact of speed of processing training on cognitive and everyday performance. *Aging Ment Health* **9**(3): 262-71.
- Erickson, K. I., Colcombe, S. J., Wadhwa, R., Bherer, L., Peterson, M. S., et al. (2007). Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging* **28**(2): 272-83.
- Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., et al. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* **14**(1 Pt 1): 21-36.
- Grady, C. L. (2008). Cognitive neuroscience of aging. *Ann N Y Acad Sci* **1124**: 127-44.
- Groth, K. E. and Allen, P. A. (2000). Visual attention and aging. *Front Biosci.* **5**: D284.
- Gunther, V. K., Schafer, P., Holzner, B. J. and Kemmler, G. W. (2003). Long-term improvements in cognitive performance through computer-assisted cognitive training: a pilot study in a residential home for older people. *Aging Ment Health* **7**(3): 200-6.
- Hale, S., Myerson, J., Smith, G. A. and Poon, L. W. (1988). Age, Variability, and Speed: Between-Subjects Diversity. *Psychology and Aging* **3**(4): 407.
- He, W., Sengupta, M. V., V.A. and DeBarros, K. A. (2005). 65+ in the United States: 2005, National Institute on Aging, US Census Bureau.
- Healey, M. K., Campbell, K. L. and Hasher, L. (2008). Chapter 22 Cognitive aging and increased distractibility: Costs and potential benefits. *Prog Brain Res* **169**: 353-63.
- Heinze, H. J., Mangun, G. R., Burchert, W., Hinrichs, H., Scholz, M., et al. (1994). Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature* **372**(6506): 543-6.
- Helfer, K. S. (1998). Auditory and auditory-visual recognition of clear and conversational speech by older adults. *J.Am.Acad.Audiol.* **9**(3): 234.
- Hershenson, M. (1962). Reaction time as a measure of intersensory facilitation. *J Exp Psychol* **63**: 289-93.
- Hu, M. H. and Woollacott, M. H. (1994a). Multisensory training of standing balance in older adults: I. Postural stability and one-leg stance balance. *J.Gerontol.* **49**(2): M52.

- Hu, M. H. and Woollacott, M. H. (1994b). Multisensory training of standing balance in older adults: II. Kinematic and electromyographic postural responses. *J. Gerontol.* **49**(2): M62.
- Hugenschmidt, C. E., Peiffer, A. M., Kraft, R. A., Casanova, R., Deibler, A. R., et al. (2008). Relating imaging indices of white matter integrity and volume in healthy older adults. *Cereb Cortex* **18**(2): 433-42.
- Hugenschmidt, C. E., Peiffer, A. M., McCoy, T. P., Hayasaka, S. and Laurienti, P. J. (in press). Preservation of crossmodal selective attention in healthy aging. *Experimental Brain Research*.
- Hultsch, D. F., MacDonald, S. W. and Dixon, R. A. (2002). Variability in reaction time performance of younger and older adults. *J Gerontol B Psychol Sci Soc Sci* **57**(2): P101-15.
- Jennings, J., Webster, L., Kleykamp, B. and Dagenbach, D. (2005). Recollection Training and Transfer Effects in Older Adults: Successful Use of a Repetition-Lag Procedure. *Aging, Neuropsychology, and Cognition (Neuropsychology, Development and Cognition)* **12**(3): 278-298.
- Johnen, A., Wagner, H. and Gaese, B. H. (2001). Spatial attention modulates sound localization in barn owls. *J Neurophysiol* **85**(2): 1009-12.
- Johnson, J. A. and Zatorre, R. J. (2006). Neural substrates for dividing and focusing attention between simultaneous auditory and visual events. *Neuroimage* **31**(4): 1673-81.
- Kalina, R. E. (1997). Seeing into the future. Vision and aging. *West J Med* **167**(4): 253-7.
- Kastner, S., De Weerd, P., Desimone, R. and Ungerleider, L. G. (1998). Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. *Science* **282**(5386): 108-11.
- Kastner, S. and Ungerleider, L. G. (2000). Mechanisms of visual attention in the human cortex. *Annu Rev Neurosci* **23**: 315-41.
- Kovács, T. (2004). Mechanisms of olfactory dysfunction in aging and neurodegenerative disorders. *Ageing Research Reviews* **3**(2): 215.
- Kramer, A. F., Hahn, S., Cohen, N. J., Banich, M. T., McAuley, E., et al. (1999). Ageing, fitness and neurocognitive function. *Nature* **400**(6743): 418-9.
- Kurz, A., Pohl, C., Ramsenthaler, M. and Sorg, C. (2009). Cognitive rehabilitation in patients with mild cognitive impairment. *Int J Geriatr Psychiatry* **24**(2): 163-8.
- Laurienti, P. J., Burdette, J. H., Maldjian, J. A. and Wallace, M. T. (2006). Enhanced multisensory integration in older adults. *Neurobiol Aging* **27**(8): 1155-63.
- Laurienti, P. J., Kraft, R. A., Maldjian, J. A., Burdette, J. H. and Wallace, M. T. (2004). Semantic congruence is a critical factor in multisensory behavioral performance. *Exp Brain Res* **158**(4): 405-14.
- Laurienti, P. J., Wallace, M. T., Maldjian, J. A., Susi, C. M., Stein, B. E., et al. (2003). Cross-modal sensory processing in the anterior cingulate and medial prefrontal cortices. *Hum Brain Mapp* **19**(4): 213-23.
- Levine, B., Stuss, D. T., Winocur, G., Binns, M. A., Fahy, L., et al. (2007). Cognitive rehabilitation in the elderly: effects on strategic behavior in relation to goal management. *J Int Neuropsychol Soc* **13**(1): 143-52.

- Li, F., Harmer, P., Fisher, K. J., McAuley, E., Chaumeton, N., et al. (2005). Tai Chi and fall reductions in older adults: a randomized controlled trial. *J Gerontol A Biol Sci Med Sci* **60**(2): 187-94.
- Liu, X. and Yan, D. (2007). Ageing and hearing loss. *The Journal of Pathology* **211**(2): 188-197.
- Loose, R., Kaufmann, C., Auer, D. P. and Lange, K. W. (2003). Human prefrontal and sensory cortical activity during divided attention tasks. *Hum Brain Mapp* **18**(4): 249-59.
- Lopez-Luengo, B. and Vazquez, C. (2003). Effects of Attention Process Training on cognitive functioning of schizophrenic patients. *Psychiatry Res* **119**(1-2): 41-53.
- Lunsman, M., Edwards, J. D., Anzel, R., Small, B. J., Ball, K. K., et al. (2008). What predicts changes in useful field of view test performance? *Psychol Aging* **23**(4): 917-27.
- Macaluso, E., Frith, C. D. and Driver, J. (2002). Directing attention to locations and to sensory modalities: multiple levels of selective processing revealed with PET. *Cereb Cortex* **12**(4): 357-68.
- Madden, D. J., Whiting, W. L., Cabeza, R. and Huettel, S. A. (2004). Age-related preservation of top-down attentional guidance during visual search. *Psychol Aging* **19**(2): 304.
- Mahncke, H. W., Connor, B. B., Appelman, J., Ahsanuddin, O. N., Hardy, J. L., et al. (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proc Natl Acad Sci U S A* **103**(33): 12523-8.
- Maki, B. E., Cheng, K. C. C., Mansfield, A., Scovil, C. Y., Perry, S. D., et al. (2008). Preventing falls in older adults: New interventions to promote more effective change-in-support balance reactions. *Journal of Electromyography and Kinesiology* **18**(2): 243-254.
- Mangun, G. R., Buonocore, M. H., Girelli, M. and Jha, A. P. (1998). ERP and fMRI measures of visual spatial selective attention. *Hum Brain Mapp* **6**(5-6): 383-9.
- Martin, A. J., Friston, K. J., Colebatch, J. G. and Frackowiak, R. S. (1991). Decreases in regional cerebral blood flow with normal aging. *J Cereb Blood Flow Metab* **11**(4): 684-9.
- McDonald, J. J., Teder-Salejari, W. A., Di Russo, F. and Hillyard, S. A. (2003). Neural substrates of perceptual enhancement by cross-modal spatial attention. *J Cogn Neurosci*. **15**(1): 10-9.
- McGurk, H. and MacDonald, J. (1976). Hearing lips and seeing voices. *Nature* **264**(5588): 746-8.
- Meredith, M. A. and Stein, B. E. (1983). Interactions among converging sensory inputs in the superior colliculus. *Science* **221**(4608): 389-91.
- Meredith, M. A. and Stein, B. E. (1986a). Spatial factors determine the activity of multisensory neurons in cat superior colliculus. *Brain Res* **365**(2): 350-4.
- Meredith, M. A. and Stein, B. E. (1986b). Visual, auditory, and somatosensory convergence on cells in superior colliculus results in multisensory integration. *J Neurophysiol* **56**(3): 640-62.

- Milham, M. P., Erickson, K. I., Banich, M. T., Kramer, A. F., Webb, A., et al. (2002). Attentional control in the aging brain: insights from an fMRI study of the stroop task. *Brain Cogn* **49**(3): 277.
- Miller, J. (1982). Divided attention: evidence for coactivation with redundant signals. *Cognit Psychol* **14**(2): 247-79.
- Miller, J. (1986). Timecourse of coactivation in bimodal divided attention. *Percept Psychophys* **40**(5): 331-43.
- Moore, C. M. and Egeth, H. (1998). How does feature-based attention affect visual processing? *J Exp Psychol Hum Percept Perform* **24**(4): 1296-310.
- Morrell, L. K. (1968). Temporal characteristics of sensory interaction in choice reaction times. *J Exp Psychol* **77**(1): 14-8.
- Morse, C. K. (1993). Does variability increase with age? An archival study of cognitive measures. *Psychol Aging* **8**(2): 156-64.
- Motter, B. C. (1993). Focal attention produces spatially selective processing in visual cortical areas V1, V2, and V4 in the presence of competing stimuli. *J Neurophysiol* **70**(3): 909-19.
- Mozolic, J. L., Hugenschmidt, C. E., Peiffer, A. M. and Laurienti, P. J. (2008a). Modality-specific selective attention attenuates multisensory integration. *Exp Brain Res* **184**(1): 39-52.
- Mozolic, J. L., Joyner, D., Hugenschmidt, C. E., Peiffer, A. M., Kraft, R. A., et al. (2008b). Cross-modal deactivations during modality-specific selective attention. *BMC Neurol* **8**: 35.
- Muir, J. L. (1997). Acetylcholine, aging, and Alzheimer's disease. *Pharmacol Biochem Behav* **56**(4): 687-96.
- Murphy, D. R., Daneman, M. and Schneider, B. A. (2006). Why do older adults have difficulty following conversations? *Psychol Aging* **21**(1): 49-61.
- Neely, A. S. and Backman, L. (1995). Effects of multifactorial memory training in old age: generalizability across tasks and individuals. *J Gerontol B Psychol Sci Soc Sci* **50**(3): P134-40.
- Niemann, H., Ruff, R. M. and Baser, C. A. (1990). Computer-assisted attention retraining in head-injured individuals: a controlled efficacy study of an outpatient program. *J Consult Clin Psychol* **58**(6): 811-7.
- Nyberg, L., Sandblom, J., Jones, S., Neely, A. S., Petersson, K. M., et al. (2003). Neural correlates of training-related memory improvement in adulthood and aging. *Proc Natl Acad Sci U S A* **100**(23): 13728-33.
- Ostroff, J. M., McDonald, K. L., Schneider, B. A. and Alain, C. (2003). Aging and the processing of sound duration in human auditory cortex. *Hear Res* **181**(1-2): 1-7.
- Oswald, W. D., Rupperecht, R., Gunzelmann, T. and Tritt, K. (1996). The SIMA-project: effects of 1 year cognitive and psychomotor training on cognitive abilities of the elderly. *Behav Brain Res* **78**(1): 67-72.
- Owsley, C. (1994). Vision and driving in the elderly. *Optom Vis Sci* **71**(12): 727-35.
- Park, N. W. and Ingles, J. L. (2001). Effectiveness of attention rehabilitation after an acquired brain injury: a meta-analysis. *Neuropsychology* **15**(2): 199-210.
- Peiffer, A. M., Mozolic, J. L., Hugenschmidt, C. E. and Laurienti, P. J. (2007). Age-related multisensory enhancement in a simple audiovisual detection task. *Neuroreport* **18**(10): 1077-81.

- Poliakoff, E., Ashworth, S., Lowe, C. and Spence, C. (2006). Vision and touch in ageing: crossmodal selective attention and visuotactile spatial interactions. *Neuropsychologia* **44**(4): 507-17.
- Posner, M. I. and Driver, J. (1992). The neurobiology of selective attention. *Curr Opin Neurobiol* **2**(2): 165-9.
- Posner, M. I. and Petersen, S. E. (1990). The attention system of the human brain. *Annu.Rev.Neurosci.* **13**: 25.
- Quiton, R. L., Roys, S. R., Zhuo, J., Keaser, M. L., Gullapalli, R. P., et al. (2007). Age-Related Changes in Nociceptive Processing in the Human Brain. *Annals of the New York Academy of Sciences* **1097**(Imaging and the Aging Brain): 175-178.
- Rapp, P. R. and Heindel, W. C. (1994). Memory systems in normal and pathological aging. *Curr Opin Neurol* **7**(4): 294-8.
- Rapp, S., Brenes, G. and Marsh, A. P. (2002). Memory enhancement training for older adults with mild cognitive impairment: a preliminary study. *Aging Ment Health* **6**(1): 5-11.
- Redfern, M. S., Jennings, J. R., Martin, C. and Furman, J. M. (2001). Attention influences sensory integration for postural control in older adults. *Gait Posture* **14**(3): 211-6.
- Rhodes, M. G. (2004). Age-related differences in performance on the Wisconsin card sorting test: a meta-analytic review. *Psychol Aging* **19**(3): 482-94.
- Roenker, D. L., Cissell, G. M., Ball, K. K., Wadley, V. G. and Edwards, J. D. (2003). Speed-of-processing and driving simulator training result in improved driving performance. *Hum Factors* **45**(2): 218-33.
- Salat, D. H., Greve, D. N., Pacheco, J. L., Quinn, B. T., Helmer, K. G., et al. (2009). Regional white matter volume differences in nondemented aging and Alzheimer's disease. *Neuroimage* **44**(4): 1247-58.
- Salthouse, T. A. (2000). Aging and measures of processing speed. *Biol Psychol* **54**(1-3): 35-54.
- Scalf, P. E., Colcombe, S. J., McCarley, J. S., Erickson, K. I., Alvarado, M., et al. (2007). The neural correlates of an expanded functional field of view. *J Gerontol B Psychol Sci Soc Sci* **62 Spec No 1**: 32-44.
- Schmolecky, M. T., Wang, Y., Pu, M. and Leventhal, A. G. (2000). Degradation of stimulus selectivity of visual cortical cells in senescent rhesus monkeys. *Nat Neurosci* **3**(4): 384-90.
- Shaffer, S. W. and Harrison, A. L. (2007). Aging of the Somatosensory System: A Translational Perspective. *PHYS THER* **87**(2): 193-207.
- Sohlberg, M. M. and Mateer, C. A. (1987). Effectiveness of an attention-training program. *J Clin Exp Neuropsychol* **9**(2): 117-30.
- Sohlberg, M. M. and Mateer, C. A. (2001). Improving attention and managing attentional problems. Adapting rehabilitation techniques to adults with ADD. *Ann.N.Y.Acad.Sci.* **931**: 359.
- Sohlberg, M. M., McLaughlin, K. A., Pavese, A., Heidrich, A. and Posner, M. I. (2000). Evaluation of attention process training and brain injury education in persons with acquired brain injury. *J Clin Exp Neuropsychol* **22**(5): 656-76.
- Sommers, M. S., Tye-Murray, N. and Spehar, B. (2005). Auditory-visual speech perception and auditory-visual enhancement in normal-hearing younger and older adults. *Ear Hear* **26**(3): 263-75.

- Spence, C. and Driver, J. (1997). On measuring selective attention to an expected sensory modality. *Percept.Psychophys.* **59**(3): 389-403.
- Spence, C., Nicholls, M. E. and Driver, J. (2001). The cost of expecting events in the wrong sensory modality. *Percept.Psychophys.* **63**(2): 330-6.
- Spence, C., Nicholls, M. E., Gillespie, N. and Driver, J. (1998). Cross-modal links in exogenous covert spatial orienting between touch, audition, and vision. *Percept.Psychophys.* **60**(4): 544-57.
- Spitzer, H., Desimone, R. and Moran, J. (1988). Increased attention enhances both behavioral and neuronal performance. *Science* **240**(4850): 338-40.
- Sreenivasan, K. K. and Jha, A. P. (2007). Selective attention supports working memory maintenance by modulating perceptual processing of distractors. *J Cogn Neurosci* **19**(1): 32-41.
- Stein, B. E., Meredith, M. A., Huneycutt, W. S. and McDade, L. (1989). Behavioral indices of multisensory integration: Orientation to visual cues is affected by auditory stimuli. *J Cogn Neurosci* **1**: 12-24.
- Stevenson, R. A. and James, T. W. (2009). Audiovisual integration in human superior temporal sulcus: Inverse effectiveness and the neural processing of speech and object recognition. *NeuroImage* **44**(3): 1210.
- Stine, E. A., Wingfield, A. and Myers, S. D. (1990). Age differences in processing information from television news: the effects of bisensory augmentation. *J Gerontol* **45**(1): P1-8.
- Strupp, M., Arbusow, V., Borges Pereira, C., Dieterich, M. and Brandt, T. (1999). Subjective straight-ahead during neck muscle vibration: effects of ageing. *Neuroreport* **10**(15): 3191-4.
- Talsma, D., Doty, T. J. and Woldorff, M. G. (2007). Selective attention and audiovisual integration: is attending to both modalities a prerequisite for early integration? *Cereb Cortex* **17**(3): 679-90.
- Talsma, D. and Woldorff, M. G. (2005). Selective attention and multisensory integration: multiple phases of effects on the evoked brain activity. *J Cogn Neurosci* **17**(7): 1098-114.
- Teder-Salejarvi, W. A., Di Russo, F., McDonald, J. J. and Hillyard, S. A. (2005). Effects of spatial congruity on audio-visual multimodal integration. *J.Cogn Neurosci.* **17**(9): 1396.
- Townsend, J., Adamo, M. and Haist, F. (2006). Changing channels: An fMRI study of aging and cross-modal attention shifts. *Neuroimage.*
- Troyer, A. K., Murphy, K. J., Anderson, N. D., Moscovitch, M. and Craik, F. I. (2008). Changing everyday memory behaviour in amnesic mild cognitive impairment: a randomised controlled trial. *Neuropsychol Rehabil* **18**(1): 65-88.
- Vatakis, A. and Spence, C. (2007). Crossmodal binding: evaluating the "unity assumption" using audiovisual speech stimuli. *Percept Psychophys* **69**(5): 744-56.
- Verhaeghen, P. and Cerella, J. (2002). Aging, executive control, and attention: a review of meta-analyses. *Neurosci Biobehav Rev* **26**(7): 849-57.
- Verhaeghen, P., Marcoen, A. and Goossens, L. (1992). Improving memory performance in the aged through mnemonic training: a meta-analytic study. *Psychol Aging* **7**(2): 242-51.

- Wallace, M. T., Meredith, M. A. and Stein, B. E. (1992). Integration of multiple sensory modalities in cat cortex. *Exp Brain Res* **91**(3): 484-8.
- West, R. and Alain, C. (2000). Age-related decline in inhibitory control contributes to the increased Stroop effect observed in older adults. *Psychophysiology* **37**(2): 179.
- Westlake, K. P. and Culham, E. G. (2007). Sensory-specific balance training in older adults: effect on proprioceptive reintegration and cognitive demands. *Phys Ther* **87**(10): 1274-83.
- Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., et al. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *Jama* **296**(23): 2805-14.
- Winocur, G., Craik, F. I., Levine, B., Robertson, I. H., Binns, M. A., et al. (2007). Cognitive rehabilitation in the elderly: overview and future directions. *J Int Neuropsychol Soc* **13**(1): 166-71.
- Woodruff, P. W., Benson, R. R., Bandettini, P. A., Kwong, K. K., Howard, R. J., et al. (1996). Modulation of auditory and visual cortex by selective attention is modality-dependent. *Neuroreport* **7**(12): 1909-13.
- Yang, L. and Hasher, L. (2007). The enhanced effects of pictorial distraction in older adults. *J Gerontol B Psychol Sci Soc Sci* **62**(4): P230-3.
- Yesavage, J. A. (1985). Nonpharmacologic treatments for memory losses with normal aging. *Am J Psychiatry* **142**(5): 600-5.
- Yordanova, J., Kolev, V., Hohnsbein, J. and Falkenstein, M. (2004). Sensorimotor slowing with ageing is mediated by a functional dysregulation of motor-generation processes: evidence from high-resolution event-related potentials. *Brain* **127**(Pt 2): 351-62.
- Yu, F., Rose, K. M., Burgener, S. C., Cunningham, C., Buettner, L. L., et al. (2009). Cognitive training for early-stage Alzheimer's disease and dementia. *J Gerontol Nurs* **35**(3): 23-9.

CHAPTER II

SUPPRESSION OF MULTISENSORY INTEGRATION BY MODALITY-SPECIFIC ATTENTION IN AGING

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Abstract

Previous research demonstrates that modality-specific selective attention attenuates multisensory integration in healthy young adults. Additionally, older adults evidence enhanced multisensory integration compared to younger adults. We hypothesized that these increases were due to changes in top-down suppression, and therefore older adults would demonstrate multisensory integration while selectively attending. Performance of older and younger adults was compared on a cued discrimination task. Older adults had greater multisensory integration than younger adults in all conditions, yet were still able to reduce integration using selective attention. This suggests that attentional processes are intact in older adults, but are unable to compensate for an overall increase in the amount of sensory processing during divided attention.

2.1 Introduction

The brain interfaces with the environment through multiple sensory channels carrying information about different forms of environmental energy. Some of these inputs are processed separately, but others are combined to form a unified percept of the surrounding world. Such multisensory interactions are governed by a combination of stimulus characteristics such as intensity, timing, and spatial coincidence (Stein et al., 1988; Stein and Meredith, 1993; Stein and Stanford, 2008), and higher-order cognitive functions such as semantic congruence (Laurienti et al., 2004) and attention (Alsius et al., 2005; Talsma and Woldorff, 2005; Talsma et al., 2007; Mozolic et al., 2008). Interestingly, older adults show increased integration of information between the senses (Laurienti et al., 2006; Peiffer et al., 2007). One potential explanation for this observed increase is age-related changes in top-down regulation of multisensory interactions, specifically attention.

Previous research has observed that attention modulates interactions between the senses (Alsius et al., 2005; Talsma and Woldorff, 2005; Talsma et al., 2007; Mozolic et al., 2008). Of particular relevance are two studies demonstrating that multisensory integration is significantly reduced when attention is selectively focused on one sensory channel compared to when attention is directed to visual and auditory modalities simultaneously (Talsma et al., 2007; Mozolic et al., 2008). Although research on the effects of aging on modality-specific or cross-modal attention is limited (Poliakoff et al., 2006), there is evidence that it may be altered in some circumstances. Poliakoff and colleagues (2006) noted that older adults were more slowed than younger adults by visual distractors when they were completing a tactile task, but not by tactile distractors in the

visual task. In addition, aging research suggests more broadly that inhibitory processes (including voluntary attention) may be impaired with increasing age (see (Healey et al., 2008) for review). If older adults are not successfully engaging selective attention, this might result in reduced regulation of multisensory interactions and increased integration relative to their younger counterparts. Therefore, the purpose of this study was to investigate the effects of aging on the ability to restrict multisensory integration with modality-specific attention. It was hypothesized that older adults would integrate more under conditions of selective attention than younger adults.

2.2 Methods

2.2.1 Subjects

Twenty-one young (mean age = 26.6, 9 women) and 20 older (mean age = 73.3, 11 women) adults completed this study. All participants were required to be in good health and have normal sensory and cognitive function. Potential participants were excluded if their mini-mental state examination (MMSE) score was greater than 2.5 standard deviations from the mean for their age and education (Bravo and Herbert, 1997). Volunteers were also excluded if they self-reported diagnoses or medications consistent with psychiatric disorders, neurological problems, head injuries, stroke, or diabetes, or showed evidence of alcoholism measured with the Alcohol Use Disorders Identification Test (Bohn et al., 1995). Volunteers who reported a diagnosis of depression were included if they had been receiving treatment for at least 3 months and were currently non-symptomatic when assessed using the Center for Epidemiological Studies Depression Scale (CES-D) (Haringsma et al., 2004). Volunteers were required to have

corrected visual acuity of 20/40 or better in both eyes measured with a modified Snell visual acuity exam and no more than moderate hearing loss, defined as 50dB measured with a digital audiometer (Digital Recordings, Halifax, Nova Scotia). Participants provided informed consent and all study procedures were approved by the Wake Forest University School of Medicine Institutional Review Board for the protection of human subjects in research and performed in accordance with the Declaration of Helsinki.

2.2.2 Study design

Participants completed a cued, multisensory discrimination task that required a choice between the colors red and blue (Mozolic et al., 2008). Participants were seated in a sound and light attenuated booth (Whisper Room, Morristown, TN, USA) with their head positioned 60 cm from a computer monitor in a comfortably adjusted chin rest. Stimuli were presented and accuracy and response time were collected using E-prime software (PST, Pittsburg, PA, USA). Each trial began with a 750 ms cue that directed participants to pay attention to the visual modality, the auditory modality, or to divide their attention across both the auditory and visual modalities. The attentional cue was visual and consisted of two white pictures on a black background, one located to the left of fixation and one to the right. The visual attention cue was two eyes, the auditory cue was two ears, and one ear and one eye directed subjects to divide their attention between the visual and auditory modalities.

After a 250 ms delay, a target was displayed for 150 ms. This target could be unisensory (e.g. a visual presentation of a red circle or an auditory presentation of the word “red”) or multisensory (e.g. participants simultaneously saw the red circle and heard

the word “red”). The target was followed by a response interval of up to 3,000 ms, during which participants were to make a quick and accurate choice between red and blue response buttons. Participants were instructed that auditory cues could be followed by auditory or multisensory targets, but they should pay attention to the auditory modality. Similarly, visual cues could be followed by visual or multisensory targets, but attention was to be focused on the visual modality. Divided attention cues could be followed by any target type. Cues were always correct, i.e. the target following an auditory attention cue always contained an auditory component. The 7 cue-target trial types are listed in Table 2.1. Participants completed 24 of each cue-target trial type, presented in a pseudorandom order over 3 trial blocks.

To compare accuracy on unisensory and multisensory trials during selective and divided attention, separate $2_{\text{age}} \times 2_{\text{attention cue}} \times 2_{\text{target}}$ mixed model ANOVAs were conducted for auditory and visual trial types. To analyze response time (RT), error trials and outliers (± 3 standard deviations) were removed, and similar ANOVAs were performed on mean RT data. Error trials were considered to be trials with an inaccurate response, e.g., pressing the blue response button on a red trial.

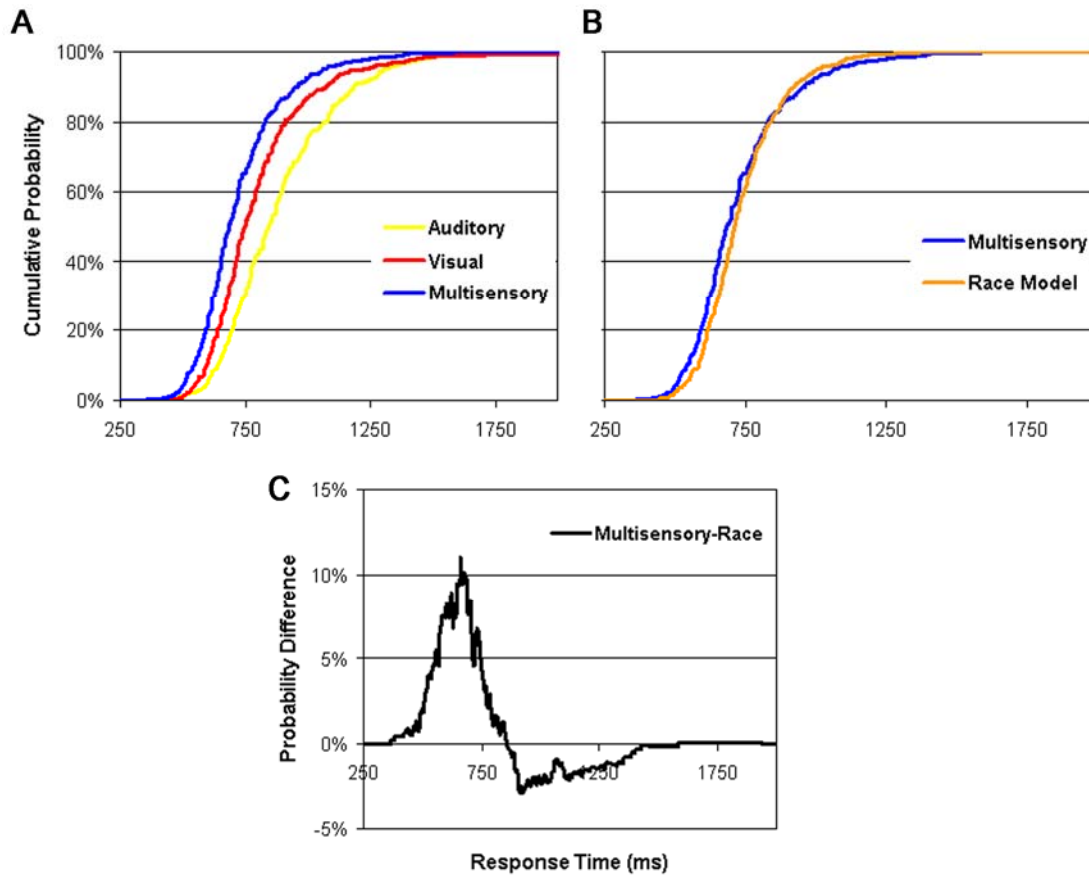
Although ANOVA analyses can identify group differences in mean performance on unisensory and multisensory trials, these tests can not account for enhancements due to the presence of two stimuli in the multisensory conditions (i.e. multisensory trials contain both an auditory and a visual component, while unisensory trials contain only one of these components). To control for the redundant nature of multisensory trials, the independent race model was used to determine if responses on multisensory trials were faster than would be predicted based on responses to both unisensory trial types (Miller,

1986). If observed responses to multisensory trials are faster than those predicted by the race model, multisensory integration is said to have occurred.

In order to complete race model analyses, participants' RTs in each attention condition were converted to cumulative distribution functions (CDFs) using 4 ms time bins. Each participant's race model curve (calculated from their unisensory CDFs) was then subtracted from their multisensory CDFs for divided and selective attention conditions (See Figure 2.1 for a diagram of a sample analysis). The 3 resulting difference curves (divided attention, selective auditory attention, and selective visual attention) were averaged across individuals in each age group, yielding mean curves where positive numbers represented intervals where responses to multisensory targets were faster than predicted by race model. One-sample t-tests were performed across these distributions to determine whether these multisensory enhancements were significantly above zero.

Because each subject has a different time course of responses, averaging difference curves across individuals may not give a complete indication of group differences. To obtain a measure of integration that is not affected by timing differences across individuals, we calculated the area under each of the subjects' 3 difference curves. Area under the curve was determined by calculating the integral for the positive region under each curve. These area values were then averaged across participants in each age group, and group differences in integration were assessed using a $2_{\text{age}} \times 3_{\text{attention cue}}$ mixed model ANOVA.

FIGURE 2.1 Sample analysis using the race model distribution



This diagram of the analysis of a representative subject depicts data only from the baseline divided attention condition. Response distributions for each target type (auditory, visual, and multisensory) were transformed into cumulative distribution functions with 4 ms response time bins (A). A race model distribution curve was then calculated from the joint probability of responses to the unisensory auditory and visual targets at each time bin (orange line in panel B is the probability summation of red and yellow lines from panel A) (B). Subtracting the race model distribution from the multisensory distribution yields a difference curve where positive deflections represent time points where responses to multisensory targets were faster than would be predicted based on independent processing of the unisensory targets; i.e., time points where multisensory integration has occurred (C).

2.3 Results

2.3.1 Accuracy

Accuracy was very high in all conditions (Table 2.1). A $2_{\text{age}} \times 2_{\text{attention cue}} \times 2_{\text{target}}$ ANOVA comparing accuracy between auditory and multisensory trials revealed no significant main effects or interactions. When visual and multisensory trials were compared, a main effect of Target was observed ($F_{1, 39} = 5.16, p < 0.03$), reflecting the fact that older and younger adults showed slightly improved accuracy to multisensory targets.

2.3.2 Response time

Average response times are reported in Table 2.1. A $2_{\text{age}} \times 2_{\text{attention cue}} \times 2_{\text{target}}$ ANOVA analyzing response times to auditory and multisensory trials showed main effects of Age ($F_{1, 39} = 28.62, p < 0.01$), Attention Cue ($F_{1, 39} = 11.37, p < 0.01$) and Target ($F_{1, 39} = 188.56, p < 0.01$). These results indicate that response times were significantly different between the two age groups (older responded more slowly), selective and divided attention (responses to selective attention were faster overall), and target type (responses to multisensory targets were faster). A significant Target x Group interaction was also observed ($F_{1, 39} = 6.10, p < 0.02$) that resulted from older adults being more speeded on multisensory trials than younger adults. A corresponding ANOVA performed on visual and multisensory trials demonstrated similar results. Main effects of Age ($F_{1, 39} = 27.01, p < 0.01$), Attention Cue ($F_{1, 39} = 32.96, p < 0.01$), and Target ($F_{1, 39} = 46.64, p < 0.01$) were observed. In addition, a Target x Group ($F_{1, 39} = 5.21, p < 0.03$) interaction was again observed because older adults were more speeded by multisensory trials than younger adults, and an Attention x Target ($F_{1, 39} = 4.42, p < 0.05$) interaction reflected that

TABLE 2.1 Mean accuracy and response time data for each attentional condition

Cue / Target Condition	Accuracy		RT	
	<i>Young</i>	<i>Older</i>	<i>Young</i>	<i>Older</i>
Auditory Attention				
auditory target	98.8 (0.6)	97.5 (1.5)	574.7 (23.5)	763.7 (24.7)
multisensory target	99.6 (0.3)	98.3 (1.5)	473.7 (20.2)	620.1 (23.0)
Visual Attention				
visual target	98.8 (0.6)	95.8 (1.9)	494.5 (18.5)	653.4 (22.3)
multisensory target	99.0 (0.4)	97.3 (1.5)	470.6 (18.3)	606.6 (24.4)
Divided Attention				
auditory target	98.4 (0.7)	98.3 (1.1)	601.6 (23.8)	784.9 (28.2)
visual target	99.0 (0.5)	94.2 (2.0)	528.7 (19.9)	700.6 (28.1)
multisensory target	99.4 (0.3)	97.9 (1.1)	491.1 (17.4)	624.2 (22.6)

Standard deviations are presented in parentheses.

both younger and older adults were more speeded by selective attention on visual trials than multisensory trials.

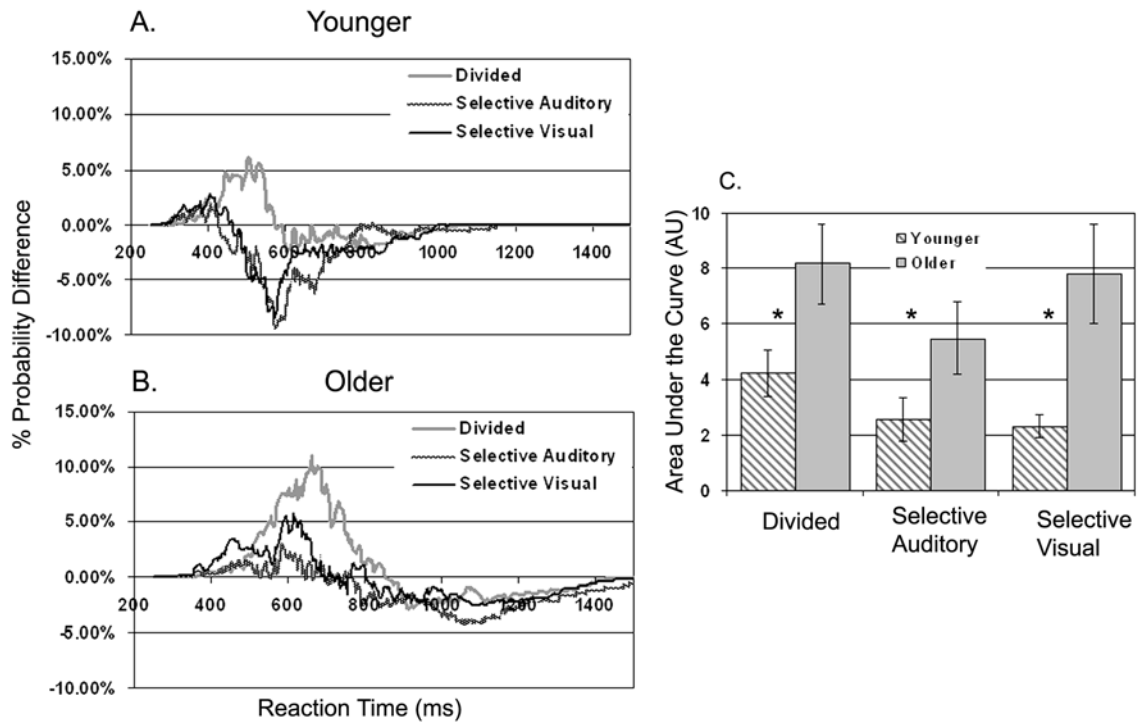
2.3.3 Race model comparisons

Positive deflections in the difference curves shown in Figure 2.2 A and B reflect time bins where observed responses to multisensory stimuli were faster than those predicted by the race model. Replicating previous results (Mozolic et al., 2008), younger adults showed evidence of multisensory integration during divided attention, with a peak of approximately 5%. However, during selective attention to both vision and hearing, multisensory integration was almost completely suppressed. In contrast, older adults showed more integration than younger adults in all conditions. While integration was reduced by selective attention, the peak of integration under visual selective attention is still as high as the peak of younger adults who were dividing their attention. Significant differences were noted between younger and older adults in the divided attention condition, but not during the selective attention conditions. The clear differences between age groups under selective attention conditions likely do not reach significance because of the way they are compared in this analysis. Due to variability between subjects and groups, areas of integration occur in different time bins. Therefore, the area under the difference curves was also compared.

Significant differences were observed between age groups for all three attention conditions when area under the race model difference curve was analyzed (Figure 2.2C).

A $2_{\text{age}} \times 3_{\text{attention cue}}$ ANOVA comparing divided and selective auditory attention

FIGURE 2.2 Age-related increases in multisensory integration illustrated in race model difference curves and mean area under the curve



Positive deflections in the race model difference curves for younger (**A**) and older (**B**) participants show time bins where multisensory integration has occurred. Divided attention curves are higher and broader than selective attention curves for both age groups, and curves for older adults are both wider and higher than those for younger adults in all conditions. These differences are shown clearly by comparing area under the curve (**C**) for each age group and attention condition. The * indicates significant differences between older and younger adults.

showed significant main effects of Age ($F_{1, 39} = 8.50, p < 0.01$) and Attention Cue ($F_{1, 39} = 3.84, p < 0.05$), arising from the fact that older adults had significantly greater area under the curve in all conditions, and selective attention significantly reduced the area under the curve for both age groups. A similar result was observed for visual selective attention where significant effects were seen for Age ($F_{1, 39} = 5.71, p < 0.05$) and Attention Cue ($F_{1, 39} = 9.64, p < 0.01$). Area under the curve was doubled for older adults relative to younger adults during divided attention and selective attention to hearing, and the difference between age groups was even larger during selective attention to vision. Interestingly, no Attention Cue x Group interaction was observed for either the auditory ($F_{1, 39} = 0.57, p = 0.45$) or visual ($F_{1, 39} = 0.74, p = 0.40$) selective attention comparisons, suggesting that there was no difference between the two age groups in the reduction of multisensory integration by selective attention.

2.4 Discussion

In this study, multisensory integration was virtually abolished in younger adults when they directed attention selectively to vision or hearing, replicating previous findings (Mozolic et al., 2008). As hypothesized, older adults exhibited increased multisensory integration relative to younger adults in all attentional conditions. However, contrary to our hypothesis, older adults did show evidence of successfully instantiating modality-specific attention. Integration was reduced under conditions of selective attention to vision or hearing relative to divided attention, and no Attention Cue x Group interactions were observed, suggesting that while older adults integrated more than younger adults, they showed a proportional reduction in integration due to modality-specific attention.

These results reinforce the idea that multisensory integration is increased with age. When attention was directed to vision and hearing simultaneously, older adults showed approximately double the integration of younger adults, both in area under the race model difference curve and in the peak of their difference curves. The same tendency was observed during selective attention, where the area under the curve was approximately doubled in older adults.

However, this difference in integration does not appear to be due to changes in top-down modulation of integration by modality-specific attention. The race model difference curves illustrate that while older adults integrate more than younger adults, integration is substantially reduced by attention. When area under the curve was compared, both Attention Cue and Age Group showed significant effects, but no interaction between Attention Cue x Age Group was observed. These findings reflect that integration was greater when participants divided their attention than when they selectively attended and older adults integrated more than younger adults, but that the reduction in integration by attention was comparable for both age groups.

Research on the effects of aging on modality-specific attention is limited. It has been consistently observed that older adults process more distracting information than younger adults both in cross-modal (Alain and Woods, 1999; Poliakoff et al., 2006) and unimodal (Andres et al., 2006; Yang and Hasher, 2007) tasks, and this has often been interpreted as evidence that older adults do not effectively engage attention. However, studies of other forms of voluntary attention show more mixed results; older adults do not differ from younger adults in their ability to attend in many situations (Groth and Allen, 2000; Madden et al., 2004). Results from this study suggest that modality-specific

attention can be effectively used by older adults and that increased processing of distractors may be due to some other mechanism, such as changes in the baseline processing of sensory information.

2.5 Conclusions

Together, these data indicate that there is a baseline increase in multisensory integration with increased age, such that older adults integrate more under all conditions than younger adults. Top-down regulation of multisensory integration by attention is still effective, suggesting that fundamental alterations in baseline state or sensory functioning may underlie this overall shift in integration in older adults.

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REFERENCES

- Alain, C. and Woods, D. L. (1999). Age-related changes in processing auditory stimuli during visual attention: evidence for deficits in inhibitory control and sensory memory. *Psychol Aging* **14**(3): 507-19.
- Alsius, A., Navarra, J., Campbell, R. and Soto-Faraco, S. (2005). Audiovisual integration of speech falters under high attention demands. *Curr Biol* **15**(9): 839-43.
- Andres, P., Parmentier, F. B. and Escera, C. (2006). The effect of age on involuntary capture of attention by irrelevant sounds: a test of the frontal hypothesis of aging. *Neuropsychologia* **44**(12): 2564-8.
- Bohn, M. J., Babor, T. F. and Kranzler, H. R. (1995). The alcohol use disorders identification test (audit): validation of a screening instrument for use in medical settings. *Journal of Studies on Alcohol* **56**: 423.
- Bravo, G. and Herbert, R. (1997). Age- and education-specific reference values for the Mini-Mental and Modified Mini-Mental State Examinations derived from a non-demented elderly population. *International Journal of Geriatric Psychiatry* **12**: 1008-1018.
- Groth, K. E. and Allen, P. A. (2000). Visual attention and aging. *Front Biosci* **5**: D284-97.
- Haringsma, R., Engels, G. I., Beekman, A. T. and Spinhoven, P. (2004). The criterion validity of the Center for Epidemiological Studies Depression Scale (CES-D) in a sample of self-referred elders with depressive symptomatology. *Int J Geriatr Psychiatry* **19**(6): 558-63.
- Healey, M. K., Campbell, K. L. and Hasher, L. (2008). Cognitive aging and increased distractibility: costs and potential benefits. *Prog Brain Res* **169**: 353-63.
- Laurienti, P. J., Burdette, J. H., Maldjian, J. A. and Wallace, M. T. (2006). Enhanced multisensory integration in older adults. *Neurobiology of Aging* **27**(8): 1155-1163.
- Laurienti, P. J., Kraft, R. A., Maldjian, J. A., Burdette, J. H. and Wallace, M. T. (2004). Semantic congruence is a critical factor in multisensory behavioral performance. *Exp Brain Res* **158**(4): 405-14.
- Madden, D. J., Whiting, W. L., Cabeza, R. and Huettel, S. A. (2004). Age-related preservation of top-down attentional guidance during visual search. *Psychol Aging* **19**(2): 304-9.
- Miller, J. (1986). Timecourse of coactivation in bimodal divided attention. *Percept Psychophys* **40**(5): 331-43.
- Mozolic, J. L., Hugenschmidt, C. E., Peiffer, A. M. and Laurienti, P. J. (2008). Modality-specific selective attention attenuates multisensory integration. *Exp Brain Res* **184**(1): 39-52.
- Peiffer, A. M., Mozolic, J. L., Hugenschmidt, C. E. and Laurienti, P. J. (2007). Age-related multisensory enhancement in a simple audiovisual detection task. *Neuroreport* **18**(10): 1077-81.
- Poliakoff, E., Ashworth, S., Lowe, C. and Spence, C. (2006). Vision and touch in ageing: crossmodal selective attention and visuotactile spatial interactions. *Neuropsychologia* **44**(4): 507-17.
- Stein, B. E., Huneycutt, W. S. and Meredith, M. A. (1988). Neurons and behavior: the same rules of multisensory integration apply. *Brain Res* **448**(2): 355-8.

- Stein, B. E. and Meredith, M. A. (1993). The merging of the senses. Cambridge, Massachusetts, MIT Press.
- Stein, B. E. and Stanford, T. R. (2008). Multisensory integration: current issues from the perspective of the single neuron. *Nat Rev Neurosci* **9**(4): 255-66.
- Talsma, D., Doty, T. J. and Woldorff, M. G. (2007). Selective attention and audiovisual integration: is attending to both modalities a prerequisite for early integration? *Cereb Cortex* **17**(3): 679-90.
- Talsma, D. and Woldorff, M. G. (2005). Selective attention and multisensory integration: multiple phases of effects on the evoked brain activity. *J Cogn Neurosci* **17**(7): 1098-114.
- Yang, L. and Hasher, L. (2007). The enhanced effects of pictorial distraction in older adults. *J Gerontol B Psychol Sci Soc Sci* **62**(4): P230-3.

CHAPTER III

A COGNITIVE TRAINING INTERVENTION IMPROVES MODALITY-SPECIFIC ATTENTION IN A RANDOMIZED CONTROLLED TRIAL OF HEALTHY OLDER ADULTS

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Melissa Rawley-Payne, and Paul J. Laurienti

The following chapter is a manuscript in press at the *Neurobiology of Aging*. Revisions to the manuscript have been made for stylistic consistency. JLM collected and analyzed the data and wrote the manuscript. ABL, ARM, and MRP assisted with data collection and analysis. PJL acted in an advisory and editorial capacity.

Abstract

Age-related deficits in cognitive and sensory function can result in increased distraction from background sensory stimuli. This randomized controlled trial investigated the effects of a cognitive training intervention aimed at helping healthy older adults suppress irrelevant auditory and visual stimuli. Sixty-six participants received eight weeks of either the modality-specific attention training program or an educational lecture control program. Participants who completed the intervention program had larger improvements in modality-specific selective attention following training than controls. These improvements also correlated with reductions in bimodal integration during selective attention. Further, the intervention group showed larger improvements than the control group in non-trained domains such as processing speed, dual-task completion, and working memory, demonstrating the utility of modality-specific attention training for improving cognitive function in healthy older adults.

3.1 Introduction

Normal aging is accompanied by changes in many sensory and cognitive domains, causing impairments in memory, communication, balance, and mobility that can lead to difficulty performing basic activities of daily living (Cahn-Weiner et al., 2000; Hedden and Gabrieli, 2004; Owsley and McGwin, 2004; Wood et al., 2005; Murphy et al., 2006; Inzitari et al., 2007; Maki et al., 2008). Thus, a major goal of aging research is to develop methods for maintaining independence and quality of life for older adults. Because the brain retains some plasticity with age, interventions aimed at training cognitive abilities may provide a means for maintaining or strengthening cognitive skills in healthy older adults (Kempermann et al., 2002; Jones et al., 2006; Acevedo and Loewenstein, 2007). In fact, several cognitive training programs have been shown to be effective at improving healthy older adults' memory, reasoning, speed of processing, and dual-task performance (Ball et al., 2002; Edwards et al., 2005; Bherer et al., 2006; Mahncke et al., 2006; Willis et al., 2006; Erickson et al., 2007).

Although the neural mechanisms that underlie age-related cognitive decline remain equivocal, age-related reductions in brain volume (Raz et al., 2004) and cortical thickness (Salat et al., 2004) are most pronounced in the prefrontal cortex, and executive processes supported by the prefrontal cortex, including attention, inhibition, and working memory, are highly susceptible to age-related declines (West, 1999; Grady and Craik, 2000; Andres et al., 2008). Deficits in these executive functions can impair older adults' performance on a broad range of cognitive tasks, as age-related increases in distraction from task-irrelevant visual stimuli, sounds, and speech can interfere with processing information that is relevant to the task (Alain and Woods, 1999; Tun et al., 2002; McPhee

et al., 2004; Andres et al., 2006; Healey et al., 2008). For example, older adults' responses to visual stimuli are slowed more than younger adults' when the visual stimulus is preceded by a novel sound (Andres et al., 2006).

In addition to the cognitive factors that influence older adults' task performance, age-related declines in sensory acuity and alterations in how stimuli from different sensory modalities are integrated together can also play a role in functional abilities (Wood et al., 2005; Murphy et al., 2006). Murphy et al. (2006) demonstrated that the comprehension and memory deficits that older adults experience when processing two-person conversations can be eliminated by compensating for older adults' hearing difficulties. However, older adults still performed worse than younger adults when the two talkers were spatially separated (Murphy et al., 2006). These results indicate that although ameliorating basic sensory impairments can improve older adults' ability to process sensory information, additional means may be required to minimize age-related deficits.

Enhancing the sensory signals that older adults receive from the environment is one method for recovering function; another technique is to reduce the amount of background noise being processed along with the relevant sensory information. Older adults exhibit enhanced integration of information from multiple sensory modalities compared to younger adults (Laurienti et al., 2006; Peiffer et al., 2007; Diederich et al., 2008). The inappropriate integration of irrelevant or non-matching sensory stimuli can serve to increase noise and interfere with processing of relevant information (Alain and Woods, 1999; Strupp et al., 1999; Andres et al., 2006). One cognitive mechanism for reducing such cross-modal noise is modality-specific selective attention, which allows us

to focus on information in one modality by suppressing the processing of stimuli in the ignored modality (Spence and Driver, 1997; Spence et al., 2001). Selective attention to either the auditory or visual modality has been demonstrated to eliminate the integration of congruent audiovisual stimuli in younger adults (Talsma et al., 2007; Mozolic et al., 2008); however, older adults still demonstrate increased multisensory integration during selective attention (Hugenschmidt et al., 2009), and it is unknown whether improving selective attention in older adults could reduce susceptibility to distraction from irrelevant sensory stimuli.

Our goal for this study was to investigate the effects of selective attention training in healthy older adults. The training program was designed to improve participants' ability to suppress background auditory and visual stimuli in an effort to decrease the amount of distraction experienced by older adults, and consequently improve their ability to process relevant information. Our hypothesis was that successful completion of the training program would reduce the influence of an ignored sensory modality on tasks that require modality-specific selective attention. Additionally, we investigated whether improvements would generalize to a wide variety of cognitive tasks, with the idea that improved sensory processing could have a positive effect on a broad range of cognitive functions that rely on the suppression of cross-modal noise.

3.2 Methods

3.2.1 Participants

Participants were recruited from the community for this randomized, controlled, single-blind study. All study procedures were approved by and conducted in accordance

with the Wake Forest University School of Medicine Institutional Review Board. All participants signed an informed consent and were compensated approximately \$20 per hour for their participation in the study. Seventy-five adults between the age of 65 and 75 were screened for eligibility. Sixty-six of these participants (mean age = 69.4, 35 women) were determined to be eligible for the study and were subsequently randomized to either the treatment or the control group. Randomization was completed in blocks of 8-10 subjects and stratified based on gender. Exclusion criteria included any of the following: visual acuity less than 20/40 with corrective lenses; colorblindness; hearing loss greater than 50 dB at 1000 or 2000 Hz; dementia or mild cognitive impairment indicated by a score on the Mini-Mental Status Exam that was below the 5th percentile for participant age and education level (Bravo and Hebert, 1997); current substance abuse indicated by a score greater than 10 on the Alcohol Use Disorders Identification Test or an evaluation of participant medical history; untreated depression, evaluated using the Medical Care Corporation survey (www.mccare.com); previous brain surgery or CNS trauma, neurological disorder, or use of antipsychotic and/or antiepileptic drugs, as determined by an evaluation of participant medical history. Demographic data for participants are summarized in Table 3.1.

3.2.2 Design

Following eligibility screening and randomization, all participants completed a battery of behavioral tests to evaluate baseline functioning in several cognitive domains. Within one week of this behavioral testing session, all participants began eight weeks of training. For both the treatment and control training programs, participants came to the

TABLE 3.1 Demographic data for participants in the treatment and control groups

	Treatment	Control	p-value
Age , years	69.4 (3.2)	69.4 (2.5)	1.00
Sex , # females	17	18	
Education , years	15.6 (2.2)	16 (3.4)	0.18
MMSE , score	28.3 (1.5)	28.5 (1.9)	0.66

Demographic data did not differ for participants randomized to the treatment and control groups on a 2-tailed t-test. Mean values are presented with standard deviations in parentheses.

laboratory for one hour each week (total training time = 8 hours). Within one week of completing their respective training programs, all participants were again administered the same battery of behavioral tests that they had completed prior to training. Participants also completed subsequent follow-up exams out to one month post-training, and a subset of these participants underwent MRI scans; these additional data will be considered in subsequent reports.

3.2.3 Interventions

Participants were randomized to receive either the attention training program or the control educational lecture program. Participants were blind to the treatment and control designations of these two groups, and were informed only that the study was designed to investigate the effects of two different training programs.

3.2.3.a Treatment group: The treatment program was an individual training program focused on visual and auditory selective attention. The goal of this program was to provide participants with repeated practice at actively suppressing distracting background noise during task performance. Training difficulty increased adaptively, so that each participant's progress through the training was based on his or her performance on previous tasks. With this training design, all participants were able to progressively improve performance at their own pace. In this way, participants were continually challenged to ignore very salient visual and auditory distractors in order to complete demanding cognitive tasks.

The program paired visual and auditory tasks with cross- and within-modality distractors, creating four different task categories: (A) visual tasks with visual distractors, (B) visual tasks with auditory distractors, (C) auditory tasks with auditory distractors, and (D) auditory tasks with visual distractors. Tasks from each of these categories were presented with equal frequency, in the following order: C, D, B, A, repeat. In each category, tasks included detecting, identifying, classifying, and/or sequencing visual or auditory presentations of letters, words, and numbers. Other tasks also included simple mathematical operations (addition or subtraction). Several task components were adapted from the APT-II (Lash & Associates Publishing / Training, Inc., Wake Forest, NC), a commercially available program that has been used to rehabilitate attentional processes in patients with brain injury (Sohlberg and Mateer, 1987; Sohlberg et al., 2000) and schizophrenia (Lopez-Luengo and Vazquez, 2003).

In order to ensure that any training effects were not due to practice with keyboards and computers, participants in the treatment group did not use a computer at any time in the training program. All visual tasks and distractors were projected onto a 4' x 5' movie screen by an overhead LCD projector. Participants were seated approximately 60 inches from the projection screen and viewed all visual stimuli on this movie screen, not on a computer monitor. All auditory tasks and distractors were presented through the speakers of the overhead LCD projector at a loud but comfortable level (70-80 dB). Stimuli and distractors were transmitted to the projector and overhead speakers from a laptop computer running Presentation software (www.neurobs.com). Participants gave responses for each task with verbal or written answers or by pressing a handheld buzzer for detection tasks. At no time did they make responses using a

computer or keyboard. An experimenter positioned behind the participant gave all task instructions, controlled stimulus presentation, monitored performance and compliance, and provided feedback to the participant.

During each visual task with visual distractors, visual stimuli were presented in the center of the screen in white font. Each number or letter subtended $\sim 1.4^\circ$ of visual angle. The number, letter, or word stimuli were presented within a black box that subtended $\sim 19^\circ$ of visual angle. Aside from this black box positioned in the center of the screen, the entire projection screen contained the visual distractors ($\sim 53^\circ$ of visual angle). Thus the visual stimuli appeared to be overlaid in front of the ongoing visual distraction. Visual distractors were series of short (5-15 sec) stock footage video clips of people, places, and events (Time Image Digital Film Library, www.timeimage.com). Several unique video clips spliced together provided distraction for the duration of each task (2-5 min). On visual tasks with auditory distractors, the visual stimuli appeared in the center of a black screen and sounds were presented via the overhead speakers. On auditory tasks with visual distractors, the entire screen contained the distraction display, except for a small black box containing a white fixation cross ($\sim 3^\circ$ of visual angle). During auditory tasks with auditory distractors, both the task and distractor stimuli were presented through overhead speakers. Task stimuli were mixed with the distractor tracks using Goldwave audio editing software (www.goldwave.com). Thus, participants heard the task stimuli embedded within the ongoing distractor noise. Auditory distractors were series of short stock audio tracks of weather, animal, instrument, machine, and crowd noises (www.soundfx.com). Several unique audio tracks edited together provided distraction for the duration of each task. One example task (category B, difficulty level 3) required

participants to complete patterns of visually presented numbers and letters (e.g. Z, Y, X, W; or 2, 3, 5, 8), while ignoring continuous auditory noise (thunderstorms, playground noise, barking dogs, city traffic, etc.).

To establish task difficulty levels, training tasks were piloted on one old (age 76) and five young (mean age = 29) subjects. Four to five tasks from each category (A-D) were grouped together in five difficulty levels, yielding a total of 88 potential tasks available for completion during the training program. Training for all participants began with easy tasks in each category, and task difficulty increased as training progressed. In order to advance to each subsequent task, participants were required to complete the current task with 80% accuracy. If a participant did not achieve 80% accuracy, the task was repeated until 80% accuracy was reached. If this accuracy level could not be reached in 6 attempts, the task was replaced by an alternate one of similar difficulty. Verbal feedback was provided to participants after completion of each task, informing them of their accuracy rate on the task and whether they would be repeating the task or beginning a new one. Additionally, participants were kept apprised of the current difficulty level and were alerted when the task difficulty would be increased. This procedure provided an adaptive training experience for each participant, as those with highly accurate performance on the tasks quickly progressed on to more difficult tasks, and those with lower accuracy rates received additional practice on each task until performance criteria was reached and the level of task difficulty could be increased. Progression through training therefore required improvements in performance, because all participants were able to advance to appropriate difficulty levels where multiple attempts were required to

reach 80% accuracy. There were no cases where a participant was not able to improve with repetition and progress from easy to harder tasks over the course of training.

3.2.3.b Control group: The control program was a small-group educational lecture series focused on topics in healthy aging. Because this program was designed to control for the time commitment and interactive nature of the treatment program, control participants visited the lab for the same duration and number of sessions. Additionally, by conducting control lecture sessions in small groups with approximately four study participants and 3 study staff members, participants in the treatment and the control groups had similar interactions with study staff. Each session began with pre-test questions, followed by a 30-minute lecture by a topical expert. Subjects then participated in an interactive component where they were encouraged to apply information from the lecture. Each participant was also required to complete a post-test covering the same questions administered before the lecture. The interaction with topical experts, including doctors, nurses, and therapists, as well as the administration of pre- and post-tests served to maintain the single-blind design of the study. That is, participants in the control group did not know that they were part of the control program; they were under the impression that they were just completing a different training regimen than the treatment group.

3.2.4 Evaluations

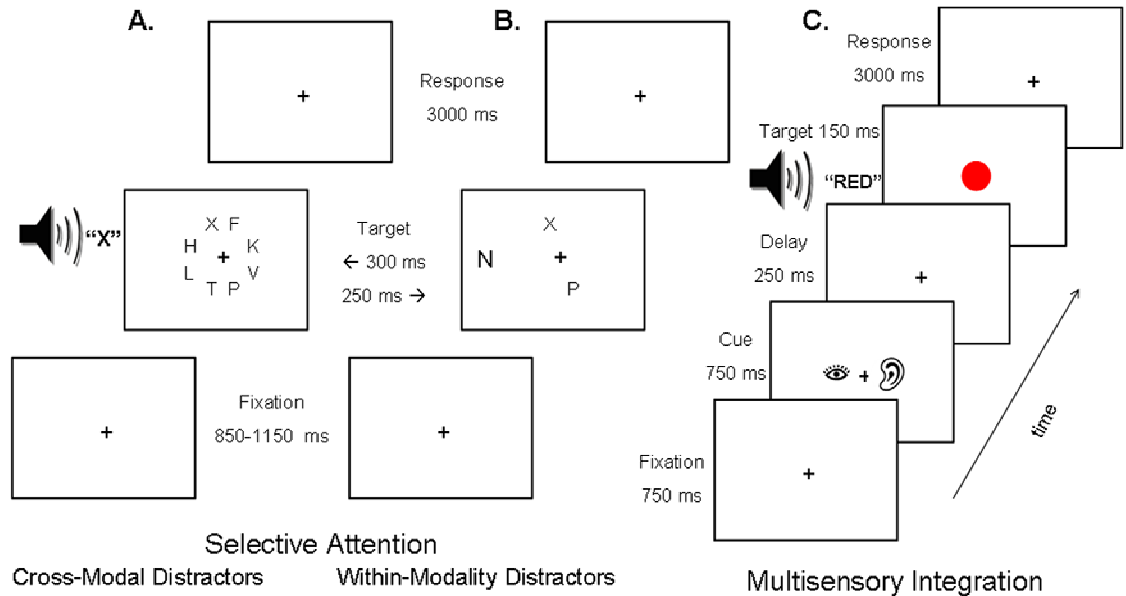
To evaluate the effects of the attention training program, we administered tests of modality-specific selective attention. Additionally, to determine if the intervention generalized to other domains, we administered several assessments of cognitive

performance and subjective feelings of well-being. As the attention training program utilized a hierarchical progression requiring mastery (80% accuracy) at low levels in order to move to more difficult levels, none of the training tasks were administered during evaluation.

3.2.4.a Primary outcomes: Our primary outcome measures in this study were accuracy and response time (RT) on two tasks of modality-specific selective attention. These response competition paradigms required participants to make a speeded choice response to a relevant visual target (the letters *X* and *N*) while ignoring irrelevant distractors. The first task, adapted from Tellinghuisen & Nowak (2003), required subjects to ignore auditory (*cross-modal*) distractors (Tellinghuisen and Nowak, 2003) and the second task, adapted from Malyor & Lavie (1998), required subjects to ignore visual (*within-modality*) distractors positioned to the left or right of the target (Malyor and Lavie, 1998). These tasks were chosen as direct measures of the effectiveness of attention training using cross- and within-modality distractors, respectively.

For the cross-modal distractor task, the target letter *X* or *N* was positioned within a circular array that could contain 1 or 7 additional letters (Fig. 3.1A). Increasing the number of letters in the array allowed us to investigate task performance at varying perceptual loads. The auditory distractors were the letters *X*, *N*, *T*, and *L*. These auditory distractors were paired with the visual targets to produce *congruent trials* (auditory letter matched the target visual letter, e.g., hear *N*, see *N*), *incongruent trials* (auditory letter was the opposite response choice, e.g., hear *X*, see *N*), and *neutral trials* (auditory letter was not a response choice, e.g., hear *T*, see *N*). All letters were presented in light gray

FIGURE 3.1 Sequence of trial events for primary and secondary outcome measures



In this trial depicted for the selective attention task with cross-modal distractors, participants were required to determine whether there was an X or an N presented in the visual array (set size = 8), while ignoring the auditory presentation of a letter (congruent trial; **A**). In the trial depicted for the selective attention task with within-modality distractors, participants were again required to determine whether there was an X or an N presented in the visual array (set size = 2); however in this paradigm they must ignore a distracting letter presented to the left or right of the central array (incongruent trial; **B**). For this example trial of the multisensory integration task, participants were cued to divide attention between the auditory and visual modalities, and then determine whether the target was the color red or blue (multisensory target; **C**).

font on black background, and subjects were instructed to maintain fixation on a cross in the center of the screen for the duration of the session. Auditory letters were presented through speakers located on either side of the monitor.

Participants completed a total of 144 trials, and equal numbers of congruent, incongruent, and neutral trial types were presented randomly within the session. The total number of letters in the array (set size = 2 or 8) and the target position within the array on each trial was also randomly ordered and counterbalanced across trial types. Participants responded by button press with the left and right index finger, and the left/right response mapping was counterbalanced across participants. Stimulus presentation and response collection were conducted using E-Prime software (www.pstnet.com). Each trial began with a fixation period of 850-1150 ms (mean = 1000 ms). The target display and auditory distractor were then presented for 300 ms, followed by a reply-terminated response interval of up to 3000 ms.

For both accuracy and RT, we computed a measure of *total interference* for each participant, which was the difference between performance on congruent trials and performance on incongruent trials. We performed analyses of variance on the group means for accuracy and RT total interference using set size and test session as the repeated measures, and training group as the between group factor. This yielded a $2_{\text{set size}} \times 2_{\text{session}} \times 2_{\text{group}}$ mixed model ANOVA for accuracy data, and a similar ANOVA for RT data. Paired-samples t-tests were used to further explore pre- to post-training changes in interference for each group at the different levels of task difficulty. Our hypothesis was that significant decreases in interference would be observed at both levels of difficulty for

the intervention group, whereas there would be no significant changes for the control group.

The within-modality distractor task (Fig. 3.1B) was very similar to the cross-modal task, with the following differences: (1) the visual distractor was a letter presented to the left or right of the central target array; (2) only neutral and incongruent trials types were presented, thus a measure of *distractor cost* was computed as the difference between performance on neutral trials and performance on incongruent trials; (3) the target and distractor were presented for 250 ms rather than 300 ms; (4) set sizes of 2 and 6 letters, rather than 2 and 8, were presented and analyzed in the 2 x 2 x 2 mixed model ANOVAs for accuracy and RT. Our hypothesis for this task was based on the work of Maylor and Lavie (1998), who demonstrated a larger distractor cost for older adults than younger adults at low perceptual loads (small set sizes), but not at higher levels of perceptual load because older adults' reduced attentional capacity prevents processing of the distractor. We predicted that if training improved within-modality selective attention, the treatment group would have reduced distractor costs at set size 2, and stable or increased distractor costs at set size 6, relative to the control group. This pattern of results in older adults after training would be more consistent with the performance of young adults on this task, who show little distraction at low perceptual loads, and more distraction at higher perceptual loads due to their capacity to process the distractor.

3.2.4.b Secondary outcomes: We hypothesized that improved modality-specific attention capabilities following attention training would be demonstrated not only on direct tests of selective attention, but that improved suppression of background sensory

noise would also be reflected in reduced integration of ignored sensory stimuli on a test of multisensory integration. Therefore, our second main outcome measure was performance on an audiovisual multisensory integration task that allowed us to evaluate the influence of stimuli in the ignored sensory modality (Laurienti et al., 2006; Mozolic et al., 2008).

This cued discrimination paradigm required participants to choose between the colors red and blue during different attention conditions (Fig. 3.1C). During each trial, stimuli were presented in either the auditory modality, the visual modality, or simultaneously in both the auditory and visual modalities. Auditory stimuli were the words *red* and *blue*, visual stimuli were red and blue color-filled circles presented on a black background, and multisensory stimuli were simultaneous presentations of matching auditory and visual stimuli. Forty-eight auditory, 48 visual, and 72 multisensory trials were presented in random order. Participants responded by button press with the left and right index finger, and the red/blue response mapping was counterbalanced across participants.

Each trial began with participants fixating on a gray cross on a black background for 750 ms. Following fixation, a 750 ms visual cue was presented to alert participants to direct their attention to the auditory modality or the visual modality, or to divide their attention across both the auditory and the visual modalities in preparation for the target. After a 250 ms delay, the target was presented for 150 ms, followed by a response interval that terminated when a response was made, or after 3000 ms if no response was made. Participants were instructed that an auditory attention cue could be followed by a unisensory auditory target or a multisensory target, but they were to pay attention to the

auditory modality. Similarly, the visual attention cue could be followed by a unisensory visual target or a multisensory target, but attention was to be focused on the visual modality. The divided attention cue could be followed by an auditory or visual unisensory target, or a multisensory target, and attention was to be directed to both the visual and auditory modalities. There were no trials in which the cue invalidly predicted the target modality (i.e., after the cue to attend to vision, the target always contained a visual component). Because all attention cues were presented in the visual modality, we can not exclude the possibility that these cues biased attention towards the visual modality; however previous studies on modality-specific attention have typically utilized visual symbols to cue participants to the target modality (Spence and Driver, 1997; Spence et al., 2001), and unpublished data from our laboratory suggests that any bias is quite small and does not alter the outcome of the task.

This task allows us to investigate responses to unisensory and multisensory stimuli under selective and divided attention conditions. Because there are two components to a multisensory stimulus (an auditory and a visual component), we used a model of statistical facilitation, known as the independent race model (Miller, 1982, 1986), to compare the distribution of multisensory responses to the joint probability of visual and auditory responses. Unlike comparisons of mean RT, this model controls for presence of two stimuli on multisensory trials, and allows us to evaluate multisensory integration, or the speeding of responses to multisensory stimuli. When the probability of responses to multisensory stimuli is significantly greater than the joint probability of responses to unisensory stimuli, this model indicates that multisensory integration has occurred.

To perform this analysis, cumulative distribution functions for each trial type were used to calculate two race distributions for each participant: one for selective attention conditions and one for divided attention conditions. Each participant's multisensory distributions were then subtracted from their race distributions to generate three curves: the first demonstrating the amount of multisensory integration that occurred during selective auditory attention, the second demonstrating the amount of multisensory integration during selective visual attention, and the third showing the amount of multisensory integration during divided attention. Thus, the area under these subtraction curves provides a quantification of the relative amount of multisensory integration occurring in various task conditions. Mean response times are reported in Table 3.2 for illustrative purposes, but due to the limitations of mean RT data for examining multisensory integration, statistical analyses were performed on area under the curve measures only. The area under the curves was used to perform a $3_{\text{condition}} \times 2_{\text{test session}} \times 2_{\text{group}}$ mixed model ANOVA to determine the impact of the training intervention on multisensory integration in the various attention conditions. Paired-samples t-tests of pre- to post-training changes for each group were used to further explore the effects of the intervention on integration during each attention condition. Our hypothesis was that attention training would result in reduced multisensory integration during auditory and visual selective attention, but no change in integration during divided attention.

3.2.4.c Indirect outcomes: In addition to determining the direct effects of attention training on selective attention and multisensory integration, we also administered several other tests to measure generalization of the intervention to different cognitive domains.

TABLE 3.2 Mean response times on the multisensory integration task by attention / target condition

	Treatment		Control	
	<i>pre</i>	<i>post</i>	<i>pre</i>	<i>post</i>
Divided Attention				
Unisensory Auditory	782.0 (37.1)	707.0 (21.6)	702.9 (30.0)	685.1 (24.0)
Unisensory Visual	701.9 (30.3)	656.4 (23.6)	646.6 (31.1)	622.4 (22.5)
Multisensory	604.9 (26.5)	581.3 (18.3)	552.1 (23.6)	555.7 (19.9)
Selective Auditory Attention				
Unisensory Auditory	742.1 (27.4)	710.0 (23.1)	673.7 (22.3)	656.5 (22.8)
Multisensory	591.4 (25.5)	583.1 (20.5)	538.6 (18.1)	534.5 (16.1)
Selective Visual Attention				
Unisensory Visual	672.9 (24.4)	615.1 (18.4)	604.1 (21.1)	581.4 (19.6)
Multisensory	574.9 (20.9)	566.7 (18.0)	537.8 (19.5)	545.7 (18.7)

Mean response times are presented in ms, with standard error of the mean in parentheses.

Each of these tests was evaluated using a $2_{\text{test session}} \times 2_{\text{group}}$ mixed model ANOVA, and our hypotheses were that pre- to post-training improvements on each test would be larger for the intervention group than for the control group.

The Symbol Digit Modalities Test (SDMT) was used to obtain a measure of general executive function and processing speed that could be normalized for each participant's age and education level (Western Psychological Services, www.wpspublish.com). This test requires participants to pair specific numbers with given geometric figures. Each participant's score was compared to the mean for his or her age and education level, and the average standard deviation from the mean was used in the analysis.

To assess interference during dual-task performance, we used a Walk and Talk paradigm that required participants to complete a 10 meter walk, and then to name animals while completing a 10 meter walk (adapted from (Beauchet et al., 2005)). An interference effect was calculated as the percent difference between time taken to complete the silent walk and the time taken to complete the walk while naming animals, thus lower interference values indicate that less slowing resulted from the addition of the second task. The number of unique animals named and the interference effect were each entered into the analyses.

To assess working memory, participants completed 1- and 2-back versions of the N-back task (Braver et al., 1997; Ragland et al., 2002; Owen et al., 2005). In this task, a series of items is presented one at a time and the participant must indicate whether or not the present item matches the one N items back. To assess performance on the 1- and 2-back tasks, we calculated d' , a measure of accuracy that controls for response biases

using the formula, $d' = Z_{\text{hit}} - Z_{\text{false alarm}}$, where Z_{hit} is the z-score for a participant's probability of correctly identifying matching letters, and $Z_{\text{false alarm}}$ is the z-score for a participant's probability of incorrectly responding to non-matching letters. Higher values of d' indicate better performance on the n-back task. Mean d' values for the 1- and 2-back tasks were then analyzed to determine the effects of attention training on working memory task performance.

The Stroop Color-Word test was administered to evaluate interference and executive function (Stroop, 1935; Langenecker et al., 2004). This task requires participants first to name the ink color of a series of non-words (e.g. XXXX, printed in blue ink), then to name the ink color of a series of non-matching color words (e.g. RED, printed in blue ink). An interference effect was calculated as the percent difference between the time taken to answer for the series of non-words and the time taken to respond for the color words. A reduction in the interference effect indicates that less slowing resulted from the incongruent pairing of ink color and written word.

The Trail-Making test was administered to evaluate planning, interference, and executive function (Arbuthnott and Frank, 2000; Bowie and Harvey, 2006). Part A of this test requires participants to connect numbered circles in order. Part B of the test requires participants to connect numbers and letters, in an alternating order (1-A-2-B-3-C, etc.). An interference effect was calculated as the percent difference in time taken to complete Parts A and B, and this interference effect was used to analyze performance.

The Hopkins Verbal Learning Test (HVLT; Psychological Assessment Resources, Inc., www.parinc.com) was used to assess verbal learning and memory. This test includes three immediate learning trials, a recognition trial, and a delayed recall trial for a

list of 12 common words. The average number of words recalled on the immediate learning trials and the delayed recall trial were each entered into separate analyses. Performance on the recognition trial was calculated using the hit rate minus the false alarm rate, and the hit-false alarm rate was also entered in an analysis.

The Profile of Mood States (POMS; Multi-Health Systems, Inc., www.mhs.com) was administered to evaluate affective states including tension, anger, depression, vigor, fatigue, and confusion. This test requires participants to rate the frequency and intensity of these feelings on a 5-point scale, and responses can be used to calculate a composite score that is used for analysis. Lower scores on this test reflect fewer negative feelings, or a more positive mood state.

The 12-Item Health Status Questionnaire (HSQ-12) was used to assess general physical and emotional health using a series of questions about activities of daily living (Pettit et al., 2001). Higher scores on this test are indicative of better self-reported health. Participants' scores on the physical and emotional subscales were each entered into separate analyses.

All primary, secondary, and indirect outcome evaluations were administered in the same testing session, which lasted for approximately 2.5 hours. Tasks were administered in the following order: 1) HVLT; 2) POMS; 3) HSQ-12; 4) SDMT; 5) Trail-Making; 6) Stroop; 7) Walk and Talk; 8) N-back; 9-11) Cross-modal Distraction, Within-modality Distraction, and Multisensory Integration were administered in a pseudorandom order, counterbalanced across participants. Each participant completed the evaluation tasks in the same order on their pre- and post-training visits.

3.3 Results

A modality-specific selective attention training program, designed to promote suppression of background auditory and visual stimuli, was administered to 33 participants. Thirty-three participants were also enrolled in a control educational lecture program. Three participants did not complete the intervention program. Two of these participants had scheduling conflicts arise that prevented them from completing the training and the third was not available for post-training evaluation due to relocation. One participant did not complete the control program due to a change in eligibility, therefore all results are reported for 62 participants (n= 30 treatment, n= 32 controls). Our retention rates (91% treatment, 97% control) were very good given the commitment level and scheduling obstacles – the study required participants to make 15 visits to the hospital or laboratory over 4 months, many within narrowly proscribed time windows. Nevertheless, all participants answered either “agree” or “strongly agree” to the statements, “Overall, I enjoyed being part of the study” and “I am glad I decided to participate” on a study exit survey.

There were no significant differences in age, education, or MMSE score between the treatment and control groups (Table 3.1). Participants in the intervention group completed an average of 58 tasks in 119 attempts, progressing on average to the third of five levels of difficulty. Additionally, all participants continued to improve their performance and progress on to increasingly difficult tasks throughout the eight weeks of attention training. That is, none of the participants reached a point where the required 80% accuracy rate could not be attained after 6 failed attempts on all tasks of a given difficulty level.

We anticipated that completion of the attention training program, relative to the educational lecture control program, would improve participants' ability to ignore irrelevant sensory stimuli, resulting in improved performance on tasks of selective attention, reduced multisensory integration during modality-specific attention, and better functioning in a variety of other cognitive domains because of reductions in interference from background sensory noise. The results from these primary, secondary, and indirect outcome measures are presented below and summarized in Table 3.3.

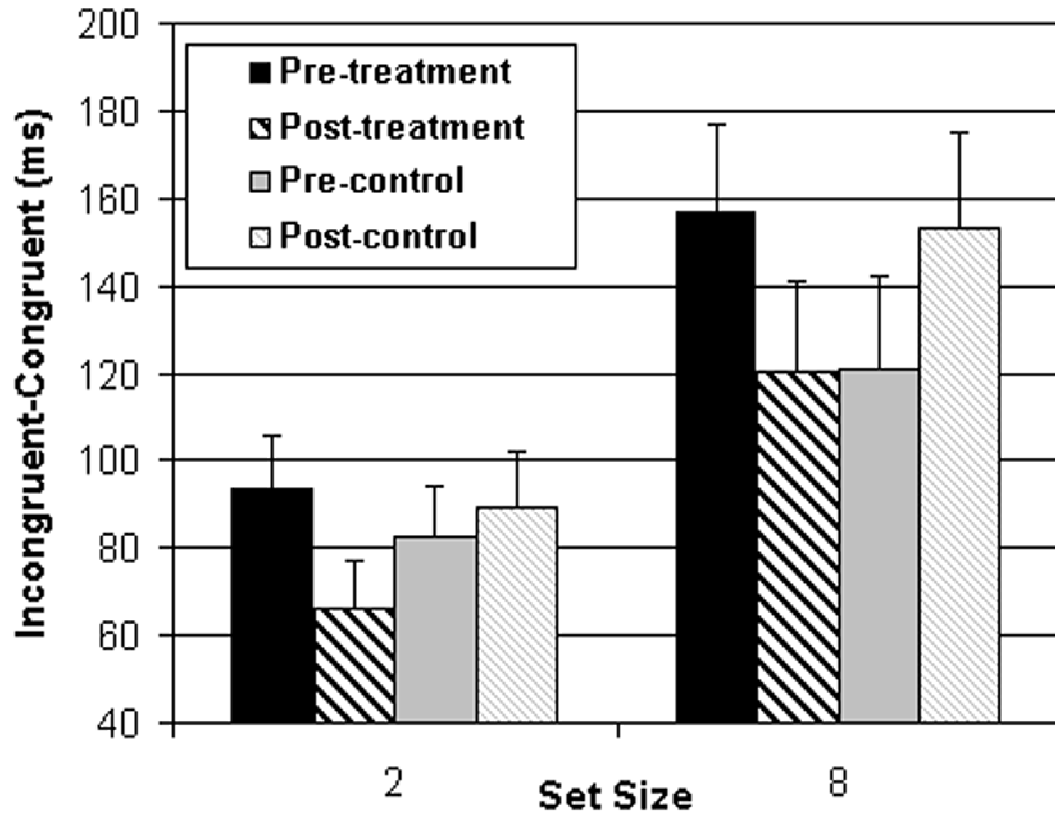
On the selective attention task with cross-modal distractors, we analyzed the effects of set size, test session, and training group to determine if the interference associated with the auditory distractors was reduced more by the attention training intervention than by the control program. The RT data indicated that there was a significant session by group interaction ($F_{1,60} = 4.63$, $p < 0.04$, Fig. 3.2), a significant effect of set size ($F_{1,60} = 24.09$, $p < 0.001$), no significant effect of session, and no significant effect of group. This indicated that the training intervention had a larger effect on RT interference than the control program and that both groups had less interference on the easier trials. To further explore these results, we performed paired-samples t-tests for each group, comparing their performance pre- and post-training. On the easier trials, the treatment group had a significant drop in RT interference following training (set-size 2, $t_{29} = 2.48$, $p < 0.02$, Fig. 3.2) but there was no significant interference change for the control group ($t_{31} = -0.19$, $p = \text{ns}$). On the more difficult trials (set-size 8) there were no significant pre- to post-training changes in performance for either group, despite a trend for interference reductions in the treatment group (treatment, $t_{29} = 1.09$, $p = \text{ns}$; control, $t_{31} = -1.06$, $p = \text{ns}$).

Table 3.3 Pre- and post-training performance on outcome measures for the treatment and control groups

	Treatment		Control	
	<i>pre</i>	<i>post</i>	<i>pre</i>	<i>post</i>
<i>Primary Outcomes</i>				
** Selective Attention (cross-modal distractors)				
set size 2 interference				
accuracy (%)	1.1 (5.0)	-0.1 (3.0)	2.1 (6.6)	0.6 (2.7)
RT (ms)	98.1 (67.0)	66.0 (61.0)	86.5 (61.3)	89.2 (73.4)
set size 8 interference				
accuracy (%)	13.0 (13.1)	10.2 (17.5)	17.5 (16.0)	7.2 (14.4)
RT (ms)	157.7 (119.0)	120.3 (113.2)	121.0 (122.7)	153.2 (122.1)
Selective Attention (within-modality distractors)				
set size 2 cost				
accuracy (%)	3.7 (8.0)	-0.6 (9.3)	1.7 (5.3)	0.9 (5.2)
RT (ms)	49.0 (66.7)	64.9 (66.0)	42.6 (72.1)	52.2 (62.8)
set size 6 cost				
accuracy (%)	-2.0 (8.9)	0.4 (9.7)	-0.5 (10.6)	0.7 (8.1)
RT (ms)	-2.6 (74.1)	-30.5 (75.9)	15.2 (93.0)	-30.5 (75.9)
<i>Secondary Outcomes</i>				
Multisensory Integration (area under curve)				
divided attention	9.7 (6.9)	8.0 (6.8)	9.8 (6.9)	8.2 (6.3)
** selective auditory attention	7.7 (6.2)	4.1 (4.4)	6.3 (5.8)	6.1 (6.5)
** selective visual attention	9.6 (8.6)	5.5 (4.5)	6.5 (5.4)	4.9 (4.9)
<i>Indirect Outcomes</i>				
* 1-Back (d')	3.0 (0.7)	3.4 (0.4)	3.1 (0.6)	3.2 (0.7)
2-Back (d')	2.2 (0.9)	2.6 (0.7)	2.3 (0.8)	2.5 (0.7)
** SMDT (standard deviation score)	0.0 (0.9)	0.4 (0.8)	0.5 (0.9)	0.6 (0.9)
Walk & Talk				
** # of animals named	9.3 (2.3)	10.5 (2.9)	9.5 (2.6)	9.4 (2.1)
interference (%)	49.6 (47.9)	55.9 (44.1)	40.1 (30.6)	39.3 (29.0)
Stroop Color-Word (% interference)	96.7 (25.7)	89.4 (32.0)	89.2 (31.6)	82.8 (31.0)
† Trail-Making (% interference)	112.4 (56.1)	141.5 (74.4)	122.5 (54.8)	116.3 (37.6)
HVLT				
immediate recall (# of words)	8.1 (1.4)	8.9 (1.6)	8.4 (1.7)	9.4 (1.4)
delayed recall (# of words)	8.2 (2.7)	9.0 (1.7)	9.4 (2.4)	9.6 (1.7)
POMS (composite score)	-0.3 (16.2)	2.8 (16.3)	4.4 (18.0)	3.3 (14.4)
HSQ-12				
physical health score	49.2 (8.8)	48.7 (9.8)	51.0 (7.1)	50.4 (8.3)
mental health score	55.3 (8.3)	56.8 (4.4)	54.5 (8.1)	55.5 (4.5)

Double asterisks (**) indicate tests on which the treatment group had significantly greater improvements than controls ($p < 0.05$), single asterisk (*) indicates the test on which there was a trend for larger improvements in the treatment group ($p < 0.10$), and the cross (†) indicates the test on which control group had significantly greater improvements than the treatment group ($p < 0.05$). Standard deviations are in parentheses.

FIGURE 3.2 Training-induced decreases in response time interference on a visual attention task with auditory distractors



On a visual attention task with auditory distractors, there was a significant training group by test session interaction ($p < 0.04$), indicating that the treatment group had larger pre- to post-training decreases in interference than controls. This interaction effect was explored using paired-samples t-tests examining pre- to post-training changes for each group. A significant training-induced drop in interference on the smaller set size conditions ($p < 0.02$, indicated by an asterisk) was found for the treatment group, however interference reductions were not significant on the larger set size trial, and the control group had no significant changes in interference at either set size. Error bars indicated standard error of the mean.

Because the interference effect is due to both speeding of responses to congruent trials versus neutral trials (benefits) and slowing of responses to incongruent trials versus neutral trials (costs), we also examined the RT benefits and costs of cross-modal distractors. The treatment group had reductions in both benefits and costs (-12.8 ms and -22.0 ms, respectively), while the control group had slight increases (5.8 ms and 11.7 ms, respectively); however, there was no significant difference in the magnitude of benefits and costs, and no significant difference between the two groups in either benefits or costs, indicating that reductions in both the speeding and slowing of responses to ignored cross-modal stimuli contributed to the overall observed decrease in interference following training.

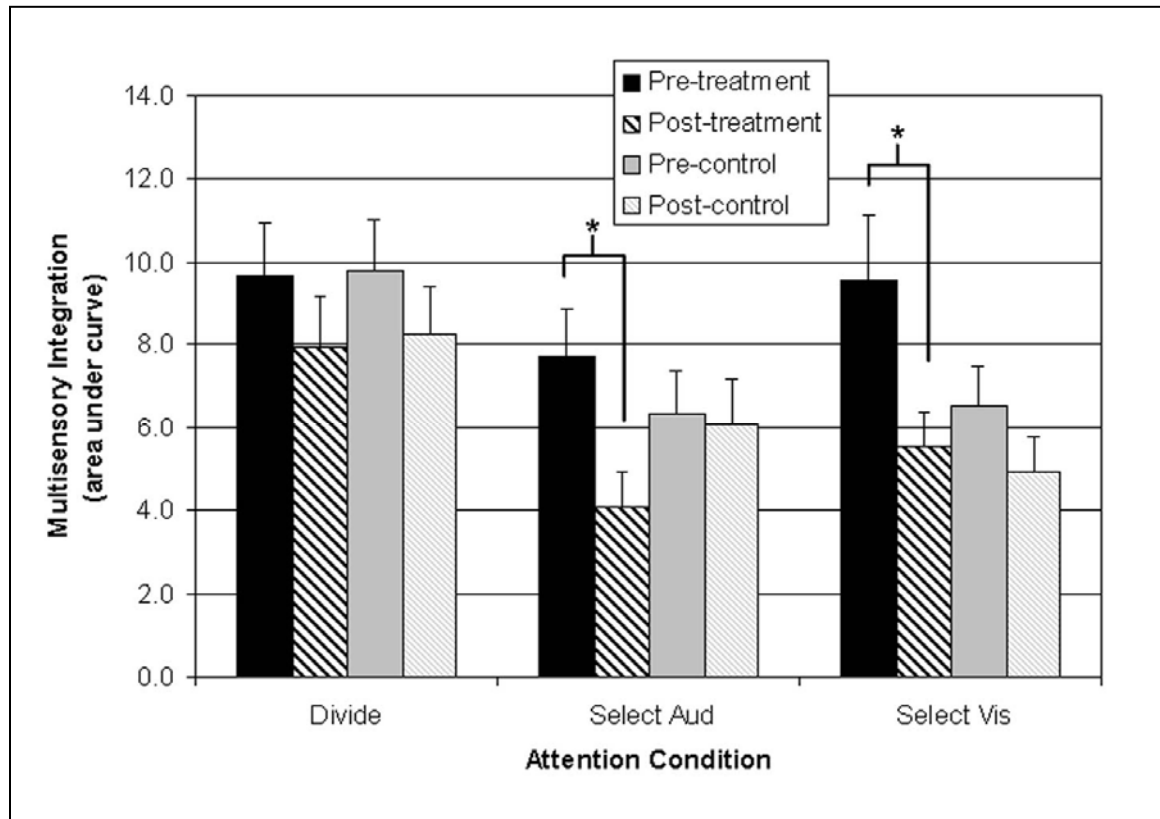
For the accuracy data, there were significant effects of set size ($F_{1,60} = 55.25$, $p < 0.001$) and test session ($F_{1,60} = 8.04$, $p < 0.006$), but no significant effect of training group, and no significant interactions. This indicated that both groups had more interference on difficult trials and that following training, both groups were more accurate on this selective attention task. This finding is consistent with a practice effect for accuracy, but no effect of the training intervention.

Similar analyses performed on the selective attention task with within-modality distractors to investigate the effects of set size, test session, and training group on the performance costs of visual distractors. Participants in both groups had lower RT costs ($F_{1,52} = 42.82$, $p < 0.001$) on trials with high perceptual load (set size 6). However, there were no significant effects of test session or training group on accuracy or response time costs for this task.

Next we investigated multisensory integration to determine if the attention training intervention would reduce integration during modality-specific selective attention. Mean RT for unisensory and multisensory targets in each attention condition are presented in Table 3.2. To examine the effects of testing session and training group on multisensory integration, we analyzed the area under the curves generated by comparing multisensory and race model response distributions. The ANOVA comparing training-induced changes in multisensory integration during divided attention, selective auditory attention, and selective visual conditions indicated that there was a significant effect of attention condition ($F_{2,120} = 11.50, p < 0.001$), a significant effect of test session ($F_{1,60} = 16.48, p < 0.001$), no effect of training group, and a trend for an interaction between session and group ($F_{1,60} = 3.55, p < 0.06$). As anticipated, these results indicated that there was significantly more integration during divided attention conditions than either selective auditory attention or selective visual attention, and a significant reduction in integration following training (Fig. 3.3). In paired-samples t-tests, the treatment group demonstrated significant reductions in integration during selective auditory ($t_{29} = 3.61, p < 0.001$) and selective visual attention ($t_{29} = 3.42, p < 0.002$), and no change in integration during divided attention ($t_{29} = 1.36, p = \text{ns}$). In contrast, the control group had no significant changes in integration during any attention condition (divided, $t_{31} = 1.14, p = \text{ns}$; auditory, $t_{31} = 0.25, p = \text{ns}$; visual, $t_{31} = 1.96, p = \text{ns}$).

Performance on the SDMT task improved significantly during the second test session ($F_{1,60} = 16.97, p < 0.001$), and these improvements in processing speed were greater for the treatment group than for controls (session x group interaction: $F_{1,60} = 6.79, p < 0.01$).

FIGURE 3.3 Training-induced decreases in multisensory integration during selective attention



On an audiovisual integration task, the treatment group demonstrated significant training-induced decreases in multisensory integration during selective auditory attention (paired t-test, $p < 0.001$) and selective visual attention (paired t-test, $p < 0.002$). There were no significant reductions in integration for the control group. Error bars indicated standard error of the mean.

On the Walk and Talk task, there was a larger increase in the number of animals named during the 10m walk for the treatment group than controls (session x group interaction: $F_{1,59} = 3.88$, $p < 0.05$). There was no significant change in dual-task interference, however, to control for differences in walking speed, we used participants' change in walking speed pre- to post-training as a covariate. This analysis indicated that there was still a trend for a larger increase in the number of animals named after attention training than after the control program, even after controlling for any changes in walking speed (session x group interaction: $F_{1,58} = 3.25$, $p < 0.08$).

Performance on the 1-back working memory task also improved significantly during the second test session ($F_{1,60} = 8.68$, $p < 0.005$), and although there was no significant effect of group, there was a trend for a session by group interaction ($F_{1,60} = 2.71$, $p < 0.10$), indicating that there were larger improvements in the treatment group than in the control group. On the 2-back task, performance improved for both groups following training ($F_{1,60} = 9.29$, $p < 0.003$), and there was no significant effect of training group, and although the interaction trend was similar to that found in the 1-back task, this interaction was not significant.

On the Stroop Color-Word task, the HVLT test of verbal learning and memory, the POMS mood profile, and the HSQ-12 survey of general health, there were no significant effects of test session or training group, and no significant interactions. On the Trail-Making test, there was a smaller drop in interference after training for the treatment group than for controls, even after controlling for differences in error rates (session x group interaction: $F_{1,58} = 4.01$, $p < 0.05$). This result was due to the fact that the treatment group improved on both part A and part B of this test, minimizing any change

in the interference effect, which represents the difference in performance on parts A and B. In contrast, the control group improved on part B only, producing a significant drop in interference after training.

3.4 Discussion

Numerous studies in animals and human subjects have demonstrated that the adult mammalian brain retains plasticity, even at advanced ages (Rosenzweig and Bennett, 1996; Colcombe et al., 2004; Bherer et al., 2006; Segovia et al., 2006; Erickson et al., 2007; Mora et al., 2007). This retention of plasticity provides a great opportunity for environmental modification of brain function and behavior. Cognitive training programs that involve repetitive practice on basic cognitive skills, such as memory, reasoning, and speed of processing, have previously been shown to be effective at improving the trained skill, and to a lesser extent, influencing performance on non-trained tasks (Kramer et al., 1995; Jennings et al., 2005; Mahncke et al., 2006; Ball et al., 2007; Rebok et al., 2007). The attention training program detailed in this report provided repetitive, adaptive practice for participants to improve their ability to focus on relevant tasks and to ignore irrelevant, but very salient and distracting stimuli. This intervention was designed to mimic the multisensory nature of the real world, where stimuli from unattended sensory modalities often distracts us, interfering with our performance of tasks such as carrying on a conversation in a busy restaurant, or writing a paper in a noisy laboratory. Because so many perceptual and cognitive processes can be influenced by cross-modal noise, techniques for minimizing the impact of irrelevant stimuli could potentially improve functioning across a variety of domains.

The primary outcome measures for this study were two tasks of visual attention: one that required participants to ignore conflicting auditory distractors, and one that required suppression of conflicting peripheral visual stimuli. Participants who completed eight weeks of the attention training program had significantly greater reductions in interference from cross-modal distractors than those who completed an educational lecture control program. The treatment group did not, however, show greater improvements than controls at disregarding within-modality distractors during the visual task. These results indicate that this training program is an effective method for minimizing the impact of cross-modal distractors, but does not limit distraction from stimuli within the task modality.

One possible source of these divergent results may be differences in the mechanisms of cross-modal distraction and within-modality distraction. The mechanisms of selective attention within the visual modality have been extensively studied (e.g. (Posner and Driver, 1992; Desimone and Duncan, 1995; Kastner and Ungerleider, 2000)), and attention to a particular visual stimulus is known to involve several factors. Visual objects must compete for the limited processing resources of the visual system, and attention can bias processing by enhancing neural responses to the attended stimulus, increasing baseline levels of activity in neurons representing the attended location, and also by counteracting the inhibition generated by nearby stimuli (Spitzer et al., 1988; Kastner et al., 1999; Reynolds et al., 1999; Pinsk et al., 2004). Similar processing enhancements during selective attention to particular sounds have also been demonstrated in the auditory system (Woldorff et al., 1993; Grady et al., 1997; Tzourio et al., 1997).

Thus, a primary mechanism for attention to a particular feature or location within a sensory modality involves increasing the relevant signal.

In contrast, the primary behavioral impact of focusing attention on one sensory modality and ignoring stimuli in a different modality is not performance enhancements in the attended modality, but rather suppressed processing of stimuli in the unattended modality (Spence and Driver, 1997; Spence et al., 2001). Additionally, a number of imaging studies demonstrate that processing stimuli in one sensory modality results in decreased activity in the other sensory cortices (Kawashima et al., 1995; Kawashima et al., 1999; Laurienti et al., 2002; Johnson and Zatorre, 2005, 2006). These data support the notion that improved information processing during modality-specific attention is through a suppression of cross-modal sensory noise. In addition, although competition for limited processing capacity is a prominent factor in within-modality distraction, it has been demonstrated that attentional resources are not as restricted when processing stimuli in multiple sensory modalities (Duncan et al., 1997; Rees et al., 2001; Talsma et al., 2006). For example Rees et al. (2001) demonstrated that neural activity in response to task-irrelevant visual stimuli was not reduced when the difficulty of an auditory task was increased. In contrast, visual activity corresponding to the task-irrelevant stimuli was attenuated when the difficulty of a concurrent visual task was increased (Rees et al., 2001).

These results indicate that there are different neurophysiological mechanisms at work when attention is engaged to filter out cross-modal distractors and within-modality distractors. These differences in suppressive effects and processing capacity within and between modalities may be differentially modified by training procedures. The training

intervention presented here successfully reduced the impact of cross-modal background noise, but did not improve task performance during within-modality distraction. Although this study was not designed to determine which training tasks produced the observed behavioral enhancements, it seems likely that cross-modal training tasks were effective at promoting suppression of cross-modal distraction. Although the within-modality training tasks may also have contributed to improved performance on the evaluation measures, alternative training paradigms may be required to better target the mechanisms of within-modality attention.

Our secondary outcome measure further demonstrated that attention training resulted in reduced susceptibility to the influence of stimuli in the ignored sensory modality. In this task, participants were directed to focus attention on just the auditory or just the visual component of a multisensory stimulus. Following training, the treatment group demonstrated significant reductions in the integration during both selective auditory and selective visual attention conditions, while the control group showed no significant changes in integration. Additionally, there were no changes in integration during divided attention conditions, indicating that the training-induced changes did not represent a global decrease in multisensory integration, but rather a specific decrease in integration when attention is deliberately focused on one sensory modality. This is important for real-world situations, where it may be helpful both for older adults to maintain the benefits gained from congruent multisensory stimuli, and also be able to effectively ignore information in just one sensory modality.

In addition to the training-induced improvements observed in attention and cross-modal suppression, the treatment group also demonstrated improvements on tests of other

cognitive functions, including processing speed, dual-task performance, and working memory. One potential source of these transfer effects is improved processing of stimuli in the non-trained tasks due to an increase in signal to noise ratio that results from better suppression of irrelevant cross-modal stimuli. None of the tests used for indirect evaluation were specifically trained; however, the attention training tasks did require speeded manipulations of letters, words, and numbers, and purposeful control of attention. Thus, practice on these elements may have contributed to improvements in the related cognitive domains.

In order to determine if participants' progression through attention training could be used to predict their level of improvement on any of the outcome evaluations, we performed a post-hoc correlation analysis. This test revealed that there was no significant relationship between the number of training tasks completed or the number of task repeats participants performed during the training sessions and their improvement on any of the outcome measures. This finding indicates that reaching a certain level of difficulty or repeating tasks a specified number of times was not required to produce improvement in the outcome evaluations. Rather, completing eight hours of the training intervention was sufficient to produce significant improvements in the primary, secondary, and several indirect outcomes, regardless of the rate of progression through the training tasks. This promising feature of the intervention program suggests that the intervention program would be helpful for a wide range of ability levels, as participants who repeated many tasks and did not reach the highest levels of difficulty benefited from the training just as much as those who had to repeat few tasks and progressed to the most difficult training tasks.

Attention training did not improve performance on several additional cognitive evaluations, including the Stroop Color-Word test, the Trail-Making test, and the HVLT. Unlike the SDMT, Walk and Talk, and N-back tasks, both the Stroop and Trail-Making tests require subjects to resolve conflict and inhibit prepotent responses. These are skills that were never practiced in the training tasks, which always utilized task-irrelevant distractors rather than stimuli that conflicted directly with the task. For example, on a training task where participants were required to sequence numbers, the distractors were everyday scenes or sounds rather than numbers. Training that includes practice suppressing conflicting cross-modal or within-modality distractors may be necessary to promote improvements in these domains, as improvements in modality-specific attention did not impact performance on tasks requiring conflict resolution and response inhibition. Training effects also did not generalize to verbal learning and memory on the HVLT. One possible explanation for this result may be that the HVLT task involves the untimed recall of word list items that have been read to the participant slowly and deliberately by the tester. In this testing situation, modality-specific attention may not affect memory for the list items. In contrast, on timed tasks requiring speeded responses to multiple stimuli such as the SDMT, Walk and Talk, and N-back, susceptibility to distracting stimuli can easily impede performance.

One additional point to consider is that although the attention training program detailed in this report successfully improved participants' ability to ignore distracting cross-modal stimuli and enhanced performance in other cognitive domains, all outcome evaluations were conducted in quiet testing rooms. Further testing will be required to determine if these trained skills would generalize to increase performance enhancements

on evaluations conducted in a noisier environment, more like the everyday conditions under which demanding cognitive tasks are normally performed.

There were no significant changes in self-reported mood, mental health or physical health status; however, in our very high-functioning and relatively small sample population, changes in these variables may be very difficult to measure. The ACTIVE study found a similar lack of change in such real-world outcomes in very large, but high-functioning intervention groups; however, after a follow-up interval of five years, participants who had completed reasoning training showed significantly less decline than controls on self-reported performance of instrumental activities of daily living such as meal preparation, finance management, and health maintenance (Willis et al., 2006). Further study involving extended follow-up periods and/or lower-functioning participants may be required to detect the impact of this intervention program on functional decline or other clinical measures.

An additional caveat of the small sample size included in this randomized controlled trial is that randomization procedures can not completely balance baseline performance between the two groups as in large scale trials. However, all analyses utilized a mixed model ANOVA, where the interaction effect was the outcome of interest. Thus, despite the relatively small sample used, we observed training-induced improvements for the intervention group in several cognitive domains that exceeded any improvements demonstrated by the control group. Larger scale follow-up studies will be required to reduce baseline differences between treatment and control groups and to further characterize the effects of the training intervention.

In conclusion, the results of the present study demonstrated that a novel training program targeting modality-specific attention successfully improved healthy older adults' ability to ignore irrelevant cross-modal stimuli. Training also generalized to non-trained cognitive tasks, suggesting that more proficient suppression of background sensory noise can promote performance enhancements on a variety of cognitive tasks. Additional research will be required to determine the potential for reducing age-related functional decline using modality-specific attention training.

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REFERENCES

- Acevedo, A. and Loewenstein, D. A. (2007). Nonpharmacological cognitive interventions in aging and dementia. *J Geriatr Psychiatry Neurol* **20**(4): 239-49.
- Alain, C. and Woods, D. L. (1999). Age-related changes in processing auditory stimuli during visual attention: evidence for deficits in inhibitory control and sensory memory. *Psychol Aging* **14**(3): 507-19.
- Andres, P., Guerrini, C., Phillips, L. H. and Perfect, T. J. (2008). Differential effects of aging on executive and automatic inhibition. *Dev Neuropsychol* **33**(2): 101-23.
- Andres, P., Parmentier, F. B. and Escera, C. (2006). The effect of age on involuntary capture of attention by irrelevant sounds: a test of the frontal hypothesis of aging. *Neuropsychologia* **44**(12): 2564-8.
- Arbuthnott, K. and Frank, J. (2000). Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. *J Clin Exp Neuropsychol* **22**(4): 518-28.
- Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., et al. (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. *Jama* **288**(18): 2271-81.
- Ball, K., Edwards, J. D. and Ross, L. A. (2007). The impact of speed of processing training on cognitive and everyday functions. *J Gerontol B Psychol Sci Soc Sci* **62 Spec No 1**: 19-31.
- Beauchet, O., Dubost, V., Gonthier, R. and Kressig, R. W. (2005). Dual-task-related gait changes in transitionally frail older adults: the type of the walking-associated cognitive task matters. *Gerontology* **51**(1): 48-52.
- Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., et al. (2006). Testing the limits of cognitive plasticity in older adults: application to attentional control. *Acta Psychol (Amst)* **123**(3): 261-78.
- Bowie, C. R. and Harvey, P. D. (2006). Administration and interpretation of the Trail Making Test. *Nat Protoc* **1**(5): 2277-81.
- Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., et al. (1997). A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage* **5**(1): 49-62.
- Bravo, G. and Hebert, R. (1997). Age- and education-specific reference values for the Mini-Mental and modified Mini-Mental State Examinations derived from a non-demented elderly population. *Int J Geriatr Psychiatry* **12**(10): 1008-18.
- Cahn-Weiner, D. A., Malloy, P. F., Boyle, P. A., Marran, M. and Salloway, S. (2000). Prediction of functional status from neuropsychological tests in community-dwelling elderly individuals. *Clin Neuropsychol* **14**(2): 187-95.
- Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., et al. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A* **101**(9): 3316-21.
- Desimone, R. and Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annu Rev Neurosci* **18**: 193-222.
- Diederich, A., Colonius, H. and Schomburg, A. (2008). Assessing age-related multisensory enhancement with the time-window-of-integration model. *Neuropsychologia* **46**(10): 2556-62.

- Duncan, J., Martens, S. and Ward, R. (1997). Restricted attentional capacity within but not between sensory modalities. *Nature* **387**(6635): 808-10.
- Edwards, J. D., Wadley, V. G., Vance, D. E., Wood, K., Roenker, D. L., et al. (2005). The impact of speed of processing training on cognitive and everyday performance. *Aging Ment Health* **9**(3): 262-71.
- Erickson, K. I., Colcombe, S. J., Wadhwa, R., Bherer, L., Peterson, M. S., et al. (2007). Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging* **28**(2): 272-83.
- Grady, C. L. and Craik, F. I. (2000). Changes in memory processing with age. *Curr Opin Neurobiol* **10**(2): 224-31.
- Grady, C. L., Van Meter, J. W., Maisog, J. M., Pietrini, P., Krasuski, J., et al. (1997). Attention-related modulation of activity in primary and secondary auditory cortex. *Neuroreport* **8**(11): 2511-6.
- Healey, M. K., Campbell, K. L. and Hasher, L. (2008). Chapter 22 Cognitive aging and increased distractibility: Costs and potential benefits. *Prog Brain Res* **169**: 353-63.
- Hedden, T. and Gabrieli, J. D. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nat Rev Neurosci* **5**(2): 87-96.
- Hugenschmidt, C. E., Mozolic, J. L. and Laurienti, P. J. (2009). Suppression of multisensory integration by modality-specific attention in aging. *Neuroreport* **20**(4): 349-53.
- Inzitari, M., Baldereschi, M., Di Carlo, A., Di Bari, M., Marchionni, N., et al. (2007). Impaired attention predicts motor performance decline in older community-dwellers with normal baseline mobility: results from the Italian Longitudinal Study on Aging (ILSA). *J Gerontol A Biol Sci Med Sci* **62**(8): 837-43.
- Jennings, J., Webster, L., Kleykamp, B. and Dagenbach, D. (2005). Recollection Training and Transfer Effects in Older Adults: Successful Use of a Repetition-Lag Procedure. *Aging, Neuropsychology, and Cognition (Neuropsychology, Development and Cognition)* **12**(3): 278-298.
- Johnson, J. A. and Zatorre, R. J. (2005). Attention to simultaneous unrelated auditory and visual events: behavioral and neural correlates. *Cereb Cortex* **15**(10): 1609-20.
- Johnson, J. A. and Zatorre, R. J. (2006). Neural substrates for dividing and focusing attention between simultaneous auditory and visual events. *Neuroimage* **31**(4): 1673-81.
- Jones, S., Nyberg, L., Sandblom, J., Stigsdotter Neely, A., Ingvar, M., et al. (2006). Cognitive and neural plasticity in aging: general and task-specific limitations. *Neurosci Biobehav Rev* **30**(6): 864-71.
- Kastner, S., Pinsk, M. A., De Weerd, P., Desimone, R. and Ungerleider, L. G. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron* **22**(4): 751-61.
- Kastner, S. and Ungerleider, L. G. (2000). Mechanisms of visual attention in the human cortex. *Annu.Rev.Neurosci.* **23**: 315-341.
- Kawashima, R., Imaizumi, S., Mori, K., Okada, K., Goto, R., et al. (1999). Selective visual and auditory attention toward utterances-a PET study. *Neuroimage* **10**(2): 209-15.

- Kawashima, R., O'Sullivan, B. T. and Roland, P. E. (1995). Positron-emission tomography studies of cross-modality inhibition in selective attentional tasks: closing the "mind's eye". *Proc Natl Acad Sci U S A* **92**(13): 5969-72.
- Kempermann, G., Gast, D. and Gage, F. H. (2002). Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Ann Neurol* **52**(2): 135-43.
- Kramer, A. F., Larish, J. F. and Strayer, D. L. (1995). Training for attentional control in dual task settings: A comparison of young and old adults. *Journal of Experimental Psychology: Applied* **1**(1): 50-76.
- Langenecker, S. A., Nielson, K. A. and Rao, S. M. (2004). fMRI of healthy older adults during Stroop interference. *Neuroimage* **21**(1): 192-200.
- Laurienti, P. J., Burdette, J. H., Maldjian, J. A. and Wallace, M. T. (2006). Enhanced multisensory integration in older adults. *Neurobiol Aging* **27**(8): 1155-63.
- Laurienti, P. J., Burdette, J. H., Wallace, M. T., Yen, Y. F., Field, A. S., et al. (2002). Deactivation of sensory-specific cortex by cross-modal stimuli. *J Cogn Neurosci* **14**(3): 420-9.
- Lopez-Luengo, B. and Vazquez, C. (2003). Effects of Attention Process Training on cognitive functioning of schizophrenic patients. *Psychiatry Res* **119**(1-2): 41-53.
- Mahncke, H. W., Connor, B. B., Appelman, J., Ahsanuddin, O. N., Hardy, J. L., et al. (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proc Natl Acad Sci U S A* **103**(33): 12523-8.
- Maki, B. E., Cheng, K. C. C., Mansfield, A., Scovil, C. Y., Perry, S. D., et al. (2008). Preventing falls in older adults: New interventions to promote more effective change-in-support balance reactions. *Journal of Electromyography and Kinesiology* **18**(2): 243-254.
- Maylor, E. A. and Lavie, N. (1998). The influence of perceptual load on age differences in selective attention. *Psychol Aging* **13**(4): 563-73.
- McPhee, L. C., Scialfa, C. T., Dennis, W. M., Ho, G. and Caird, J. K. (2004). Age differences in visual search for traffic signs during a simulated conversation. *Hum Factors* **46**(4): 674-85.
- Miller, J. (1982). Divided attention: evidence for coactivation with redundant signals. *Cognit Psychol* **14**(2): 247-79.
- Miller, J. (1986). Timecourse of coactivation in bimodal divided attention. *Percept Psychophys* **40**(5): 331-43.
- Mora, F., Segovia, G. and del Arco, A. (2007). Aging, plasticity and environmental enrichment: structural changes and neurotransmitter dynamics in several areas of the brain. *Brain Res Rev* **55**(1): 78-88.
- Mozolic, J. L., Hugenschmidt, C. E., Peiffer, A. M. and Laurienti, P. J. (2008). Modality-specific selective attention attenuates multisensory integration. *Exp Brain Res* **184**(1): 39-52.
- Murphy, D. R., Daneman, M. and Schneider, B. A. (2006). Why do older adults have difficulty following conversations? *Psychol Aging* **21**(1): 49-61.
- Owen, A. M., McMillan, K. M., Laird, A. R. and Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp* **25**(1): 46-59.

- Owsley, C. and McGwin, G., Jr. (2004). Association between visual attention and mobility in older adults. *J Am Geriatr Soc* **52**(11): 1901-6.
- Peiffer, A. M., Mozolic, J. L., Hugenschmidt, C. E. and Laurienti, P. J. (2007). Age-related multisensory enhancement in a simple audiovisual detection task. *Neuroreport* **18**(10): 1077-81.
- Pettit, T., Livingston, G., Manela, M., Kitchen, G., Katona, C., et al. (2001). Validation and normative data of health status measures in older people: the Islington study. *International Journal of Geriatric Psychiatry* **16**(11): 1061-1070.
- Pinsk, M. A., Doniger, G. M. and Kastner, S. (2004). Push-pull mechanism of selective attention in human extrastriate cortex. *J Neurophysiol* **92**(1): 622-9.
- Posner, M. I. and Driver, J. (1992). The neurobiology of selective attention. *Curr Opin Neurobiol* **2**(2): 165-9.
- Ragland, J. D., Turetsky, B. I., Gur, R. C., Gunning-Dixon, F., Turner, T., et al. (2002). Working memory for complex figures: an fMRI comparison of letter and fractal n-back tasks. *Neuropsychology* **16**(3): 370-9.
- Raz, N., Gunning-Dixon, F., Head, D., Rodrigue, K. M., Williamson, A., et al. (2004). Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. *Neurobiol Aging* **25**(3): 377-96.
- Rebok, G. W., Carlson, M. C. and Langbaum, J. B. (2007). Training and maintaining memory abilities in healthy older adults: traditional and novel approaches. *J Gerontol B Psychol Sci Soc Sci* **62 Spec No 1**: 53-61.
- Rees, G., Frith, C. and Lavie, N. (2001). Processing of irrelevant visual motion during performance of an auditory attention task. *Neuropsychologia* **39**(9): 937-49.
- Reynolds, J. H., Chelazzi, L. and Desimone, R. (1999). Competitive mechanisms subserve attention in macaque areas V2 and V4. *J. Neurosci.* **19**(5): 1736-53.
- Rosenzweig, M. R. and Bennett, E. L. (1996). Psychobiology of plasticity: effects of training and experience on brain and behavior. *Behav Brain Res* **78**(1): 57-65.
- Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., et al. (2004). Thinning of the cerebral cortex in aging. *Cereb Cortex* **14**(7): 721-30.
- Segovia, G., Yague, A. G., Garcia-Verdugo, J. M. and Mora, F. (2006). Environmental enrichment promotes neurogenesis and changes the extracellular concentrations of glutamate and GABA in the hippocampus of aged rats. *Brain Res Bull* **70**(1): 8-14.
- Sohlberg, M. M. and Mateer, C. A. (1987). Effectiveness of an attention-training program. *J Clin Exp Neuropsychol* **9**(2): 117-30.
- Sohlberg, M. M., McLaughlin, K. A., Pavese, A., Heidrich, A. and Posner, M. I. (2000). Evaluation of attention process training and brain injury education in persons with acquired brain injury. *J Clin Exp Neuropsychol* **22**(5): 656-76.
- Spence, C. and Driver, J. (1997). On measuring selective attention to an expected sensory modality. *Percept. Psychophys.* **59**(3): 389-403.
- Spence, C., Nicholls, M. E. and Driver, J. (2001). The cost of expecting events in the wrong sensory modality. *Percept. Psychophys.* **63**(2): 330-6.
- Spitzer, H., Desimone, R. and Moran, J. (1988). Increased attention enhances both behavioral and neuronal performance. *Science* **240**(4850): 338-40.
- Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* **18**(6): 643-662.

- Strupp, M., Arbusow, V., Borges, P. C., Dieterich, M. and Brandt, T. (1999). Subjective straight-ahead during neck muscle vibration: effects of ageing. *Neuroreport* **10**(15): 3191.
- Talsma, D., Doty, T. J., Strowd, R. and Woldorff, M. G. (2006). Attentional capacity for processing concurrent stimuli is larger across sensory modalities than within a modality. *Psychophysiology* **43**(6): 541-9.
- Talsma, D., Doty, T. J. and Woldorff, M. G. (2007). Selective attention and audiovisual integration: is attending to both modalities a prerequisite for early integration? *Cereb Cortex* **17**(3): 679-90.
- Tellinghuisen, D. J. and Nowak, E. J. (2003). The inability to ignore auditory distractors as a function of visual task perceptual load. *Percept Psychophys* **65**(5): 817-28.
- Tun, P. A., O'Kane, G. and Wingfield, A. (2002). Distraction by competing speech in young and older adult listeners. *Psychol Aging* **17**(3): 453-67.
- Tzourio, N., Massiou, F. E., Crivello, F., Joliot, M., Renault, B., et al. (1997). Functional anatomy of human auditory attention studied with PET. *Neuroimage* **5**(1): 63-77.
- West, R. (1999). Visual distraction, working memory, and aging. *Mem Cognit* **27**(6): 1064-72.
- Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., et al. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *Jama* **296**(23): 2805-14.
- Woldorff, M. G., Gallen, C. C., Hampson, S. A., Hillyard, S. A., Pantev, C., et al. (1993). Modulation of early sensory processing in human auditory cortex during auditory selective attention. *Proc Natl Acad Sci U S A* **90**(18): 8722-6.
- Wood, K. M., Edwards, J. D., Clay, O. J., Wadley, V. G., Roenker, D. L., et al. (2005). Sensory and cognitive factors influencing functional ability in older adults. *Gerontology* **51**(2): 131-41.

CHAPTER IV

A COGNITIVE TRAINING INTERVENTION INCREASES RESTING CEREBRAL BLOOD FLOW IN HEALTHY OLDER ADULTS

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The following chapter has been submitted for review to *Human Brain Mapping*. Revisions to the manuscript were made for stylistic consistency. JLM performed the experiments and wrote the manuscript, SH created the power maps, and PJL worked in an advisory and editorial capacity.

Abstract

Healthy aging is typically accompanied by some decline in cognitive performance, as well as by alterations in brain structure and function. Here we report the results of a randomized, controlled trial designed to determine the effects of a novel cognitive training program on resting cerebral blood flow and gray matter volume in healthy older adults. Sixty-six healthy older adults participated in eight weeks of either a training program targeting attention and distractibility or an educational control program. This training program produced significantly larger increases in resting cerebral blood flow to the prefrontal cortex than the control program. Increases in blood flow were associated with reduced susceptibility to distraction after training, but not with alterations in gray matter volume. These data demonstrate that cognitive training can improve resting cerebral blood flow in healthy older adults and that cerebral perfusion rates may be a more sensitive indicator of the benefits of cognitive training than volumetric analyses.

4.1 Introduction

Changes that occur in the aging brain can produce alterations in a variety of sensory and cognitive functions. Even healthy older adults typically exhibit significant deficits in memory, attention, and other executive functions (Park et al., 2002; Verhaeghen and Cerella, 2002; Buckner, 2004; Rhodes, 2004; Isingrini et al., 2008). For example, in a large sample of adults age 20 to 92, Park and colleagues (2002) demonstrated age-related declines in across several cognitive domains, including speed of processing, working memory, and long-term memory. A number of studies also indicate that older adults process more extraneous sensory information and are more distractible than their young counterparts (Alain and Woods, 1999; Rowe et al., 2006; Yang and Hasher, 2007; Hugenschmidt et al., 2009).

The frontal cortex, which supports many of these higher-level cognitive functions, is known to be particularly susceptible to many age-related changes, including reductions in blood flow (Martin et al., 1991; Schultz et al., 1999; Meltzer et al., 2000; Parkes et al., 2004; Asllani et al., 2009; Bertsch et al., 2009), metabolic rates (Marchal et al., 1992; Bentourkia et al., 2000), white matter integrity (Salat et al., 2005; Hugenschmidt et al., 2008), tissue volume (Good et al., 2001; Resnick et al., 2003; Raz et al., 2004; Raz et al., 2005; Salat et al., 2009), and cortical thickness (Salat et al., 2004; Fjell et al., 2009). Brain atrophy, or age-related decreases in the amount of gray matter relative to white matter or cerebrospinal fluid present in a given voxel, can artificially inflate measured differences in cerebral blood flow (CBF) between younger and older adults; however, a recent study by Asllani et al. (2009) reported that older adults have a global decrease in CBF of ~15%, even after correcting for these partial volume effects. In addition to

confirming that there are *global* reductions in CBF, these experiments also demonstrated that tissue loss did not fully account for *local* age-related decreases in CBF in several brain areas, including the cingulate gyrus, the frontal cortex, and the hippocampus (Asllani et al., 2009).

Despite these age-related alterations in brain structure and function, the aging brain does maintain some ability to adapt and change in response to environmental demands (Churchill et al., 2002; Kempermann et al., 2002; Kramer et al., 2004; Burke and Barnes, 2006; Mora et al., 2007; Jessberger and Gage, 2008). Several interventional studies have capitalized on this plasticity to improve cognitive function in older adults with training programs that target memory, attention, reasoning, and speed of processing (Kramer et al., 1995; Ball et al., 2002; Jennings et al., 2005; Mahncke et al., 2006; Erickson et al., 2007; Bherer et al., 2008; Buschkuhl et al., 2008; Dahlin et al., 2008b; Mozolic et al., in press). In a large, randomized controlled trial known as the ACTIVE study, participants trained in memory, speed of processing, or reasoning showed significant improvements in the trained domains, and these improvements were maintained over a 5-year follow-up interval (Ball et al., 2002; Willis et al., 2006).

A number of other studies have used neuroimaging to identify modifications in brain structure and function that are associated with various training regimens (Draganski et al., 2004; Golestani and Zatorre, 2004; Olesen et al., 2004; Draganski et al., 2006; May et al., 2007; Ilg et al., 2008; Hyde et al., 2009); however, fewer have investigated training-induced plasticity in the *aging* brain (Nyberg et al., 2003; Colcombe et al., 2004; Colcombe et al., 2006; Erickson et al., 2007; Pereira et al., 2007; Boyke et al., 2008; Dahlin et al., 2008a). Colcombe et al. (2004) demonstrated that cardiovascular fitness

training in older adults improved performance and increased activity in the prefrontal and parietal cortex during performance on a task of executive function. Similar aerobic exercise interventions have also been shown to increase both gray matter (GM) volume in the anterior cingulate, right frontal, and left temporal cortices and white matter (WM) volume in the anterior corpus callosum (Colcombe et al., 2006), and to increase cerebral blood volume in the hippocampus in healthy older adults (Pereira et al., 2007). Cognitive training interventions have also been shown to successfully alter task-related neural activity in older adults (Nyberg et al., 2003; Erickson et al., 2007; Dahlin et al., 2008a), yet little is known about alterations in resting brain activity or blood flow following cognitive training in older adults.

We have recently reported on the behavioral improvements that result from a multisensory attention training program in older adults (Mozolic et al., in press); however it is unknown how these improvements may relate to underlying changes in brain function or structure. After completing an eight-week cognitive training program designed to decrease distractibility, older adults exhibited significantly greater reductions in interference from cross-modal distractors than controls. Improvements for participants in the treatment group also generalized to several other measures of executive function (Mozolic et al., in press). In the present report, we investigate the effects of this training program on regional CBF during rest and GM volume. To our knowledge, this is the first reported investigation of cognitive training-induced changes in brain structure and resting CBF in healthy older adults. Specifically, we hypothesized that this training regimen, which required repeated practice at suppressing distracting stimuli during demanding cognitive tasks, would increase resting CBF in the prefrontal cortex (PFC), a brain area

known to be involved in attention and inhibition (Corbetta and Shulman, 2002; Fassbender et al., 2004; Shomstein and Yantis, 2004; Weissman et al., 2004). Additionally, we expected that there would be an increase in GM volume in regions of the PFC supporting these executive functions trained during the intervention. Finally, we anticipated that changes in regional CBF and GM volume would be correlated with the behavioral improvements produced by this novel training program.

4.2 Methods

This study used a single-blind, randomized controlled design to determine the effects of attention training on cerebral blood flow and gray matter volume in healthy older adults. Details of the interventions and the behavioral improvements resulting from this attention training program have been detailed previously (Mozolic et al., in press), and will not be the focus of this report.

4.2.1 Participants

Seventy-five healthy older adults between the ages of 65 and 75 were recruited from the community and screened for eligibility in this study. Sixty-six participants were determined to be eligible for the study and were randomized to either the treatment or the control group. Due to scheduling constraints and MR incompatibility, only 58 subjects completed all scanning and training sessions and will be considered in the remainder of this report ($n_{\text{treatment}} = 27$, $n_{\text{control}} = 31$, mean age = 69.5, 31 females). Technical limitations precluded the interpretation of perfusion data collected from 10 of the participants, so all CBF data reported are for 48 subjects $n_{\text{treatment}} = 23$, $n_{\text{control}} = 25$, mean

age = 69.3, 26 females). Demographic data for participants is reported in Table 4.1. All participants signed an informed consent and were compensated approximately \$20 per hour for their participation in the study. All study procedures were approved by and conducted in accordance with the Wake Forest University School of Medicine Institutional Review Board.

Potential participants had to meet all of the following inclusion criteria for enrollment in the study: corrected visual acuity of 20/40 or better in both eyes; normal color vision; hearing loss no greater than 50 dB at 1000 and 2000 Hz; a Mini-Mental Status Exam score within 2.5 standard deviations of the mean for their age and education level (Bravo and Hebert, 1997); no evidence of current substance abuse, indicated by a score below 10 on the Alcohol Use Disorders Identification Test (Bohn et al., 1995) and an evaluation of participant medical history; no evidence of depression, evaluated using the Medical Care Corporation survey (www.mccare.com); no previous brain surgery, CNS trauma, neurological disorder, or use of antipsychotic or antiepileptic drugs, as determined by an evaluation of participant medical history.

4.2.2 Design

Once participants were enrolled and randomized into the study, they completed a pre-training MRI scan to evaluate resting cerebral blood flow and anatomical structure. Participants then began eight weeks of either the treatment or control training program. Participants in both groups came to the laboratory for one hour each week (total training time = eight hours). After finishing their respective training programs, all participants

TABLE 4.1 Demographic data for imaging study participants

<i>Imaging study participants</i>			
	Treatment	Control	p-value
Age, years	69.5 (3.2)	69.5 (2.5)	1.00
Sex, # females	14	17	
Education, years	15.1 (2.0)	16.0 (3.2)	0.20
MMSE, score	28.3 (1.6)	28.5 (1.9)	0.80
<i>Subset included in CBF analyses</i>			
Age, years	69.3 (3.2)	69.4 (2.4)	0.95
Sex, # females	12	14	
Education, years	15.0 (2.0)	16.2 (3.0)	0.11
MMSE, score	28.3 (1.6)	28.7(1.6)	0.33

Standard deviations are in parentheses and p-values are from the results of two-tailed t-tests comparing the means of the treatment and control groups.

completed a post-training MRI scan to re-evaluate cerebral blood flow brain structure. All participants also completed pre- and post-training cognitive evaluations.

4.2.3 Interventions

Briefly, the treatment program was an individualized attention training program targeting auditory and visual attention that significantly decreased cross-modal distraction in this population. During training, participants practiced active suppression of irrelevant distractors while completing visual and auditory attention tasks. Visual and auditory tasks were paired with cross- and within-modality distractors. Tasks required detecting, classifying, and/or sequencing visual or auditory presentations of letters, words, and numbers while ignoring very salient auditory or visual distractors. Several of these task components were adapted from the commercially available APT-II program (Lash & Associates Publishing / Training, Inc., Wake Forest, NC; (Sohlberg and Mateer, 1987; Sohlberg et al., 2000; Lopez-Luengo and Vazquez, 2003). Distractors were series of short video clips (for visual distractors) or sound clips (for auditory distractors) of people, places, and events that provided distraction for the entire duration of each task (2-5 min). All task stimuli and distractors were presented to participants on a movie screen and overhead speakers via an LCD projector and participants made responses on each task by giving verbal or hand-written answers. Stimuli were sent to the LCD projector from a laptop computer with Presentation software (www.neurobs.com). A member of the study staff was always present in the training room to record responses, monitor performance, provide feedback, and control task presentation. Task difficulty for each participant increased adaptively, based on their performance on previous tasks. This

design provided participants with repeated, continually challenging practice at suppressing distracting stimuli within and across modalities while completing demanding cognitive tasks.

The goal of the control program was to provide control participants with the same number and duration of laboratory visits, as well as similar interactions with study staff as participants in the treatment group, but without focused training on suppressing distractors. This was achieved using a small-group educational lecture program that required control participants to come into the laboratory one hour each week for eight weeks, just like the treatment group. Instead of completing the distractor tasks, however, the control group attended interactive lectures on various health topics (nutrition, heart disease, etc.). Administration of pre- and post-lecture quizzes, as well as weekly interactions with doctors, nurses, and therapists during these control sessions, helped maintain the single-blind design of the study. That is, participants were told that the purpose of the study was to evaluate the effects of two different training programs, and they were unaware that one training program had been designated the treatment group and the other was a control group.

4.2.4 MRI evaluations

During each MRI scan session, three different types of scans were performed: (1) a perfusion scan for evaluation of resting cerebral blood flow; (2) a T-1 weighted, high-resolution structural scan; and (3) two BOLD fMRI scans of functional activity during cognitive tasks. Data from the functional scans will be presented in the following chapter.

The perfusion scan measured regional CBF using pulsed arterial spin labeling (PASL), a non-invasive MRI technique that uses magnetically labeled arterial blood water as an endogenous tracer for quantifying blood flow (Yang, 2002). By subtracting sequential images acquired with and without spin labeling, it is possible to obtain a measure of tissue perfusion (Wong et al., 1998). During the 8.5-minute perfusion scan, participants rested quietly with their eyes open. Participants viewed a gray cross on a black background, presented through MR-compatible goggles with an integrated infrared eye tracker (Resonance Technology, Inc., Northridge, CA) to ensure that subjects kept their eyes open throughout the experiment. A high-resolution anatomical image acquired for each participant was used to assess voxel-wise changes in gray matter volume with voxel-based morphometry (VBM).

4.2.5 MRI acquisition and Image Processing

All images were acquired with a 1.5T GE scanner using a 4-channel, quadrature phased array, neurovascular head coil (GE Medical Systems, Milwaukee, WI). To assess CBF, the PASL scan employed Quantitative Imaging of Perfusion using a Single Subtraction with thin slice periodic saturation with a Flow-sensitive Alternating Inversion Recovery (Q2TIPS-FAIR) (Kim and Tsekos, 1997; Luh et al., 1999). Q2TIPS-FAIR acquires data in label/control pairs that are subtracted to generate a perfusion-weighted image. Imaging parameters were as follows: echo time= 28ms; TI_1 = 800ms; TI_{1s} = 1200ms; TI = 2000ms; TR = 3000ms; receiver bandwidth= 62.5 kHz; flip angle= 90 degrees; field of view= 24 cm (frequency) x 18 cm (phase); and acquisition matrix= 64 x 48 (11 slices, 8 mm thickness, 0 mm slice gap). A diffusion gradient with an equivalent b

value of 5.25 mm²/sec is added to suppress intra-arterial spins (Yang et al., 1998). Prior to statistical analyses, motion correction was applied to the perfusion weighted volumes with a six-parameter rigid body transformation. After motion correction, the difference images were averaged together and quantitative perfusion maps were calculated from the equation:

$$CBF = \frac{\Delta M(TI_2)}{2 M_{0,blood} \alpha TI_1 q_p(T_{1,tissue}, T_{1,blood}, TI_2)} e^{\left(\frac{TI_2}{T_{1,blood}}\right)}$$

where $\Delta M(TI_2)$ is the mean difference in signal intensity between label and control images, $M_{0,blood}$ is the equilibrium magnetization of blood, α is the tagging efficiency, TI_1 is the time duration of the tagging bolus, TI_2 is the inversion time of each slice, $T_{1,blood}$ is the longitudinal relaxation time of blood, and q_p is a correction factor that accounts for the difference between T1 of blood and T1 of brain tissue (Wong et al., 1998). All other parameters are known or assumed to be constant ($\alpha = 0.95$, $TI_1 = 800$ ms, $T_{1,blood} = 1200$ ms). These quantitative CBF maps measure perfusion in each voxel in units of ml of blood / 100 g of tissue / minute. Quantitative CBF maps for each subject were normalized to the EPI template in SPM5 (Wellcome Department of Cognitive Neurology, London, www.fil.ion.ucl.ac.uk/spm/software/spm5/).

High-resolution, T1-weighted structural scans were obtained using an inversion recovery 3D spoiled gradient echo sequence (matrix size= 256 x 256; field of view= 24 cm; 1.5 mm sections, no gap; 128 slices; in-plane resolution= 0.94 mm). To assess local changes in tissue volume, we used VBM, implemented in SPM5. This method segments each participant's structural image into tissue types (GM, WM, and CSF), performs bias correction (for image intensity inhomogeneities), and spatially normalizes the image to

the standard MNI template in a unified, iterative process (Ashburner and Friston, 2005). To investigate the absolute volume of gray matter rather than relative concentrations, voxel values were modulated by the Jacobian determinants derived during the spatial normalization (Good et al., 2001).

4.2.6 Statistical analysis

All statistical analyses were performed in SPM5, implemented in Matlab (Mathworks, Inc., Sherborn, MA). To compare training-induced changes in regional CBF between the groups, we first created a perfusion difference map for each subject by subtracting their pre-training image from their post-training image. These difference images were smoothed with an 8 x 8 x 10 mm Gaussian kernel. A two-sample t-test was then used to compare voxel-wise differences in CBF changes between the treatment and control groups. Results were thresholded at $p < 0.001$ with an extent correction of $p < 0.05$. To confirm that any changes in CBF were local, rather than global, we also performed a $2_{\text{group}} \times 2_{\text{session}}$ mixed ANOVA on whole-brain average GM perfusion values. A p-value less than 0.05 was considered statistically significant for this analysis.

We followed a similar procedure to evaluate group differences in GM volume changes. Difference maps were created by subtracting each participant's modulated, normalized, segmented GM image pre-training image from the post-training one. These images were then smoothed with an 8 mm isotropic Gaussian kernel. A two-sample t-test compared differences in training-induced GM changes between the two groups. In addition to the whole-brain VBM analyses, we also evaluated GM changes in a region of interest (ROI) created from the group CBF analysis. This ROI was defined by a binary

mask of all significant voxels found in the whole-brain group comparison of CBF changes. A $2_{\text{group}} \times 2_{\text{session}}$ ANOVA was used to assess changes in GM volume in the ROI.

To determine whether there was a significant relationship between regional CBF change and alterations in GM structure with training, we performed a voxel-wise correlation analysis between CBF difference images and GM difference images for each participant using the Biological Parametric Mapping (BPM) toolbox (Casanova et al., 2007). BPM utilizes the general linear model to perform multimodal image analyses on a voxel-by-voxel basis, so this analysis completed a unique correlation between the perfusion image and the anatomical GM image at each voxel.

To assess the relationship between the imaging results and behavioral improvements following attention training, we also performed a correlation between perfusion change values extracted from the CBF ROI (defined above) and response time interference on a cross-modal distraction task performed by participants during pre- and post-training cognitive testing. In this task, auditory distractors can interfere with responses to visual targets. After completion of the training program, however, the treatment group demonstrated significant reductions in interference, relative to controls (Mozolic et al., in press). Therefore, we expected larger training-induced increases in regional CBF among participants who showed greater reductions cross-modal distraction.

Finally, to explore the power of our findings and plan for future studies, we calculated voxel-wise power maps (Hayasaka et al., 2007) to depict the statistical power and number of subjects needed to detect training-induced changes in cerebral blood flow in regions that did not achieve significance in the current study. Power maps were based

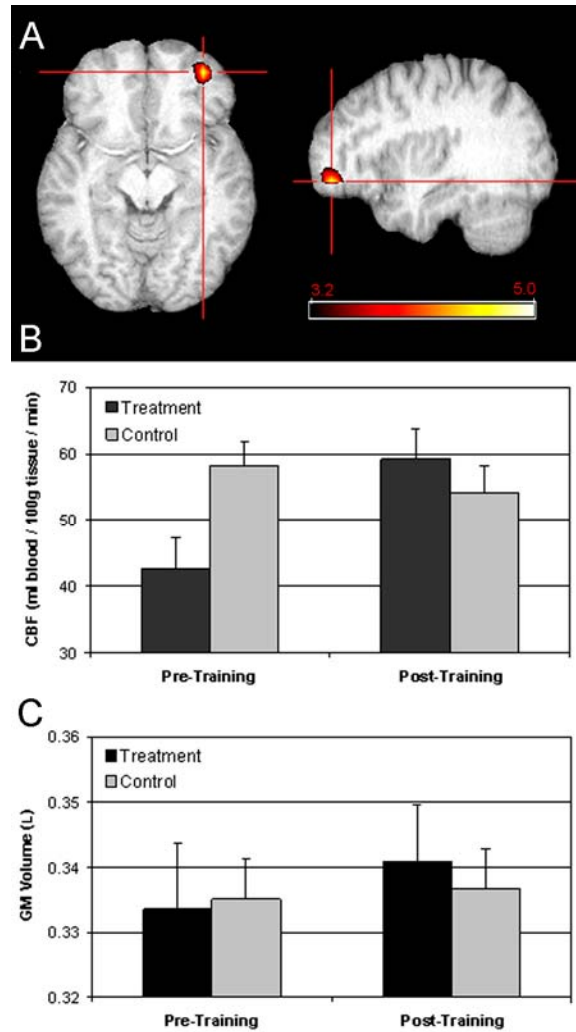
on the effect size produced by the following group contrast: $\Delta \text{CBF}_{\text{treatment}} > \Delta \text{CBF}_{\text{control}}$. In each voxel, we performed 2 calculations: (1) the number of subjects required in each group to detect a significant finding with 80% power and $p < 0.05$ with a family-wise error rate (FWE) correction for multiple comparisons; and (2) the power ($1-\beta$) to detect significant changes, given $n = 50$ subjects in each group. These analyses generated one map where the intensity in each voxel represents the number of subjects that would be required to detect a significant finding in that voxel, and a second map where the intensity represents the power that would be achieved in that voxel if the study included 50 subjects per group.

4.3 Results

In a voxel-wise analysis of CBF, the treatment group had significantly larger training-induced increases in perfusion than controls in right inferior frontal cortex (IFC; peak voxel MNI coordinates: 40, 48, -15; Figure 4.1A). Mean perfusion values extracted from this cluster increased from 42.6 to 59.2 ml / 100 g tissue / min for the treatment group, and decreased slightly for the control group, from 58.1 to 54.2 ml / 100 g tissue / min (Figure 4.1B).

When the treatment group and control group were each analyzed separately, there were no brain regions that showed significant pre- to post-training increases for either group; however, there were sub-threshold ($p < 0.001$, uncorrected) increases in CBF to the left anterior cingulate cortex (peak voxel: -8, 36, -10) and the right inferior frontal cortex (peak voxel: 24, 48, -10) after the treatment intervention. No sub-threshold changes were observed for the control group. When the pre-training and post-training time points were

FIGURE 4.1 Results of a whole-brain voxel-wise analysis of training-induced changes in regional CBF, and ROI analyses of quantitative perfusion and gray matter volume



Whole-brain voxel-wise analysis of training-induced changes in CBF indicated that the treatment program produced larger increases in CBF to the right inferior prefrontal cortex than the control program (A). Quantitative perfusion values extracted from the region shown in Fig. 4.1A increased from 43.6 to 59.2 ml / 100 g / min for the treatment group and decreased slightly, from 58.1 to 54.2 ml / 100 g / min for the control group (B). There were no significant changes in GM volume in this region for either the treatment group or controls (C).

each considered separately, no voxels differed significantly between the two groups at either time point; however, there was a region of the left inferior frontal cortex (peak voxel: -12, 40, -20) that showed lower CBF for the treatment group relative to controls prior to training (sub-threshold; $p < 0.001$, uncorrected). Post-training, there were no differences between the two groups at this lowered threshold. These sub-threshold results are reported to aid in the overall interpretation of the findings; however, only the between-group comparison of training-induced changes in regional CBF, reported at the beginning of this section, yielded significant findings.

The analysis of whole-brain average GM perfusion yielded no significant effects of group or session and no significant group $\times$ session interaction (all $F_{1,46} < 2.0$, all $p > 0.10$). These results suggest that larger increases in regional CBF for the treatment group, relative to controls, reflect local changes in perfusion and are not an artifact of global differences in blood flow.

In a whole-brain evaluation of GM volume, there were no areas of significant difference between the treatment and control groups. We also restricted our analysis of GM volume changes to the brain areas that showed training-induced increases in CBF. However, this ROI analysis yielded no significant effects of group or session, and no significant group $\times$ session interaction (all $F_{1,55} < 2.7$, all $p > 0.10$; Figure 4.1C). To further investigate any relationship between changes in CBF and GM volume, we performed a voxel-wise correlation analysis for each between pre-to-post CBF values and pre-to-post GM volumes for each participant. We found no significant correlation in any brain region between training-induced changes in perfusion and GM volume. These

results indicate that increased CBF to the right IFC following cognitive training was not accompanied by measureable alterations in GM volume.

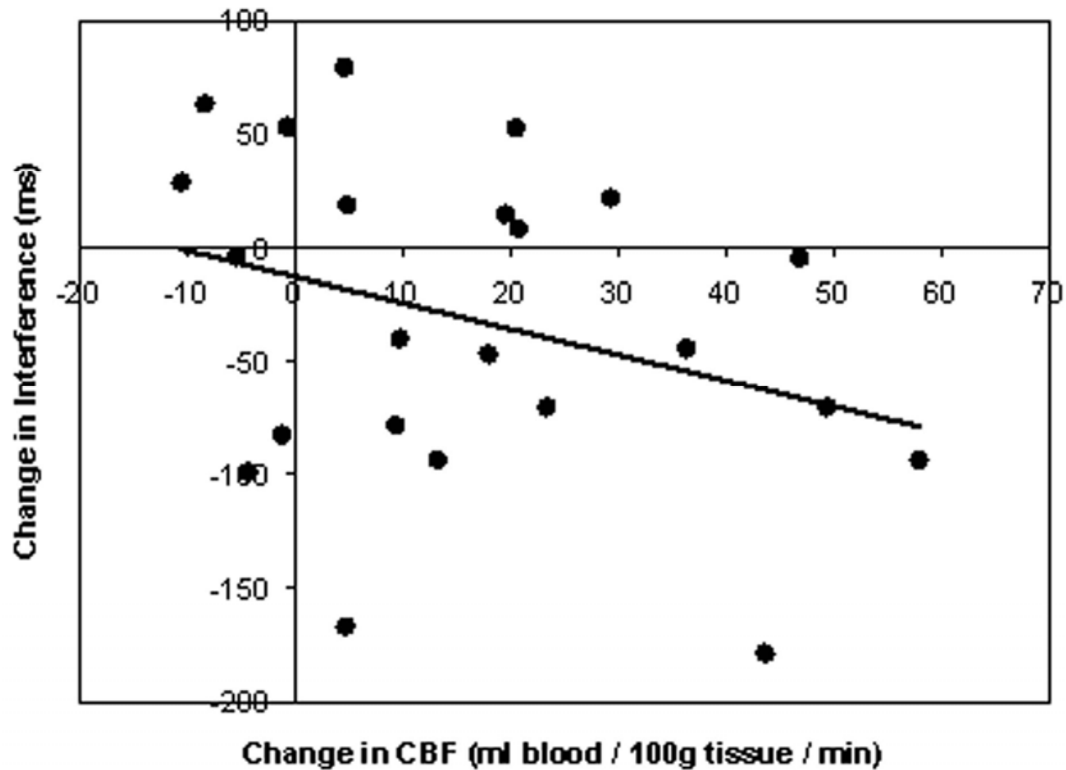
A correlation analysis of CBF changes and behavioral outcomes following training indicated that there was a modest relationship between increased perfusion in the right IFC ROI and reduced cross-modal distraction (Pearson's $r_{21} = -0.32$, $p < 0.07$; Figure 4.2). Importantly, these data suggest that participants who demonstrated larger increases in perfusion following attention training were also likely to be better at suppressing distracting cross-modal stimuli.

Voxel-wise power calculations based on the effect size observed in this study were used to generate a map of the number of subjects per group that would be required to detect significant training-induced increased in regional CBF (at 80% power, $p < 0.05$ FWE correction; Figure 4.3A). This map demonstrates that the addition of several subjects in each group could reveal further areas of CBF increase, including bilateral IFC, rostral anterior cingulate cortex (ACC), and medial frontal cortex (MFC). A second map generated using the voxel-wise power calculations indicated that the statistical power to detect training-induced effects, given $n = 50$ subjects per group, would be near 70% for regions in right IFC, rostral ACC, and MFC (Figure 4.3B)

4.4 Discussion

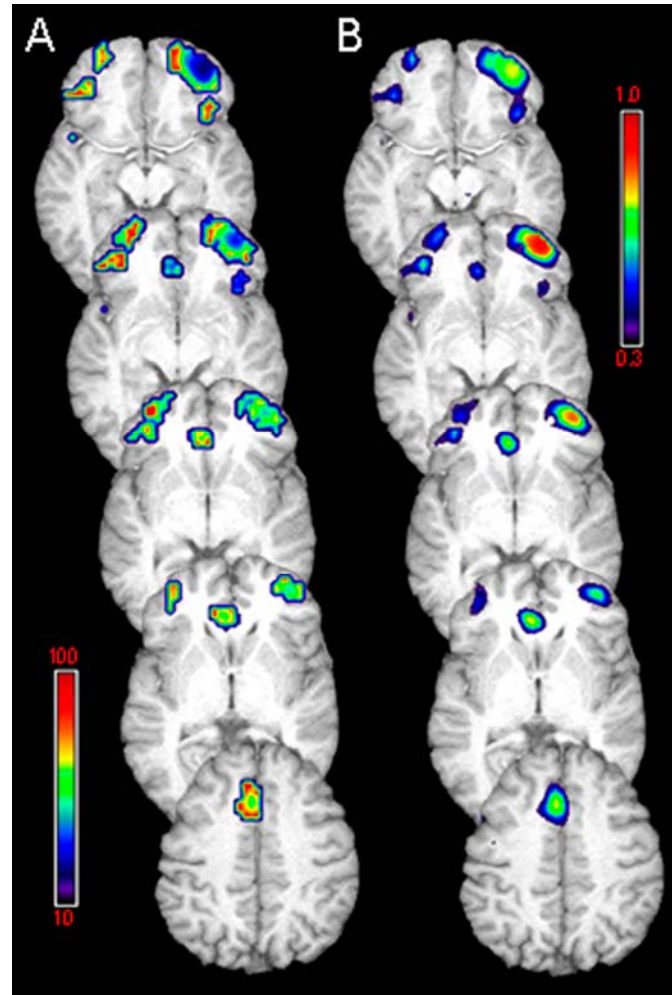
The data presented here demonstrate that a cognitive training program aimed at reducing distractibility in older adults produces larger increases in resting CBF than a control program. These are, to our knowledge, the first data demonstrating that a cognitive training intervention can improve resting perfusion rates in healthy older adults.

FIGURE 4.2 Correlation analysis of training-induced increases in regional CBF at rest and behavioral reductions in cross-modal interference



Training-induced increases in resting CBF in the right inferior PFC were modestly correlated with behavioral reductions in cross-modal interference after training. Analysis of individual perfusion change values (extracted from the region depicted in Fig. 4.1A) and changes in the response time to visual targets during auditory distraction yielded a marginally significant negative correlation (Pearson's $r = -0.32$, $p < 0.07$). Decreases in response time to visual targets during auditory distraction were indicative of reductions in behavioral interference.

FIGURE 4.3 Exploratory analyses of sample size and power level for prospective detection of significant training-related changes in regional CBF



Exploratory analyses based on observed changes in CBF for treatment versus controls yielded voxel-wise estimates of the number of subjects required in each group to detect a significant finding with 80% power (A), and the power to detect significant changes, given 50 subjects in each group (B). Future studies that add several subjects to each group could reveal more extensive areas of CBF increase, including bilateral IFC, rostral ACC, and MFC (A - voxel intensity represents number of subjects required for significant finding, $p < 0.05$, FWE corrected). The statistical power to detect training-induced effects, with 50 subjects per group, would be near 70% for right IFC, rostral ACC, and MFC (B - voxel intensity indicates power level with $n = 50$).

In a whole-brain analysis of training-induced changes, the right IFC exhibited larger CBF increases in the treatment group than in the control group. Further, there was a modest correlation between enhanced CBF in this region and reduced cross-modal distraction following training, suggesting an important link between perfusion increases and behavioral improvements.

The rostral inferior region of the prefrontal cortex (corresponding with Brodmann's Area 10) that exhibited training-induced CBF increases is highly interconnected with other areas of the PFC, as well as the cingulate cortex (Barbas and Pandya, 1989; Arikuni et al., 1994; Ramnani and Owen, 2004). Cells of the rostral PFC also have a very high density of dendritic spines relative to other areas of the PFC, suggesting that this area plays an important role in integrating incoming information (Jacobs et al., 2001; Ramnani and Owen, 2004). Additionally, this region has been implicated in a number of the functions required for successful completion of training tasks, including maintenance of attentional set, prospective memory, and multi-tasking (Koechlin et al., 1999; Burgess et al., 2001; Velanova et al., 2003; Burgess et al., 2007; Dreher et al., 2008). For example, a representative training task visually presented a series of words during ongoing auditory noise. Participants were required to press a buzzer only on target words (i.e. words that contained one more letter than the previous words) and to ignore salient auditory distractors. Repeated engagement of rostral frontal cortex networks during such training tasks that exercise prospective memory and multiple task demands may have altered synaptic connectivity or metabolic demand and resulted in the observed increase in resting perfusion rates.

The results of this study are also in accord with data from a number of experiments demonstrating that increased frontal activity corresponds with improved outcomes for older adults on a wide range of cognitive tasks (Grady, 1996; Reuter-Lorenz et al., 2000; Cabeza et al., 2002; Langenecker and Nielson, 2003; Cabeza et al., 2004; Grady et al., 2005); although see also (Colcombe et al., 2005; Rypma et al., 2005). For example, Cabeza and colleagues (2002) have shown that older adults who exhibited increased bilateral PFC activity compared to young adults during source memory retrieval also displayed superior performance on this task relative to older adults who did not increase bilateral frontal activity. Increased regional CBF observed in our study may be a compensatory mechanism activated by training to overcome neural or metabolic declines in the PFC, although evidence for this hypothesis is limited by the lack of a young control group in this study.

Because this was a relatively small pilot study powered to detect behavioral changes associated with training, we also examined the power of the perfusion finding and the sample size required to detect changes in regions that did not achieve significance in this study. These exploratory analyses indicated that sub-threshold increases in CBF extended bilaterally in the rostral IFC and also included regions of the anterior cingulate cortex. Thus, future studies with larger sample sizes may be able to detect more widespread increases in perfusion after cognitive training.

In contrast to the perfusion results and our initial hypothesis, we observed no significant change in GM volume following training. Voxel-wise correlations between Δ CBF and Δ GM volume also indicated that there was no significant relationship between perfusion changes and alterations in brain structure. These results suggest that training-

induced increases in resting CBF were not accompanied by any detectable growth of cortical or subcortical tissue. Based on these findings, it is possible that the cerebral vasculature response to cognitive training may be a more sensitive marker for evaluating short-term interventional outcomes than VBM. Although previous studies have demonstrated increases in tissue volume following training in older adults, these interventions involved aerobic exercise (Colcombe et al., 2006) or skill learning (Boyke et al., 2008), rather than cognitive training. Animal models indicate that environmental enrichment, which typically encourages both motor activity and spatial learning, can promote neuronal proliferation and survival in the hippocampus as well as dendritic branching in the cerebellum of aging rodents (Greenough et al., 1986; Churchill et al., 2002; Kempermann et al., 2002). It may be possible that cognitive training alone is not sufficient to produce noticeable changes in GM volume; however, combining practice on cognitive and motor tasks with cardiovascular fitness training regimens could yield larger results than any individual component.

In conclusion, the results of this study demonstrate that a cognitive training program that reduces cross-modal distraction in older adults also produces larger increases in CBF to the prefrontal cortex than a control program. These changes were not accompanied by alterations in tissue volume, but were modestly correlated with behavioral improvements, suggesting that CBF may be a more sensitive marker of training-induced improvements than GM volume. Future trials that integrate various training modalities or larger study populations may generate more widespread functional and structural brain changes and additional functional gains for older adults.

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REFERENCES

- Alain, C. and Woods, D. L. (1999). Age-related changes in processing auditory stimuli during visual attention: evidence for deficits in inhibitory control and sensory memory. *Psychol Aging* **14**(3): 507-19.
- Arikuni, T., Sako, H. and Murata, A. (1994). Ipsilateral connections of the anterior cingulate cortex with the frontal and medial temporal cortices in the macaque monkey. *Neurosci Res* **21**(1): 19-39.
- Ashburner, J. and Friston, K. J. (2005). Unified segmentation. *Neuroimage* **26**(3): 839-51.
- Asllani, I., Habeck, C., Borogovac, A., Brown, T. R., Brickman, A. M., et al. (2009). Separating function from structure in perfusion imaging of the aging brain. *Hum Brain Mapp*.
- Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., et al. (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. *Jama* **288**(18): 2271-81.
- Barbas, H. and Pandya, D. N. (1989). Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *J Comp Neurol* **286**(3): 353-75.
- Bentourkia, M., Bol, A., Ivanoiu, A., Labar, D., Sibomana, M., et al. (2000). Comparison of regional cerebral blood flow and glucose metabolism in the normal brain: effect of aging. *J Neurol Sci* **181**(1-2): 19-28.
- Bertsch, K., Hagemann, D., Hermes, M., Walter, C., Khan, R., et al. (2009). Resting cerebral blood flow, attention, and aging. *Brain Res*.
- Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., et al. (2008). Transfer effects in task-set cost and dual-task cost after dual-task training in older and younger adults: further evidence for cognitive plasticity in attentional control in late adulthood. *Exp Aging Res* **34**(3): 188-219.
- Bohn, M. J., Babor, T. F. and Kranzler, H. R. (1995). The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. *J.Stud.Alcohol* **56**(4): 423.
- Boyke, J., Driemeyer, J., Gaser, C., Buchel, C. and May, A. (2008). Training-induced brain structure changes in the elderly. *J Neurosci* **28**(28): 7031-5.
- Bravo, G. and Hebert, R. (1997). Age- and education-specific reference values for the Mini-Mental and modified Mini-Mental State Examinations derived from a non-demented elderly population. *Int J Geriatr Psychiatry* **12**(10): 1008-18.
- Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron* **44**(1): 195-208.
- Burgess, P. W., Gilbert, S. J. and Dumontheil, I. (2007). Function and localization within rostral prefrontal cortex (area 10). *Philos Trans R Soc Lond B Biol Sci* **362**(1481): 887-99.
- Burgess, P. W., Quayle, A. and Frith, C. D. (2001). Brain regions involved in prospective memory as determined by positron emission tomography. *Neuropsychologia* **39**(6): 545-55.
- Burke, S. N. and Barnes, C. A. (2006). Neural plasticity in the ageing brain. *Nat Rev Neurosci* **7**(1): 30-40.

- Buschkuhl, M., Jaeggi, S. M., Hutchison, S., Perrig-Chiello, P., D'Äpp, C., et al. (2008). Impact of working memory training on memory performance in old-old adults. *Psychology and Aging* **23**(4): 743.
- Cabeza, R., Anderson, N. D., Locantore, J. K. and McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage*. **17**(3): 1394.
- Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., et al. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cereb Cortex* **14**(4): 364-75.
- Casanova, R., Srikanth, R., Baer, A., Laurienti, P. J., Burdette, J. H., et al. (2007). Biological parametric mapping: A statistical toolbox for multimodality brain image analysis. *Neuroimage* **34**(1): 137-43.
- Churchill, J. D., Galvez, R., Colcombe, S., Swain, R. A., Kramer, A. F., et al. (2002). Exercise, experience and the aging brain. *Neurobiol Aging* **23**(5): 941-55.
- Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., et al. (2006). Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci* **61**(11): 1166-70.
- Colcombe, S. J., Kramer, A. F., Erickson, K. I. and Scalf, P. (2005). The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychol Aging* **20**(3): 363-75.
- Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., et al. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A* **101**(9): 3316-21.
- Corbetta, M. and Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat.Rev.Neurosci.* **3**(3): 201-215.
- Dahlin, E., Neely, A. S., Larsson, A., Backman, L. and Nyberg, L. (2008a). Transfer of learning after updating training mediated by the striatum. *Science* **320**(5882): 1510-2.
- Dahlin, E., Nyberg, L., Backman, L. and Neely, A. S. (2008b). Plasticity of executive functioning in young and older adults: Immediate training gains, transfer, and long-term maintenance. *Psychology and Aging* **23**(4): 720.
- Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., et al. (2004). Neuroplasticity: changes in grey matter induced by training. *Nature* **427**(6972): 311-2.
- Draganski, B., Gaser, C., Kempermann, G., Kuhn, H. G., Winkler, J., et al. (2006). Temporal and spatial dynamics of brain structure changes during extensive learning. *J Neurosci* **26**(23): 6314-7.
- Dreher, J. C., Koechlin, E., Tierney, M. and Grafman, J. (2008). Damage to the fronto-polar cortex is associated with impaired multitasking. *PLoS ONE* **3**(9): e3227.
- Erickson, K. I., Colcombe, S. J., Wadhwa, R., Bherer, L., Peterson, M. S., et al. (2007). Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging* **28**(2): 272-83.
- Fassbender, C., Murphy, K., Foxe, J. J., Wylie, G. R., Javitt, D. C., et al. (2004). A topography of executive functions and their interactions revealed by functional magnetic resonance imaging. *Brain Res.Cogn Brain Res.* **20**(2): 132.

- Fjell, A. M., Westlye, L. T., Amlien, I., Espeseth, T., Reinvang, I., et al. (2009). High Consistency of Regional Cortical Thinning in Aging across Multiple Samples. *Cereb Cortex*.
- Golestani, N. and Zatorre, R. J. (2004). Learning new sounds of speech: reallocation of neural substrates. *NeuroImage* **21**(2): 494.
- Good, C. D., Johnsruide, I. S., Ashburner, J., Henson, R. N., Friston, K. J., et al. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* **14**(1 Pt 1): 21-36.
- Grady, C. L. (1996). Age-related changes in cortical blood flow activation during perception and memory. *Ann N Y Acad Sci* **777**: 14-21.
- Grady, C. L., McIntosh, A. R. and Craik, F. I. (2005). Task-related activity in prefrontal cortex and its relation to recognition memory performance in young and old adults. *Neuropsychologia* **43**(10): 1466-81.
- Greenough, W. T., McDonald, J. W., Parnisari, R. M. and Camel, J. E. (1986). Environmental conditions modulate degeneration and new dendrite growth in cerebellum of senescent rats. *Brain Res* **380**(1): 136-43.
- Hayasaka, S., Peiffer, A. M., Hugenschmidt, C. E. and Laurienti, P. J. (2007). Power and sample size calculation for neuroimaging studies by non-central random field theory. *Neuroimage* **37**(3): 721-30.
- Hugenschmidt, C. E., Mozolic, J. L. and Laurienti, P. J. (2009). Suppression of multisensory integration by modality-specific attention in aging. *Neuroreport* **20**(4): 349-53.
- Hugenschmidt, C. E., Peiffer, A. M., Kraft, R. A., Casanova, R., Deibler, A. R., et al. (2008). Relating imaging indices of white matter integrity and volume in healthy older adults. *Cereb Cortex* **18**(2): 433-42.
- Hyde, K. L., Lerch, J., Norton, A., Forgeard, M., Winner, E., et al. (2009). Musical Training Shapes Structural Brain Development. *J. Neurosci.* **29**(10): 3019-3025.
- Ilg, R., Wohlschlager, A. M., Gaser, C., Liebau, Y., Dauner, R., et al. (2008). Gray Matter Increase Induced by Practice Correlates with Task-Specific Activation: A Combined Functional and Morphometric Magnetic Resonance Imaging Study. *J. Neurosci.* **28**(16): 4210-4215.
- Isingrini, M., Perrotin, A. and Souchay, C. (2008). Aging, metamemory regulation and executive functioning. *Prog Brain Res* **169**: 377-92.
- Jacobs, B., Schall, M., Prather, M., Kapler, E., Driscoll, L., et al. (2001). Regional dendritic and spine variation in human cerebral cortex: a quantitative golgi study. *Cereb Cortex* **11**(6): 558-71.
- Jennings, J., Webster, L., Kleykamp, B. and Dagenbach, D. (2005). Recollection Training and Transfer Effects in Older Adults: Successful Use of a Repetition-Lag Procedure. *Aging, Neuropsychology, and Cognition (Neuropsychology, Development and Cognition)* **12**(3): 278-298.
- Jessberger, S. and Gage, F. H. (2008). Stem-cell-associated structural and functional plasticity in the aging hippocampus. *Psychol Aging* **23**(4): 684-91.
- Kempermann, G., Gast, D. and Gage, F. H. (2002). Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Ann Neurol* **52**(2): 135-43.

- Kim, S. G. and Tsekos, N. V. (1997). Perfusion imaging by a flow-sensitive alternating inversion recovery (FAIR) technique: application to functional brain imaging. *Magn Reson Med* **37**(3): 425-35.
- Koechlin, E., Basso, G., Pietrini, P., Panzer, S. and Grafman, J. (1999). The role of the anterior prefrontal cortex in human cognition. *Nature* **399**(6732): 148-51.
- Kramer, A. F., Bherer, L., Colcombe, S. J., Dong, W. and Greenough, W. T. (2004). Environmental influences on cognitive and brain plasticity during aging. *J.Gerontol.A Biol.Sci.Med.Sci.* **59**(9): M940.
- Kramer, A. F., Larish, J. F. and Strayer, D. L. (1995). Training for attentional control in dual task settings: A comparison of young and old adults. *Journal of Experimental Psychology: Applied* **1**(1): 50-76.
- Langenecker, S. A. and Nielson, K. A. (2003). Frontal recruitment during response inhibition in older adults replicated with fMRI. *Neuroimage* **20**(2): 1384.
- Lopez-Luengo, B. and Vazquez, C. (2003). Effects of Attention Process Training on cognitive functioning of schizophrenic patients. *Psychiatry Res* **119**(1-2): 41-53.
- Luh, W. M., Wong, E. C., Bandettini, P. A. and Hyde, J. S. (1999). QUIPSS II with thin-slice T1 periodic saturation: a method for improving accuracy of quantitative perfusion imaging using pulsed arterial spin labeling. *Magn Reson Med* **41**(6): 1246-54.
- Mahncke, H. W., Connor, B. B., Appelman, J., Ahsanuddin, O. N., Hardy, J. L., et al. (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proc Natl Acad Sci U S A* **103**(33): 12523-8.
- Marchal, G., Rioux, P., Petit-Taboue, M. C., Sette, G., Traverre, J. M., et al. (1992). Regional cerebral oxygen consumption, blood flow, and blood volume in healthy human aging. *Arch Neurol* **49**(10): 1013-20.
- Martin, A. J., Friston, K. J., Colebatch, J. G. and Frackowiak, R. S. (1991). Decreases in regional cerebral blood flow with normal aging. *J Cereb Blood Flow Metab* **11**(4): 684-9.
- May, A., Hajak, G., Ganssbauer, S., Steffens, T., Langguth, B., et al. (2007). Structural Brain Alterations following 5 Days of Intervention: Dynamic Aspects of Neuroplasticity. *Cereb. Cortex* **17**(1): 205-210.
- Meltzer, C. C., Cantwell, M. N., Greer, P. J., Ben-Eliezer, D., Smith, G., et al. (2000). Does cerebral blood flow decline in healthy aging? A PET study with partial-volume correction. *J Nucl Med* **41**(11): 1842-8.
- Mora, F., Segovia, G. and del Arco, A. (2007). Aging, plasticity and environmental enrichment: structural changes and neurotransmitter dynamics in several areas of the brain. *Brain Res Rev* **55**(1): 78-88.
- Mozolic, J. L., Long, A. B., Morgan, A. R., Rawley-Payne, M. and Laurienti, P. J. (in press). A cognitive training intervention improves modality-specific attention in a randomized controlled trial of healthy older adults. *Neurobiol Aging*.
- Nyberg, L., Sandblom, J., Jones, S., Neely, A. S., Petersson, K. M., et al. (2003). Neural correlates of training-related memory improvement in adulthood and aging. *Proc Natl Acad Sci U S A* **100**(23): 13728-33.
- Olesen, P. J., Westerberg, H. and Klingberg, T. (2004). Increased prefrontal and parietal activity after training of working memory. *Nat Neurosci* **7**(1): 75-9.

- Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., et al. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychol Aging* **17**(2): 299-320.
- Parkes, L. M., Rashid, W., Chard, D. T. and Tofts, P. S. (2004). Normal cerebral perfusion measurements using arterial spin labeling: reproducibility, stability, and age and gender effects. *Magn Reson Med* **51**(4): 736-43.
- Pereira, A. C., Huddleston, D. E., Brickman, A. M., Sosunov, A. A., Hen, R., et al. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci U S A* **104**(13): 5638-43.
- Ramnani, N. and Owen, A. M. (2004). Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. *Nat Rev Neurosci* **5**(3): 184-94.
- Raz, N., Gunning-Dixon, F., Head, D., Rodrigue, K. M., Williamson, A., et al. (2004). Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. *Neurobiol Aging* **25**(3): 377-96.
- Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., et al. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex* **15**(11): 1676-89.
- Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B. and Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J Neurosci* **23**(8): 3295-301.
- Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., et al. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *J Cogn Neurosci* **12**(1): 174-87.
- Rhodes, M. G. (2004). Age-related differences in performance on the Wisconsin card sorting test: a meta-analytic review. *Psychol Aging* **19**(3): 482-94.
- Rowe, G., Valderrama, S., Hasher, L. and Lenartowicz, A. (2006). Attentional disregulation: a benefit for implicit memory. *Psychol Aging* **21**(4): 826-30.
- Rypma, B., Berger, J. S., Genova, H. M., Rebbeschi, D. and D'Esposito, M. (2005). Dissociating age-related changes in cognitive strategy and neural efficiency using event-related fMRI. *Cortex* **41**(4): 582-94.
- Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., et al. (2004). Thinning of the cerebral cortex in aging. *Cereb Cortex* **14**(7): 721-30.
- Salat, D. H., Greve, D. N., Pacheco, J. L., Quinn, B. T., Helmer, K. G., et al. (2009). Regional white matter volume differences in nondemented aging and Alzheimer's disease. *Neuroimage* **44**(4): 1247-58.
- Salat, D. H., Tuch, D. S., Hevelone, N. D., Fischl, B., Corkin, S., et al. (2005). Age-related changes in prefrontal white matter measured by diffusion tensor imaging. *Ann N Y Acad Sci* **1064**: 37-49.
- Schultz, S. K., O'Leary, D. S., Boles Ponto, L. L., Watkins, G. L., Hichwa, R. D., et al. (1999). Age-related changes in regional cerebral blood flow among young to mid-life adults. *Neuroreport* **10**(12): 2493-6.
- Shomstein, S. and Yantis, S. (2004). Control of attention shifts between vision and audition in human cortex. *J. Neurosci.* **24**(47): 10702-10706.
- Sohlberg, M. M. and Mateer, C. A. (1987). Effectiveness of an attention-training program. *J Clin Exp Neuropsychol* **9**(2): 117-30.

- Sohlberg, M. M., McLaughlin, K. A., Pavese, A., Heidrich, A. and Posner, M. I. (2000). Evaluation of attention process training and brain injury education in persons with acquired brain injury. *J Clin Exp Neuropsychol* **22**(5): 656-76.
- Velanova, K., Jacoby, L. L., Wheeler, M. E., McAvoy, M. P., Petersen, S. E., et al. (2003). Functional-anatomic correlates of sustained and transient processing components engaged during controlled retrieval. *J Neurosci* **23**(24): 8460-70.
- Verhaeghen, P. and Cerella, J. (2002). Aging, executive control, and attention: a review of meta-analyses. *Neurosci Biobehav Rev* **26**(7): 849-57.
- Weissman, D. H., Warner, L. M. and Woldorff, M. G. (2004). The neural mechanisms for minimizing cross-modal distraction. *J Neurosci* **24**(48): 10941-9.
- Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., et al. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *Jama* **296**(23): 2805-14.
- Wong, E. C., Buxton, R. B. and Frank, L. R. (1998). Quantitative imaging of perfusion using a single subtraction (QUIPSS and QUIPSS II). *Magn Reson Med* **39**(5): 702-8.
- Yang, L. and Hasher, L. (2007). The enhanced effects of pictorial distraction in older adults. *J Gerontol B Psychol Sci Soc Sci* **62**(4): P230-3.
- Yang, Y. (2002). Perfusion MR imaging with pulsed arterial spin-labeling: basic principles and applications in functional brain imaging. *Concepts in Magnetic Resonance Imaging* **14**(5): 347-357.
- Yang, Y., Frank, J. A., Hou, L., Ye, F. Q., McLaughlin, A. C., et al. (1998). Multislice imaging of quantitative cerebral perfusion with pulsed arterial spin labeling. *Magn Reson Med* **39**(5): 825-32.

CHAPTER V

EVALUATING THE NEURAL EFFECTS OF ATTENTION TRAINING IN OLDER ADULTS WITH FMRI

Jennifer L. Mozolic and Paul J. Laurienti

Abstract

Previous studies have demonstrated that older adults exhibit altered patterns of neural activity and deficits in behavioral performance on tasks of attention and other executive functions relative to younger adults. In the preceding chapters we have reported on the reductions in cross-modal distraction and the increases in resting blood flow that are associated with a novel cognitive intervention in healthy older adults. Here we describe the training-related effects on functional magnetic resonance imaging (fMRI) measures of neural activation during two attention tasks. Fifty-eight participants completed a visual spatial attention task and an audiovisual cross-modal distraction task before and after completion of either the training intervention or the control program. We found no specific training effects on the spatial attention task; however, training did result in changes in auditory interference during visual targets on the cross-modal distraction task. As this is the first reported use of the cross-modal distraction task during fMRI, we also documented pre-training activation and deactivation patterns associated with the various task conditions. Potential explanations for the divergent effects of training and suggested design modifications for future studies are discussed.

5.1 Introduction

As reviewed in the previous chapters, older adults display alterations in distractibility and multisensory processing that can be remediated through cognitive training. After completing a novel attention training program, participants exhibited reduced behavioral interference from cross-modal distractors and decreased multisensory integration during modality specific attention (Chapter 3). Participants in the treatment group also showed larger increases in resting cerebral blood flow to the prefrontal cortex than control subjects who did not undergo intensive cognitive training (Chapter 4). An additional goal of this thesis was to determine the magnitude and extent of changes in neural activity during tasks of attention and cross-modal distraction following training. This chapter will address the findings from the functional magnetic resonance imaging (fMRI) component of the trial, which was designed to investigate training-induced changes in brain activation patterns.

It is well established that older adults exhibit different patterns of neural activity when performing the same cognitive tasks as younger adults; however there is some debate about the nature of these differences (for review see (Grady, 2008)). This debate can be attributed to the fact that studies contrasting the activation patterns of younger and older adults have found several different outcomes. One potential result is that older adults could have reduced activity in regions that younger adults activate during task performance. This outcome has been demonstrated in a number of studies showing that decreased activity in task-related brain areas is associated with poorer task performance in older adults relative to young (e.g. (Milham et al., 2002; Mitchell et al., 2006)). However, the opposite outcome has also been observed. That is, many studies have

shown that older adults have increased neural activity in the same regions activated by younger adults, or actually recruit additional brain regions, yet the older adults are still impaired on the task (e.g. (Colcombe et al., 2005; Rypma et al., 2007)). Of particular interest for our study are the patterns of neural activity observed in older adults who maintain levels of task performance that are similar to those seen in younger adults. A number of studies have demonstrated that increased bilateral activity in the frontal cortex in older adults is associated with better task performance (e.g. (Reuter-Lorenz et al., 2000; Cabeza et al., 2002)). These reductions in functional asymmetry are suggested to be a compensatory mechanism by which older adults recruit contralateral cortical regions to counteract functional losses (Cabeza, 2002).

Based on these data, one potential hypothesis for our study was that training-related improvements in cognitive task performance would be associated with increased bilateral activity in the frontal cortex. This study used two tasks that engaged visual attention and inhibition of within and cross-modality distractors, functions that rely on processing in prefrontal brain networks (Hopfinger et al., 2000; Weissman et al., 2004; Wager et al., 2005). Increased bilateral activation has been observed in older adults who perform well on tasks of visual attention (Cabeza et al., 2004) and response inhibition (Langenecker and Nielson, 2003); thus, a compensatory increase in activity associated with improved task performance after training was one potential outcome for the present study.

Another possibility was that training would improve processing efficiency, resulting in improved task performance but less neural activity in prefrontal brain regions typically over-activated by older adults. In a study of dual-task training, Erikson and

colleagues (2007) observed a decrease in bilateral dorsolateral prefrontal cortex activation concomitant with behavioral improvements on dual-task paradigms. These results indicate that older adults exhibited more “young-like” patterns of limited activation after training, rather than compensatory increases (Erickson et al., 2007). Based on these data, another plausible outcome of our study was that improved attention and ability to ignore distractors following training would be associated with a reduction in bilateral frontal cortex activity.

The primary goal of this fMRI study was to characterize the neural changes that accompany behavioral improvements after training. Participants completed tasks that required attention and suppression of distracting stimuli in the MR scanner before and after the completion of either a cognitive training intervention or a control program. We then examined behavioral changes in task performance and training-related changes in the BOLD signal.

5.2 Methods

5.2.1 Participants

Seventy-five healthy older adults between the ages of 65 and 75 were recruited from the community and screened for eligibility in this study. Eligibility criteria included normal sensory and cognitive function, as well as compatibility with the scanner environment. Sixty-six participants were determined to be eligible for the study and were randomized to either the treatment or the control group. Fifty-eight subjects completed all scanning and training sessions and the remainder of the data presented here will be based on these participants ($n_{\text{treatment}} = 27$, $n_{\text{control}} = 31$, mean age = 69.5, 31 females). All participants signed an informed consent and were compensated approximately \$20 per

hour for their participation in the study. All study procedures were approved by and conducted in accordance with the Wake Forest University School of Medicine Institutional Review Board.

5.2.2 Study Design

Once participants were enrolled and randomized into the study, they completed a pre-training scan session to assess baseline fMRI activity patterns during a series of cognitive tasks. Participants then began eight weeks of either the treatment or control training program. Details on the training interventions are reported in Chapter 3. After finishing their respective training programs, all participants completed a post-training scan to re-evaluate functional brain activity. All participants also completed pre- and post-training cognitive evaluations (Chapter 3) and MR assessments of brain structure and cerebral perfusion (Chapter 4).

5.2.3 fMRI Tasks

Inside the scanner, all participants completed two different tasks: (1) a modified version of the Eriksen flanker task (Eriksen and Eriksen, 1974); and (2) a discrimination task comprised of visual letter arrays and auditory distractors (Tellinghuisen and Nowak, 2003).

The flanker task was used to determine if older adults who participated in the treatment showed altered patterns of neural activity during visual spatial attention compared to the control group following training. For this task, participants were required to determine whether a central arrow was pointing to the left or right while

ignoring flanking stimuli. These flankers could either be pointing in the same direction (*compatible* trials <<<<<) or the opposite direction (*incompatible* trials >><>>) as the central arrow. A slower, less accurate response rate is typically observed for incompatible trials relative to compatible trials, and this is referred to as the *interference effect*. Successful completion of the flanker task requires spatially selective visual attention to the central stimulus and inhibition of potential interference from flanking stimuli, and it has been shown to activate brain regions involved in attention, including the lateral prefrontal, anterior cingulate, and parietal cortices (Hazeltine et al., 2000; Bunge et al., 2002). Subjects completed two 5.5 minute runs of 80 trials, each with 40 compatible and 40 incompatible trials presented in random order. Each stimulus trial began with a fixation cross in the center of the display. After a randomly jittered interval of 1000-3000 ms, the cross brightened for 250-750 ms as an alerting cue. Following the alerting cue, the stimulus display containing five arrows was presented for 500 ms. Participants responded using their right hand to press the keys on an MR-compatible button box (i.e., index finger for a left-pointing central arrow, middle finger for a central arrow pointing to the right).

The letter array task, similar to that described in Chapter 3, was used to determine the extent to which the training program resulted in altered patterns of neural activity evoked during cross-modal distraction. This task required participants to identify which of two target letters ('X' or 'N') appeared in a circular array. In addition to the target letter, the circular array also contained a variable number of non-target letters. Zero, one, three, or five non-target letters could be presented along with the target, yielding a total set size of one, two, four, or six elements in the array. Each time the circular array was

presented, participants also heard an auditory distractor. This distractor was the verbalization of a letter that could be congruent to the visual target (e.g. see 'X', hear 'X'), incongruent to the visual target (e.g. see 'X', hear 'N'), or neutral (e.g. see 'X', hear 'L'). Participants were instructed to ignore the auditory stimulus and respond only to visual stimuli. Incongruent trials produce slower reaction times and poorer accuracy when compared to neutral trials (referred to as *costs*), while faster reaction times and increased accuracy on congruent trials are referred to as *benefits*. Additionally, the overall difference in accuracy or response time between incongruent and congruent trials is referred to as the *total interference* (i.e., total interference = costs + benefits). On each trial, the visual stimuli and auditory distractor were presented simultaneously for 300 ms. Inter-stimulus intervals were jittered randomly between 2600 and 3000 ms, and null trials were presented randomly between stimulus trials. Participants completed three, 4.5-minute runs of this paradigm, with 72 trials in each run. Equal numbers of congruent, incongruent, and neutral trials of each array size were presented randomly in each block.

For both tasks, stimuli were presented through MR-compatible goggles and headphones (Resonance Technology, Inc., Northridge, CA) using Eprime software (Psychology Software Tools, Pittsburg, PA) to control stimulus presentation and collect accuracy and response time data. Task order was counter-balanced, with half of the participants completing the flanker task first and the other half completing the letter array task first; however, the task order was consistent for each participant's pre- and post-training visit.

5.2.4 MRI acquisition and preprocessing

Images were acquired with a 1.5T GE scanner using a 4-channel, quadrature phased array, neurovascular head coil (GE Medical Systems, Milwaukee, WI). A high-resolution T1-weighted structural scans was obtained for each participant using an inversion recovery 3D spoiled gradient echo sequence (matrix size= 256 x 256; field of view= 24cm; 1.5mm sections, no gap; 128 slices; in-plane resolution= 0.94mm). Whole-brain activation was assessed with the BOLD signal by measuring changes in the T2*-relaxation rate that accompany changes in blood oxygenation during cortical activation (Ogawa et al., 1990; Turner et al., 1998). Functional imaging used multi-slice gradient-echo planar imaging (EPI) with the following parameters: TR= 2100 ms; TE= 40 ms; field of view= 24 cm (frequency) x 15 cm (phase); matrix size= 64 x 64; 28 slices, 5 mm thickness, no skip; voxel resolution= 3.75 x 3.75 x 5 mm. Images were processed using Statistical Parametric Mapping 99 (SPM99, Wellcome Department of Cognitive Neurology, UK; (Friston et al., 1995; Friston et al., 1998) implemented in Matlab (Mathworks, Inc. Sherborn MA, USA). Prior to performing statistics, the following preprocessing steps were completed: to correct for motion, all functional images were realigned to first functional image in the series; to normalize images to a common space, the T1 structural image was warped to the MNI T1 template and the resulting parameters were applied to the realigned EPI images; to smooth functional images, an 8 x 8 x 10 mm Gaussian kernel was applied.

5.2.5 Data Analysis

Accuracy and response time (RT) on compatible trials, incompatible trials, and the interference effect in the flanker task were each analyzed using $2_{\text{session}} \times 2_{\text{group}}$ ANOVAs, where session was the pre- or post-training repeated measures factor, and treatment vs. control was the between group factor. We were interested in the session $\times$ group interaction term, where a significant F-value ($p < 0.05$) would indicate that training-induced changes in performance on compatible trials, incompatible trials, or the interference effect were not equivalent for the treatment and control groups.

For the letter array task, we used a $4_{\text{set size}} \times 2_{\text{session}} \times 2_{\text{group}}$ ANOVA to assess changes in benefits, costs, and total interference. A significant session $\times$ group 2-way interaction would indicate that training had altered task performance differently for the two groups. Alternatively, a 3-way set size $\times$ session $\times$ group interaction would indicate that differences in training-induced changes for the two groups were not equivalent across all set sizes.

The primary goal of the MRI analysis was determine if patterns of functional activity during each task were differentially affected by the treatment and control procedures. Using the general linear model (GLM), we modeled the relationship between stimulus presentation and timecourse of the BOLD signal. For the flanker task, we modeled compatible trials and incompatible trials. For the letter array task we modeled congruent, incongruent, and neutral trials for each set size (1, 2, 4, and 6). Parameter estimates for each trial type were weighted to produce contrast images for the flanker task (compatible, incompatible, and interference effects) and the letter array task (congruent, incongruent, neutral, cost, benefit, and total interference effects at each set size). In a

second fixed effects analysis, additional contrasts were applied to identify pre- to post-training differences for each subject. These images were then loaded into a random effects analysis, where a two-sample t-test was performed to assess between-group differences in training-induced changes.

In addition, since there are no reports in the literature that use the letter array task in the MR scanner, we also wanted to determine the baseline pattern of activation associated with performance of this task. Similar steps were taken as outlined above; however, contrast images from all subjects, prior to training, were combined in a random-effects analysis that used a one-sample t-test to evaluate the activity patterns associated with performance of this task in the entire sample of older adults. Areas of significant activation and deactivation during the task were also used to restrict the investigation of training-induced changes in an ROI analysis. All imaging analyses were corrected for multiple comparisons using a family-wise error rate (FWE) of $p < 0.05$, and all voxel locations are reported in MNI coordinates.

5.3 Results

5.3.1 Flanker task

Due to an acquisition error, flanker data was not collected on seven participants, therefore the followed results are presented for $n_{\text{treatment}} = 24$ and $n_{\text{control}} = 27$. The results of the 2 x 2 ANOVAs for accuracy indicated that there was a significant main effect of group on compatible trials ($F_{1,49} = 4.5$, $p < 0.04$) and a significant effect of session on incompatible trials ($F_{1,49} = 4.5$, $p < 0.04$). Means and standard deviations for accuracy on all conditions are presented in Table 5.1. These results indicate that treatment group

TABLE 5.1 Mean accuracy and response time data for visual spatial and cross-modal attention tasks performed during fMRI

Condition	Pre-Training				Post-Training			
	Treatment		Control		Treatment		Control	
	Accuracy	RT	Accuracy	RT	Accuracy	RT	Accuracy	RT
<i>Flanker task</i>								
compatible	95.1 (4.8)	618.3 (110.1)	93.6 (4.2)	573.7 (75.3)	96.2 (4.0)	622.4 (98.9)	93.4 (4.1)	558.5 (74.2)
incompatible	94.2 (4.8)	727.0 (115.3)	93.4 (6.0)	684.0 (91.7)	96.0 (4.8)	718.3 (94.3)	94.7 (4.3)	656.0 (81.7)
interference	0.9 (5.7)	108.7 (38.9)	0.3 (6.8)	110.3 (58.3)	0.3 (5.3)	95.9 (41.3)	-1.1 (6.1)	97.5 (45.3)
<i>Letter array task</i>								
benefit 1	-1.1 (4.7)	11.5 (36.3)	-0.6 (5.2)	8.2 (34.8)	-1.0 (4.8)	3.9 (41.8)	-1.3 (5.1)	13.1 (43.9)
benefit 2	-0.9 (5.7)	64.1 (63.1)	0.0 (5.5)	71.1 (58.3)	0.0 (4.7)	42.7 (72.6)	2.2 (6.2)	63.4 (55.2)
benefit 4	6.0 (16.7)	91.3 (119.4)	0.7 (13.1)	60.8 (86.4)	3.6 (11.2)	90.3 (126.9)	2.6 (12.7)	65.6 (85.4)
benefit 6	1.3 (13.3)	74.6 (136.6)	5.4 (16.0)	82.5 (125.5)	3.7 (11.9)	57.2 (82.7)	8.7 (11.3)	111.5 (129.7)
cost 1	0.4 (5.1)	16.2 (47.4)	0.0 (6.1)	10.6 (31.4)	-0.2 (4.5)	26.1 (52.3)	1.2 (3.3)	11.6 (36.4)
cost 2	0.4 (6.7)	-23.9 (74.7)	0.2 (7.2)	-6.5 (61.5)	-0.2 (5.0)	-11.5 (58.3)	-1.4 (7.3)	-24.4 (63.5)
cost 4	9.7 (15.3)	90.0 (140.7)	9.7 (12.6)	87.7 (134.5)	7.7 (11.7)	40.7 (102.1)	9.9 (15.2)	90.5 (131.7)
cost 6	4.6 (13.7)	34.1 (116.9)	3.1 (16.6)	57.5 (104.1)	8.8 (13.8)	23.4 (97.9)	-1.4 (13.8)	16.6 (133.1)
total 1	-0.6 (4.5)	27.7 (36.5)	-0.6 (5.8)	18.9 (39.6)	-1.2 (5.4)	30.0 (47.6)	-0.2 (4.1)	24.7 (38.2)
total 2	-0.4 (4.5)	40.2 (86.4)	0.3 (7.6)	64.6 (52.0)	-0.1 (5.4)	31.2 (71.1)	0.8 (4.7)	39.0 (52.4)
total 4	15.7 (12.9)	181.3 (111.2)	10.4 (11.0)	148.4 (115.1)	11.2 (12.2)	130.9 (155.7)	12.4 (12.5)	156.1 (122.0)
total 6	5.7 (15.5)	108.7 (132.0)	8.6 (16.8)	140.0 (98.5)	12.4 (12.2)	80.6 (98.8)	7.3 (14.4)	128.1 (68.2)

RT= response time; standard deviations are in parentheses

made fewer errors on compatible trials than controls and that both groups made fewer errors on incompatible trials during the post-training scan. Importantly, however, there were no significant session x group interactions for accuracy rates on compatible trials, incompatible trials, or the interference effect (all $F < 2.0$, all $p > 0.05$).

The ANOVAs for RT indicated that there was a significant main effect of group on compatible trials ($F_{1,49} = 5.1$, $p < 0.03$), significant main effects of session ($F_{1,49} = 5.0$, $p < 0.03$) and group ($F_{1,49} = 4.2$, $p < 0.05$) on incompatible trials, and a significant main effect of session on RT interference ($F_{1,49} = 7.5$, $p < 0.009$). Means and standard deviations for RT on all conditions are presented in Table 5.1. These data indicate that the control group was faster than the treatment group on both compatible and incompatible trials, and that both groups were faster and had less interference after training. Similar to the accuracy results, however, there were no significant interaction terms in the RT analyses for the three conditions (all $F < 2.0$, all $p > 0.05$). These data suggest that the attention training program did not serve to specifically improve performance on the flanker task.

Although these findings are contrary to our hypothesis that the treatment group would exhibit greater reductions in interference than controls, the imaging data were in accord with these behavioral results. There were no voxels that showed larger changes in activity for one group than for the other. Based on these null results, we completed no further analyses of the data from the flanker task.

5.3.2 Letter array task

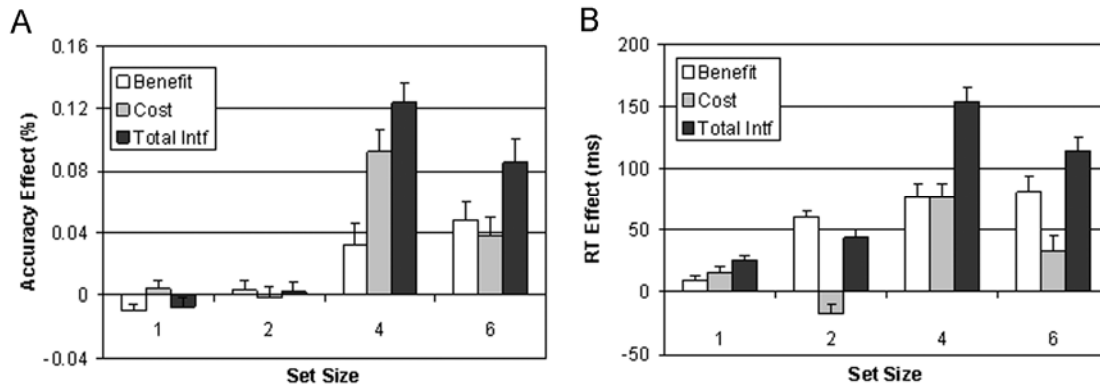
A 3 x 2 x 2 ANOVA on accuracy for the letter array task yielded a significant

effect of set size for benefits ($F_{3,54} = 7.0$, $p < 0.001$), costs ($F_{3,54} = 18.8$, $p < 0.001$), and total interference ($F_{3,54} = 40.7$, $p < 0.001$). Post-hoc tests revealed that the magnitude of benefits, costs, and total interference was not constant across set size (Figure 5.1A). The accuracy benefit increased with increasing set size until leveling off at set size six. The accuracy cost was similar at set sizes one and two, then increased at set size four, and dropped back down at set size six. Total accuracy interference followed a similar pattern as the accuracy cost. In addition to the main effect of set size, there was also a significant 3-way interaction of set size, session, and group for interference accuracy ($F_{3,54} = 3.4$, $p < 0.03$), which indicated that training-induced changes in interference across the set sizes were not the same for both groups (Figure 5.2). Post-hoc analyses showed that this was due to a trend for pre- to post-training decreases in interference at set size four and a significant increase in interference at set size six for the treatment group. The control group did not exhibit any changes in interference accuracy after training.

Similar to the accuracy results, the ANOVAs for RT on the letter array task yielded a significant main effect of set size for benefits ($F_{3,54} = 13.7$, $p < 0.001$), costs ($F_{3,54} = 18.5$, $p < 0.001$), and total interference ($F_{3,54} = 52.1$, $p < 0.001$). Further tests showed that the RT benefits, costs, and interference varied by set size (Figure 5.1B); however there were no significant interactions, indicating that the training programs did not have a differential effect on RT in this task.

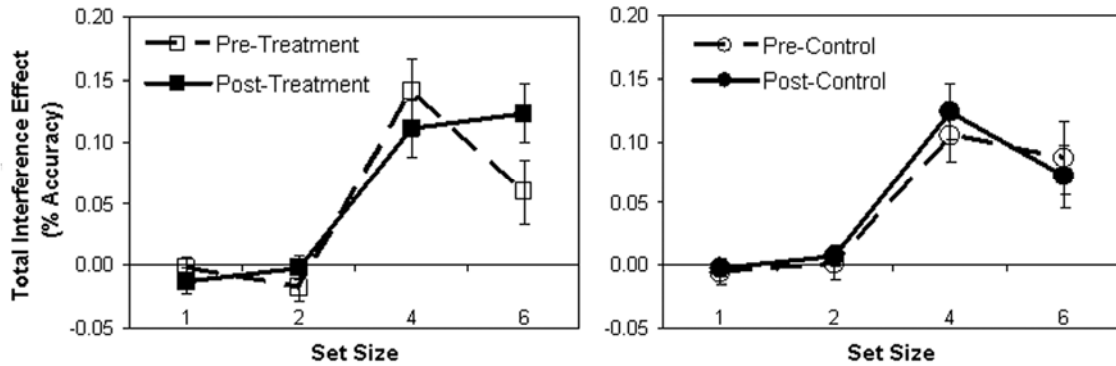
Because there is no existing literature on the patterns of neural activity associated with this task, we first characterized the activations and deactivations observed in all study participants during the pre-training scan. There were no differences in activation patterns for congruent, incongruent, and neutral trials (either across all set sizes or

FIGURE 5.1 Main effect of set size on accuracy and response time interference in the cross-modal attention task



There was a main effect of set size indicating that the magnitude of accuracy (**A**) and RT effects (**B**) were not constant across set sizes. Benefits, costs, and total interference (Tot Intf) effects are collapsed across groups and scan sessions to depict the main set size effect. Error bars represent standard error of the mean.

FIGURE 5.2 Interaction of set size, scan session, and training group on accuracy interference in the cross-modal attention task

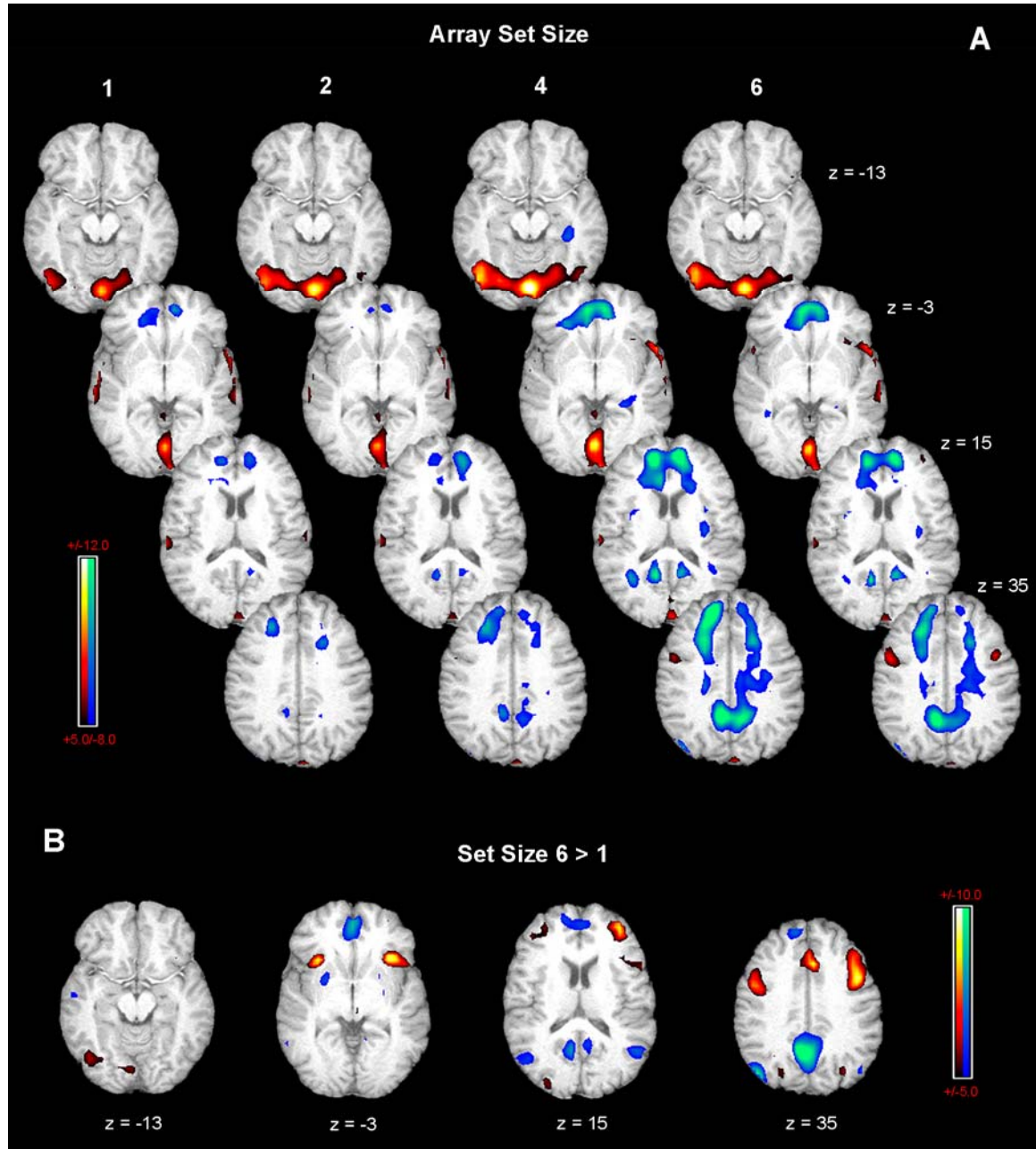


Changes in accuracy interference varied by set size, scan session, and training group for the letter array task performed in the MR scanner. Post hoc tests on the 3-way interaction indicated that the treatment group had a trend for decreased interference at set size four and a significant increase in interference at set size six. The control group did not show any pre- to post-training changes.

at each set size individually) so we collapsed across all trial types to examine how activity changed as the array set size increased. Figure 5.3A depicts the patterns of activation observed in this task at each set size. Using a paired-samples t-test, we also compared activity for set sizes one versus six. Table 5.2 and Figure 5.3B show that increasing set size produced greater activations in a number of areas, including bilateral prefrontal cortex, medial frontal cortex, bilateral insula, bilateral parietal cortex, bilateral thalamus, and primary and secondary visual cortices. Increasing set size in this task also resulted in greater deactivations in several regions, including right motor cortex, precuneus, posterior cingulate cortex, medial frontal cortex, bilateral angular gyrus, and bilateral parahippocampal gyrus.

To determine how training influenced neural activity associated with this task, we compared pre- to post-training differences in activation across the two groups. Because the behavioral outcomes on this task indicated that attention training resulted in a marginal decrease in interference at set size four and an increase in interference at set size six, we first focused on activity associated with these trials. Whole-brain analyses indicated that there were no significant group differences in activation patterns on set size four. For set size six, there was a small region in the left postcentral gyrus (peak voxel: -56, -33, 54; cluster size: 3 voxels; Figure 5.4) where there was a larger increase in activation for the treatment group than for controls. A series of post hoc analyses was used to determine the underlying source of this interaction. The first finding was that none of the interference effects for the individual groups or scan sessions survived correction for multiple comparison, thus all the contributing effects are small, sub-threshold changes. These analyses also indicated that the treatment group had a slight

FIGURE 5.3 BOLD activations and deactivation patterns as a function of set size



BOLD activations and deactivation increased as the letter array set size increased. (A) Axial images at several levels show regions where activity increased above resting baseline level (warm colors) and regions where activity decreased below resting levels (cool colors) for each set size. The t-threshold for activity decreases has been raised for display purposes to limit artifactual white matter deactivations. At each set size, analyses were collapsed across training group and trial condition (congruent, incongruent, and neutral). (B) This comparison shows brain regions where there were significant increases and decreases in activity levels during set size six versus set size one. T-thresholds for activation and deactivations here are matched ($t = 5.0$, $p < 0.05$, FWE-corrected).

TABLE 5.2 Peak coordinates for regions of significant activation and deactivation in the comparison: *set size six greater than set size one*

Region	BA	Peak Coordinates		
		x	y	z
Activations				
Medial frontal gyrus	32	0	24	45
L superior frontal gyrus	10	-32	52	20
R superior frontal gyrus	46/10	36	48	20
L middle frontal gyrus	10	-44	44	15
R middle frontal gyrus	9	44	12	30
L middle frontal gyrus	6	-36	-8	60
L insula	45/13	-32	20	5
L inferior frontal gyrus	9	-52	12	30
R inferior frontal gyrus	45	32	24	5
L inferior parietal lobule	40/7	-32	-60	45
L superior parietal lobule	7	-24	-72	55
R superior parietal lobule	7	32	-60	50
L precuneus	7	-16	-76	50
R precuneus	19	32	-76	35
L fusiform gyrus	19	-32	-72	-20
L lingual gyrus	18	-4	-84	-10
R thalamus		12	-4	5
L thalamus		-12	-4	5
Deactivations				
Anterior cingulate	32	0	50	0
L posterior cingulate	29/30	-12	-52	5
L superior frontal gyrus	8	-20	36	50
R precentral gyrus	4	40	-24	70
R postcentral gyrus	5	24	-40	75
L precuneus	31/7	-8	-56	30
L precuneus	39/19	-48	-76	35
R middle temporal gyrus	39	52	-64	20
L middle temporal gyrus	21	-60	-16	-15
L hippocampus		-28	-16	-20
R hippocampus		24	-12	-20
L putamen		-24	4	-5
R putamen		24	4	-5

L = left; R = right; BA = Brodmann area; x, y, and z are MNI atlas coordinates

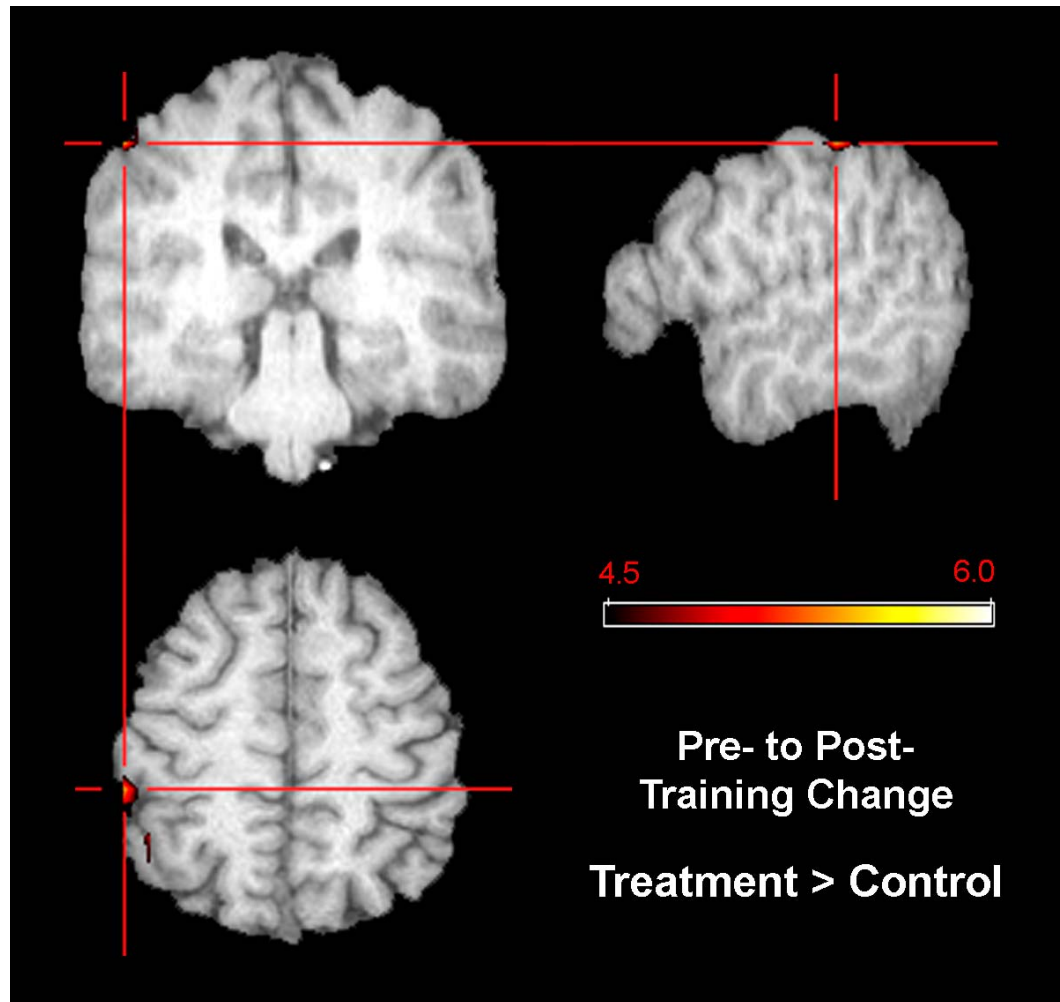
increase in interference at set size six, while the control group had a modest decrease in interference. The opposing direction of these sub-threshold effects in the two groups is what produced the significant interaction depicted in Figure 5.4. Direct comparisons of activity during congruent trials or during incongruent trials for the two groups, however, yielded no significant findings. Additional analyses using ROIs defined by masks of significant activation and deactivation from the analysis of all subjects' pre-training scan (set size 6 versus 1; from Figure 5.3b) also yielded no significant group differences in training-induced activity changes.

5.4 Discussion

We conducted this fMRI study to characterize the effects of our cognitive training program on functional brain activity. Although this training program successfully improved behavioral measures of cross-modal attention and promoted increased blood flow in prefrontal cortex, the effects of training on neural activity remain equivocal.

Despite the fact that performance on the flanker task has been shown to decrease with age (Colcombe et al., 2005), and that task performance and neural activity can be improved with cardiovascular fitness training (Colcombe et al., 2004), our intervention did not alter behavioral or imaging indices of performance on this task. Both the treatment and the control group exhibited significantly less RT interference after training, suggesting that there was a practice effect caused by repeated performance of the task, but there was no evidence that the treatment program provided any benefits over the control program. While these results were unexpected at the outset of the trial, they are not entirely surprising given that the training program did not affect participants'

FIGURE 5.4 Training-related changes in interference-associated BOLD activity during the cross-modal attention task



The treatment group had larger training-induced increases in activity associated with total interference at set size six than controls in the left parietal cortex.

susceptibility to within-modality distractors. Benefits for the treatment group were observed in cross-modal attention and multisensory processing paradigms, but training produced no behavioral gains in measures of within-modality attention. As discussed in Chapter 3 (pp. 77-79), these results may be due to the divergent neural mechanisms subserving within- and cross-modal attention. Briefly, focusing attention on a particular location within the visual modality primarily involves *increasing* neural and behavioral responses to stimuli in the attended location (Spitzer et al., 1988; Kastner et al., 1999). In contrast, the primary effect of modality-specific attention is *decreased* processing of stimuli in the unattended modality (Spence et al., 2001; Mozolic et al., 2008). Because successful completion of the flanker task involves primarily spatial attention, alternative forms of training that enhance spatial processing, rather than cross-modal suppression, may be required to influence patterns of neural activity associated with this task.

We used the letter array task to assess the effects of training on BOLD signal activity associated with cross-modal distraction. Although this task has been used in younger adults (Tellinghuisen and Nowak, 2003) and has been shown to be sensitive to the effects of cognitive training in older adults (Mozolic et al., in press), to our knowledge this is the first characterization of the letter array task in the MR scanner. The task activated visual and auditory cortices as well as dorsal and ventral prefrontal areas and these activations increased with increasing set size or task difficulty (Figure 5.3). This observed pattern of activation is in accord with our expectations and with similar tasks that involve processing visual and auditory stimuli and require attention and inhibition (Fassbender et al., 2004; McNab et al., 2008). This task also produced significant deactivations in structures of the default mode network, including medial

frontal/anterior cingulate, precuneus/posterior cingulate, and lateral parietal areas (Buckner et al., 2008). Deactivations during this task also increased as the number of elements in the letter array increased, a finding that supports previous data demonstrating that deactivation of the default mode network increases with increasing task difficulty (McKiernan et al., 2003).

Contrary to our expectations and to accuracy and RT data showing differential performance across the trial types, we did not detect any BOLD signal differences between congruent, incongruent, and neutral trials. Contrasts between these conditions did show small, sub-threshold differences; however, it is likely that we were underpowered to detect between-condition differences due to the small sample size of this pilot study, and to the multi-trial type design of this paradigm. In the event-related design, we included 12 different trial types (three congruency conditions and four set sizes), so there was a limited number of repeats for each type of trial. Future studies employing this letter array task could reduce the number of trial types to include fewer set sizes (e.g. two and six only) or add additional runs to increase the power.

Training-related effects on the letter array task also diverged from our hypothesized outcomes. We have previously demonstrated that cognitive training reduced RT interference on this task at both small and large set sizes (Chapter 3). However, when participants performed this task in the MR scanner, rather than in a quiet testing room, they exhibited no training-related effects on RT interference. Instead, they showed both decreases and increases in interference accuracy. For the treatment group, there was no change in accuracy interference at set size one or two, a slight decrease at

set size four, and an increase at set size six. The control group showed no change in accuracy interference at any set size.

These differences in task performance between the behavioral testing room and the MR scanner could be due to the increased auditory noise present in the scanner environment. The drop in interference noted at set size six for performance in the scanner suggests that participants had a limited capacity to process the visual and auditory stimuli. That is, when there were only four elements in the visual array, participants were distracted by the auditory letter; however when there were six visual stimuli to process, fewer attentional resources were available to process the auditory letter, and thus participants were less distracted by it. This pattern of responses is seen normally when the distractor is presented visually, rather than aurally, suggesting that we have a limited capacity to process stimuli within the visual modality (Lavie et al., 2004). Interestingly, older adults have been shown to exhaust their attentional capacity at smaller set sizes than younger adults (Maylor and Lavie, 1998). Previously, when this task has employed auditory distractors rather than visual distractors, no capacity limitations have been observed (Tellinghuisen and Nowak, 2003; Mozolic et al., in press). That is, the magnitude of interference, or distraction, continues to increase even at very large set sizes, suggesting that auditory processing relies on a pool of attentional resources separate from that used to process the visual stimuli (Tellinghuisen and Nowak, 2003). Although this held true for older adults in a quiet testing room, it is possible that the noisy scanner environment made this a more difficult task, taxing participants' attentional resources and limiting their processing of distractors. Following training, however, the treatment group displayed a significant increase in interference at the largest

set size. This is actually the expected result if attention training successfully increased attentional capacity. Further investigation of the effects of training on capacity could help to determine the source of training-related increases in interference.

As outlined above, behavioral performance on the letter array task in the MR scanner did not replicate results previously reported for younger adults or for these participants in a quiet testing room; therefore, the imaging results are also somewhat difficult to interpret. Post-hoc analyses indicated that the treatment group had a significant increase in accuracy interference at set size six, and the fMRI analyses also indicated that there was a significantly larger training-induced increase in activity in left parietal cortex for the treatment group than for controls. This region has been shown to be activated during selective attention and distraction (Behrmann et al., 2004; Olesen et al., 2007). However, the BOLD signal effect in this region was driven by very small, sub-threshold changes in interference for the two groups. As discussed above, the power to detect training effects on this task was limited by our small sample size and the multi-trial type design, and additional studies will be needed to better characterize the neural substrates underlying behavioral improvements.

REFERENCES

- Behrmann, M., Geng, J. J. and Shomstein, S. (2004). Parietal cortex and attention. *Curr.Opin.Neurobiol.* **14**(2): 212-217.
- Buckner, R. L., Andrews-Hanna, J. R. and Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* **1124**: 1-38.
- Bunge, S. A., Hazeltine, E., Scanlon, M. D., Rosen, A. C. and Gabrieli, J. D. (2002). Dissociable contributions of prefrontal and parietal cortices to response selection. *Neuroimage* **17**(3): 1562-71.
- Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol.Aging* **17**(1): 85.
- Cabeza, R., Anderson, N. D., Locantore, J. K. and McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage.* **17**(3): 1394.
- Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., et al. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cereb Cortex* **14**(4): 364-75.
- Colcombe, S. J., Kramer, A. F., Erickson, K. I. and Scalf, P. (2005). The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychol Aging* **20**(3): 363-75.
- Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., et al. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A* **101**(9): 3316-21.
- Erickson, K. I., Colcombe, S. J., Wadhwa, R., Bherer, L., Peterson, M. S., et al. (2007). Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging* **28**(2): 272-83.
- Eriksen, B. A. and Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics* **16**: 143-149.
- Fassbender, C., Murphy, K., Foxe, J. J., Wylie, G. R., Javitt, D. C., et al. (2004). A topography of executive functions and their interactions revealed by functional magnetic resonance imaging. *Brain Res.Cogn Brain Res.* **20**(2): 132.
- Friston, K. J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M. D., et al. (1998). Event-related fMRI: characterizing differential responses. *Neuroimage* **7**(1): 30.
- Friston, K. J., Frith, C. D., Frackowiak, R. S. and Turner, R. (1995). Characterizing dynamic brain responses with fMRI: a multivariate approach. *Neuroimage* **2**(2): 166.
- Grady, C. L. (2008). Cognitive neuroscience of aging. *Ann N Y Acad Sci* **1124**: 127-44.
- Hazeltine, E., Poldrack, R. and Gabrieli, J. D. (2000). Neural activation during response competition. *J Cogn Neurosci* **12 Suppl 2**: 118-29.
- Hopfinger, J. B., Buonocore, M. H. and Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nat Neurosci* **3**(3): 284-91.
- Kastner, S., Pinsk, M. A., De Weerd, P., Desimone, R. and Ungerleider, L. G. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron* **22**(4): 751-61.

- Langenecker, S. A. and Nielson, K. A. (2003). Frontal recruitment during response inhibition in older adults replicated with fMRI. *Neuroimage* **20**(2): 1384.
- Lavie, N., Hirst, A., de Fockert, J. W. and Viding, E. (2004). Load theory of selective attention and cognitive control. *J Exp Psychol Gen* **133**(3): 339-54.
- Maylor, E. A. and Lavie, N. (1998). The influence of perceptual load on age differences in selective attention. *Psychol Aging* **13**(4): 563-73.
- McKiernan, K. A., Kaufman, J. N., Kucera-Thompson, J. and Binder, J. R. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *J Cogn Neurosci* **15**(3): 394-408.
- McNab, F., Leroux, G., Strand, F., Thorell, L., Bergman, S., et al. (2008). Common and unique components of inhibition and working memory: An fMRI, within-subjects investigation. *Neuropsychologia* **46**(11): 2668.
- Milham, M. P., Erickson, K. I., Banich, M. T., Kramer, A. F., Webb, A., et al. (2002). Attentional control in the aging brain: insights from an fMRI study of the stroop task. *Brain Cogn* **49**(3): 277.
- Mitchell, K. J., Raye, C. L., Johnson, M. K. and Greene, E. J. (2006). An fMRI investigation of short-term source memory in young and older adults. *Neuroimage* **30**(2): 627-33.
- Mozolic, J. L., Joyner, D., Hugenschmidt, C. E., Peiffer, A. M., Kraft, R. A., et al. (2008). Cross-modal deactivations during modality-specific selective attention. *BMC Neurol* **8**: 35.
- Mozolic, J. L., Long, A. B., Morgan, A. R., Rawley-Payne, M. and Laurienti, P. J. (in press). A cognitive training intervention improves modality-specific attention in a randomized controlled trial of healthy older adults. *Neurobiol Aging*.
- Ogawa, S., Lee, T. M., Kay, A. R. and Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A* **87**(24): 9868-72.
- Olesen, P. J., Macoveanu, J., Tegner, J. and Klingberg, T. (2007). Brain activity related to working memory and distraction in children and adults. *Cereb Cortex* **17**(5): 1047-54.
- Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., et al. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *J Cogn Neurosci* **12**(1): 174-87.
- Rypma, B., Eldreth, D. A. and Rebbelchi, D. (2007). Age-related differences in activation-performance relations in delayed-response tasks: a multiple component analysis. *Cortex* **43**(1): 65-76.
- Spence, C., Nicholls, M. E. and Driver, J. (2001). The cost of expecting events in the wrong sensory modality. *Percept. Psychophys.* **63**(2): 330-6.
- Spitzer, H., Desimone, R. and Moran, J. (1988). Increased attention enhances both behavioral and neuronal performance. *Science* **240**(4850): 338-40.
- Tellinghuisen, D. J. and Nowak, E. J. (2003). The inability to ignore auditory distractors as a function of visual task perceptual load. *Percept Psychophys* **65**(5): 817-28.
- Turner, R., Howseman, A., Rees, G. E., Josephs, O. and Friston, K. (1998). Functional magnetic resonance imaging of the human brain: data acquisition and analysis. *Exp Brain Res* **123**(1-2): 5-12.

- Wager, T. D., Sylvester, C. Y., Lacey, S. C., Nee, D. E., Franklin, M., et al. (2005). Common and unique components of response inhibition revealed by fMRI. *Neuroimage* **27**(2): 323-40.
- Weissman, D. H., Warner, L. M. and Woldorff, M. G. (2004). The neural mechanisms for minimizing cross-modal distraction. *J Neurosci* **24**(48): 10941-9.

CHAPTER XI

DISCUSSION

Jennifer L. Mozolic and Paul J. Laurienti

Section 6.2 of this chapter has been modified from the manuscript, “Multisensory integration in aging”, by Jennifer L. Mozolic, Christina E. Hugenschmidt, Ann M. Peiffer, and Paul J. Laurienti, a chapter in review for inclusion in the book, Frontiers in the Neural Bases of Multisensory Processes, edited by Mark Wallace, Micah Murray, Sid Simon, and Miguel Nicolelis.

6.1 Summary of results

The central goals of this thesis were to investigate a potential source of altered multisensory processing in older adults, to assess the efficacy of a cognitive training program aimed at reducing distractibility in healthy aging, and to evaluate the impact of this training program on brain structure and function. To this end, we performed a study comparing multisensory integration during modality-specific attention in younger and older adults and completed a randomized, controlled trial of a novel behavioral intervention in 66 healthy older adults. These studies generated several important and novel findings.

First, using multisensory integration as an index of distractibility, we showed that older adults process more extraneous sensory information during modality-specific attention than younger adults. This finding was observed despite evidence showing that older adults are able to successfully engage selective attention. In addition, we also demonstrated that completion of an eight-week cognitive training program can significantly reduce cross-modal distraction in healthy older adults. Although the training intervention did not affect within-modality distraction, modest benefits from the intervention did transfer to non-trained domains such as processing speed, dual-task performance, and working memory. Additionally, participants in the treatment group exhibited larger increases in regional cerebral blood flow (CBF) to the prefrontal cortex during rest than the control group. The prefrontal cortex is a critical component in brain networks supporting working memory, attention, inhibition, and other executive functions, and typically exhibits hypoperfusion with age. Although our results also indicated that training-related increases in CBF were not associated with underlying

structural brain changes or with altered patterns of neural activity during cognitive tasks, to our knowledge, this study is the first to demonstrate that a cognitive training intervention can modulate resting cerebral blood flow.

In subsequent sections of this discussion we will present further support for the seemingly contradictory notion that older adults maintain their ability to engage selective attention, yet still process more extraneous sensory information than younger adults due to age-related increases in baseline sensory processing. These data will highlight evidence of increased baseline sensory processing levels in older adults, explore age-related changes in the neural mechanisms of baseline brain functioning, and suggest avenues to consider in future studies. Next, several additional sections will address behavioral and neural plasticity as potential mechanisms for improving cognitive function in older adults. Finally, this discussion will review issues related to training efficacy and maintenance, and explore the implications of our findings for the design of future cognitive interventions.

6.2 Attention and distractibility in older adults

Based on results indicating that modality-specific selective attention can attenuate multisensory integration (Mozolic et al., 2008) and a number of studies suggesting that older adults have deficits in attentional control (Alain and Woods, 1999; Gazzaley et al., 2005; Andres et al., 2008), we hypothesized that older adults were exhibiting more pronounced multisensory integration than younger adults because of an inability to engage selective attention. As a consequence, we anticipated that older adults would not be able to reduce interactions between bimodal sensory stimuli by limiting their attention

to a single sensory modality. Instead, we observed that older adults were capable of invoking the same level of attention-mediated suppression as younger adults on a cued multisensory discrimination paradigm. Due to the fact that the older adults experienced more multisensory integration during the baseline divided attention condition, however, an equivalent drop in integration for the age groups during selective attention still left the older adults with higher levels of integration than their young counterparts.

A useful analogy for this concept is that of water flowing through garden hose: if there is an intermediate amount of water flowing through a hose, twisting the shut-off valve a given number of turns will stop the flow of water; however, if there is more water flowing through the hose initially, the same number of turns to the valve will allow some water to continue to flow. In this analogy, the amount of sensory information processed at baseline resting state in younger adults is akin to an intermediate flow of water. Engaging selective attention, or twisting the valve, can block the processing of extraneous background sensory information. In older adults, there is more sensory processing occurring during the baseline resting state. Although they can engage selective attention commensurately with young adults, represented by twisting this shut-off valve the same number of turns, older adults will continue to process more sensory information than younger adults due to their increased baseline processing levels.

6.2.1 Increased baseline sensory processing in older adults

The results presented in Chapter 2 indicate that enhanced integration in older adults is not due to deficits in engaging top-down selective attention mechanisms, but instead stems from age-related increases in baseline cross-modal interactions. Additional

evidence for differences in background sensory processing comes from a study by Hugenschmidt and colleagues (in press-a) comparing regional CBF during rest and during a visual steady-state task in younger and older adults. During rest and visual stimulation, older adults had increased CBF in the auditory cortex associated with processing irrelevant MR-scanner noise, relative to their young counterparts. Additionally, despite the fact that both older and younger adults exhibited comparable reductions in auditory CBF when engaged in a visual task, the older adults still had higher CBF in the auditory cortex in response to the ongoing, but task-irrelevant, scanner noise (Hugenschmidt et al., in press-a). These blood flow results parallel the behavioral data presented in Chapter 2, showing that, despite maintaining the ability to reduce responses to irrelevant auditory noise when focusing on a visual task, older adults still exhibited an increased level of response to the background auditory stimulation relative to younger adults. Not only does this concept of increased baseline sensory processing offer a potential mechanism for age-related alterations in multisensory integration, but it may also help to account for the seemingly contradictory evidence that older adults are both more distractible than younger adults (Alain and Woods, 1999; Rowe et al., 2006), and equally able to engage selective attention (Verhaeghen and Cerella, 2002; Hugenschmidt et al., in press-b).

Another factor to consider is that environmental conditions and task demands can determine whether or not extraneous sensory stimuli are beneficial or detrimental to performance. In certain controlled laboratory paradigms, processing more sensory information can be beneficial. For example, enhanced processing of both a visual target and a spatially coincident, semantically congruent auditory stimulus can result in speeded

response time (Laurienti et al., 2004). In the real world, however, we are constantly bombarded with information from all sensory modalities. Selective attention allows both younger and older adults to focus on important and task-relevant sensory information and filter out irrelevant and distracting stimuli. Yet, because their baseline levels of sensory processing are elevated, older adults are still more distracted than younger adults when incoming sensory streams contain irrelevant or conflicting information. However, if the extraneous sensory information becomes task relevant, older adults will exhibit larger gains than younger adults, as information that was previously interfering with task performance becomes helpful in completing the task.

This phenomenon is illustrated by two experiments testing for interference between picture and word stimuli. In one experiment, Yang and Hasher (2007) demonstrated that older adults were more distracted by irrelevant pictures than younger adults in a task that required participants to make semantic judgments about words that appeared superimposed on the pictures. In a very similar paradigm that modified task demands, however, older adults had an advantage (Rowe et al., 2006). In this experiment, younger and older adults were required to make same/different judgments about the pictures that appeared beneath an overlay containing irrelevant words. On a subsequent test of implicit memory for the irrelevant words, older adults actually showed better memory, indicating that they had indeed processed more “noise” or irrelevant background information than younger adults (Rowe et al., 2006). Although the relative contributions of deficits in attentional control and increased baseline sensory processing can not be determined through these studies, the findings do support the notion that older adults are more distractible than younger adults because they do not adequately filter

sensory noise. Additionally, these results clearly show that when to-be-ignored information becomes relevant, older adults can actually benefit from increased sensory processing.

6.2.2 Age-related alterations in the default mode network

In spite of the accumulating evidence that there are changes in baseline sensory processing associated with advancing age, there is no clear evidence for an underlying neural mechanism. One potential source of age-related changes in baseline filtering parameters is dysregulation of the default mode network (DMN), an anatomically and physiologically defined system of structures that is thought to be involved in monitoring internal thoughts and the external environment at rest (Raichle et al., 2001; Greicius and Menon, 2004; Buckner et al., 2008). Composed of regions such as the anterior cingulate, the posterior cingulate / precuneus region, and the parietal cortex, the default mode network is most active during rest and becomes less active during most goal-directed behaviors (Raichle et al., 2001; Greicius and Menon, 2004; Buckner et al., 2008). Several studies have reported that the DMN is not suppressed as effectively during external tasks in older adults as in younger adults (Lustig et al., 2003; Grady et al., 2006; Persson et al., 2007). Failure to suppress default mode network activity has also been implicated in reduced goal-directed processing during attentional lapses, increased frequency of task-unrelated thoughts, and increased error rates (McKiernan et al., 2006; Weissman et al., 2006; Li et al., 2007).

A recent study by Stevens and colleagues (2008) directly linked increased background activity in auditory cortex during a visual task to DMN activity. In this fMRI

study, older and younger adults were asked to complete a visual working memory task in a noisy MRI scanner environment. When older adults made errors on this task, they had increased activity in auditory cortex. In younger adults, however, error trials were not associated with increased auditory activation. This suggests that older adults were processing more background information than younger adults and that the increased processing was related to distraction by irrelevant auditory stimulation. Furthermore, increased auditory activity was associated with increased DMN activity, indicating that older adults' vulnerability to distraction may be linked to age-related differences in suppression of the DMN (Stevens et al., 2008). It seems likely, therefore, that further characterization of the default mode network in aging may be important for understanding the neural basis of altered baseline sensory processing, distractibility, and enhanced multisensory integration in older adults.

6.3 Plasticity and the aging brain

In addition to determining the underlying causes of alterations in baseline sensory processing associated with advancing age, it will also be critical to establish effective methods for promoting optimal sensory and cognitive function in older adults. For many years, the prevailing neuroscientific dogma asserted that the adult brain was largely a static system, destined for inevitable decline and deterioration in old age. Over the past several decades, however, considerable evidence has emerged in support of the notion that the brain maintains its ability to change in response to both informal experience and structured training throughout the lifespan (Rosenzweig and Bennett, 1996).

6.3.1 Animal models of experience-dependent brain plasticity

Hubel and Wiesel performed some of the most well known studies on experience-dependent neural plasticity, demonstrating that monocular deprivation in young cats could vastly alter the development of the visual system (Wiesel and Hubel, 1963, 1965). Specifically, these experiments showed that once the previously occluded eye was opened, the cat was still functionally blind in this eye because cells in the contralateral visual cortex had developed to respond to visual input from the normal eye, rather than the occluded eye (Wiesel and Hubel, 1963). These studies were some of the first to document that events or experiences occurring during critical developmental periods could permanently disrupt neural circuitry. Less well known, but more pertinent to this thesis, are pioneering experiments performed by Rosenzweig and colleagues in the 1960s which showed that rats trained to solve complex problems or housed in enriched environments exhibited alterations in neurochemistry and neuroanatomy compared to control animals (Krech et al., 1960; Rosenzweig et al., 1962; Bennett et al., 1964). These data have since been replicated and extended to show that a number of different training and enrichment paradigms can alter many measures of brain structure and function, including cortical thickness (Diamond et al., 1976; Murtha et al., 1990), neurogenesis (Kempermann et al., 1997; van Praag et al., 1999; Olson et al., 2006) dendritic branching (Volkmar and Greenough, 1972; Gelfo et al., 2009), and neurotransmitter activity (Zhu et al., 2005; Nichols et al., 2007). Importantly, these changes are seen even in the oldest animals tested (Diamond et al., 1985; Kempermann et al., 1998; Kempermann et al., 2002; van Praag et al., 2005).

6.3.2 Aging, experience, and plasticity in humans

In humans, epidemiological data shows a consistent link between both physical activity and complex mental activity and maintenance of cognitive function in advanced age (Spirduso, 1975; Emery et al., 1995; Bunce et al., 1996; Hultsch et al., 1999; Schooler et al., 1999; Valenzuela and Sachdev, 2006). For example, Spirduso and colleagues (1975) reported that older athletes exhibited significantly less age-related cognitive slowing than inactive older adults. Similarly, Schooler et al. (1999) demonstrated that intellectual functioning was higher among workers who engaged in more complex tasks at work, and that this positive relationship grew stronger as the workers aged. Taken together, this body of literature lends a great deal of support to the idea that exercise of the body and the mind can promote healthy brain aging. This notion has also been articulated in the theory of cognitive reserve. Based on evidence that the same degree of Alzheimer's disease neuropathology can produce severe symptoms of dementia in some patients while other patients, often those with higher education or mentally complex occupations, show no behavioral manifestations of the disease, the cognitive reserve hypothesis proposes that lifelong physical and mental activity may protect against cognitive decline despite neurophysiological insult (Katzman et al., 1988; Stern et al., 1994; Scarmeas and Stern, 2003; Whalley et al., 2004).

Although these correlational data leave open the possibility that older adults with healthy brain function are those that are willing or able to participate in physically or mentally demanding pursuits, several randomized controlled trials have now demonstrated a causal link between experience and cognitive enhancement in older adults (Dustman et al., 1984; Kramer et al., 1999; Edwards et al., 2005; Mahncke et al., 2006;

Willis et al., 2006; Bugos et al., 2007). For example, a meta-analysis of 18 aerobic exercise interventions suggests that cardiovascular fitness training has a robust effect on cognition in older adults, with the largest improvements observed in executive control processes (Colcombe and Kramer, 2003). Willis and colleagues (2006) targeted older adults with existing processing difficulties for training in processing speed, and demonstrated not only that participants' initial deficits could be remediated with training, but also that their performance on everyday activities was improved.

6.3.3 Mechanisms of training-induced plasticity

Although the exact sequence of neurobiological events underlying training-related cognitive enhancement is not completely understood, rodent models of environmental enrichment have provided a wealth of information about the molecular and cellular changes that can occur with training. Several studies have reported increases in brain-derived neurotrophic factor (BDNF) and other neurotrophins in the cerebral cortex and hippocampus of mice and rats housed in complex environments (Ickes et al., 2000; Wolf et al., 2006). Additionally, environmental enrichment has been shown to modify AMPA and NMDA glutamate receptor function, leading to alterations in the mechanisms of long-term potentiation and depression that play a vital role in learning and memory (Gagne et al., 1998; Naka et al., 2005; Andin et al., 2007). Even more striking are changes in the expression of genes involved in synaptic plasticity that can be detected after as little as one hour of enrichment (Rampon et al., 2000).

In addition to these rapid molecular changes, environmental enrichment has also been shown to produce longer-term structural modifications. Dendritic arborization and

spine density of frontal and parietal cortex pyramidal neurons are increased in rats housed in complex environments, suggesting modified synaptic circuitry in these animals who also demonstrate superior spatial abilities relative to animals housed in standard environments (Leggio et al., 2005; Gelfo et al., 2009). The rate of hippocampal neurogenesis has also been shown to be five times greater for older animals exposed to a complex environment during adulthood than for controls (Kempermann et al., 2002). Glial cells such as astrocytes and oligodendrocytes can also increase in volume in response to experience in adult animals, further modifying neuronal interactions (Anderson et al., 1994; Markham and Greenough, 2004; Fields, 2005). Vascular plasticity may be another important factor mediating experience-induced cognitive enhancements, as complex environments can stimulate angiogenesis in the adult rat brain (Black et al., 1987; Black et al., 1989; Black et al., 1990; Churchill et al., 2002; Valenzuela et al., 2007)

The tools used for in vivo neuroimaging in humans preclude the observation of microscopic-level processes like neurogenesis and synaptogenesis, however, macroscopic changes in tissue volume and BOLD activation patterns have been observed after physical exercise and cognitive training regimens in older adults (Nyberg et al., 2003; Colcombe et al., 2004; Colcombe et al., 2006; Erickson et al., 2007; Boyke et al., 2008; Dahlin et al., 2008a). Valenzuela and colleagues (2003) have also used magnetic resonance spectroscopy to examine the neurochemical effects of memory training. In a group of healthy older adults, five weeks of training improved verbal memory and increased hippocampal levels of creatine and choline, chemicals involved in cellular membrane turnover and energy metabolism (Valenzuela et al., 2003). In addition, the

results presented in Chapter 4 of this thesis are first to demonstrate increases in resting cerebral blood flow following cognitive training, suggesting that elevated neuronal activity during cognitive training can increase regional resting metabolic rates.

Despite ample evidence from the animal and human literature demonstrating that the aging brain retains some ability to modify its structure and function in response to experience and training, consistent findings also indicate that neural and behavioral plasticity are diminished in older adults (Verhaeghen et al., 1992; Kempermann et al., 1998; Burke and Barnes, 2006; Jones et al., 2006; Dahlin et al., 2008b). This reduced capacity to adapt to environmental demands is one likely source of age-related cognitive decline, and may also place some limits on the magnitude of behavioral improvements that can be generated through cognitive training interventions implemented in late life (Burke and Barnes, 2006; Mora et al., 2007). However, a physically active and intellectually challenging lifestyle may be the best means for maintaining brain health and preventing neurodegenerative disease (Churchill et al., 2002; Scarmeas and Stern, 2003; Kramer et al., 2004; Hillman et al., 2008).

6.4 Factors influencing the efficacy of cognitive training

Although inherent levels of plasticity or neuropathology may influence the efficacy of cognitive training, there are also many extrinsic factors that can potentially affect the success of a given training program (Schmidt and Bjork, 1992; Green and Bavelier, 2008). In this section we will review several of these inter-related factors, including task difficulty, stimulus variability, feedback, and motivation, and how they were incorporated into our intervention.

First, the difficulty level of tasks used for training and the progression through these tasks are important aspects of any training regimen. Intuitively, the best way to promote learning is not to begin with the most complicated task, but to start with a relatively simple task and then move on to incrementally more difficult tasks as each one is mastered. Linkenhoker and Knudsen (2002) have experimentally validated this notion with a visual-auditory learning paradigm in barn owls. These experiments demonstrated that when adult owls were exposed to small, incremental shifts in their visual field using prism lenses, they were able to adjust their auditory localization abilities to accommodate very large shifts in their visual field. In contrast, owls that were tested only with a large visual shift rather than incrementally increasing shifts were never able to adapt to the altered visual environment (Linkenhoker and Knudsen, 2002). Our training intervention was also based on this principle, with participants beginning their training with very basic tasks, and then completing progressively more difficult tasks as their level of competency increased.

Task variability is another feature of a training program that may influence not only how participants progress through the training, but also how they apply the skills learned during training to other situations (Schmidt and Bjork, 1992; Green and Bavelier, 2008). Evidence from object recognition (Brady and Kersten, 2003), language acquisition (Clopper and Pisoni, 2004), and motor learning (Hall and Magill, 1995) suggests that greater variability among training tasks or sample items may subtly slow acquisition of new tasks, but can promote significant flexibility in applying learned skills to new situations. For instance, on a dialect categorization task, Clopper and Pisoni (2004) demonstrated that participants who heard several different speakers in each dialect

group were better able to correctly categorize the dialect of new speakers than were participants who had practiced the task repeatedly, but with only one speaker in each dialect group.

Promoting transfer of skills learned in the training environment to novel situations is generally the underlying goal of cognitive training interventions in older adults. That is, we want participants who are being trained in memory, or attention, or executive function not only to improve in those trained domains, but also to benefit in everyday situations that require those cognitive functions, such as shopping or driving. Despite several studies showing some generalization of training effects (Jennings et al., 2005; Ball et al., 2007; Bherer et al., 2008), designing interventions that produce gains on real-world outcomes is still a major challenge in cognitive aging research. Our training program generated improvements on a number of tasks that were not practiced during the training sessions, and several of these transfer effects were seen in domains not directly targeted with the training program (e.g. dual-task performance, processing speed). Based on the literature reviewed above, this could be the result of the highly variable training stimuli. In contrast to other training regimens, our program incorporated several different categories of cognitive tasks (e.g. simple detection, sequencing, categorization, etc.) that were presented in both the auditory and visual modalities using hundreds of different stimuli, including numbers, letters, words, and sentences. Additionally there were also several hundred different visual and auditory distractor stimuli with highly variable features in many domains (e.g. color, motion, form, object, volume, pitch, voice, etc.).

A third factor that could influence the efficacy of training is the feedback that participants receive during the course of training (Schmidt and Bjork, 1992; Green and

Bavelier, 2008). Many theories of learning suggest that feedback plays an important role in learning, whether that feedback is just an error signal or a more informative comment on a given response (Jones, 1968; Herzog and Fahle, 1997; Clariana and Koul, 2006; Jou and Foreman, 2007). For example, Jou and Foreman (2007) reported that participants who were given feedback about their performance during a paradigm designed to assess false-memory formation were better able to resist forming false memories in subsequent testing than control participants who received no feedback during the training phase. For our training program, we provided feedback to participants after they completed each multiple-trial task, giving general information about their accuracy rates. This method of providing feedback about average performance on a set of trials has been demonstrated to facilitate retention and transfer of learning (Wulf et al., 1993). In contrast, other paradigms have utilized more specific trial-by-trial feedback, which may encourage faster acquisition of the training task (Goodman et al., 2004; Bherer et al., 2006). Another potentially useful feedback manipulation is to reduce the frequency of feedback to mimic the real-life environment, where the consequences of our actions may be somewhat removed from the actual behavior. Such a schedule where feedback is only given after a prolonged series of responses might promote transfer to complex skills in the real world (Green and Bavelier, 2008).

A fourth set of issues in training efficacy that is inextricably associated with each of the previous three factors is motivation and arousal (Green and Bavelier, 2008). It makes sense that training might be more effective if participants are engaged and interested in the program. Task difficulty and variability play an obvious role in motivation, as administering easy, repetitive tasks can easily induce boredom and apathy,

while requiring the completion of highly variable, complex tasks can provoke frustration and resignation. This basic concept is consistent with learning theories proposing that learning and intrinsic motivation occur most readily when tasks are challenging, but resolvable (Vygotsky, 1978; Green and Bavelier, 2008). Evidence also suggests that situations where arousal levels are very low (boredom) or excessively high (frustration), are not as conducive to learning as paradigms that encourage an intermediate level of arousal (Eysenck, 1976; Frankenhaeuser and Gardell, 1976; Baldi and Bucherelli, 2005). Additionally, learning can also be motivated by feedback, especially positive, informative feedback (Goodman et al., 2004; Clariana and Koul, 2006), like that given during our training sessions. Our intervention could perhaps have been improved by individually adapting the initial degree of task difficulty in order to optimally challenge each participant. In addition, a more game-like interface might also have increased arousal for some participants.

6.5 Maintenance of cognitive training

The factors outlined above that influence the efficacy of cognitive training can also have an impact on the long-term retention of training gains. Obviously, if the immediate benefits of an intervention are very small, we would not expect to see larger effects after some delay or follow-up interval. Several studies, however, have recently demonstrated the potential for successful cognitive training interventions to yield significant long-term effects (Oswald et al., 1996; Ball et al., 2002; Gunther et al., 2003; Willis et al., 2006; Dahlin et al., 2008b). A five-year follow-up of participants from the ACTIVE study showed that those who had received training in reasoning, speed of

processing, or memory retained benefits in the trained cognitive domain. Additionally, those trained in reasoning reported less functional decline than control participants (Willis et al., 2006).

In addition to an evaluation of training effects conducted within the first few days after training completion, our study design also incorporated one-week and one-month follow-up behavioral assessments. We found that there was a trend for maintenance of our primary outcome, reductions in cross-modal interference (session x group interaction effect: $F_{3,60} = 2.4$, $p < 0.07$). This interaction was driven by the treatment group, who exhibited a significant decrease in cross-modal interference immediately following training, which was maintained at the one-week and one-month follow-up visits. In contrast, the control group did not exhibit any significant change in interference. We also found that significant training effects on a transfer task measure of processing speed were maintained at both the one-week and one-month follow-up visits (session x group interaction effect: $F_{3,60} = 3.1$, $p < 0.03$). Again, this interaction was driven by the treatment group, which exhibited a large increase in processing speed immediately after training. These improvements remained stable at each follow-up visit, while the control group exhibited only marginal improvements each visit. Although training-induced improvements on measures of multisensory integration, dual-task performance, and working memory were still present at the follow-up visits, these gains no longer passed statistical thresholds.

A number of studies that have demonstrated long-term maintenance of training effects have included “booster sessions” of training, where participants return intermittently to continue with the training regimen (McDougall, 1999; Ball et al., 2002;

Willis et al., 2006). Although some gains were maintained in the ACTIVE trial without any additional practice, booster training did produce significant enhancements in processing speed and reasoning performance measured at the five-year follow-up visit (Willis et al., 2006). Based on these data, it is possible that additional booster sessions of training could enhance the longer-term preservation of gains from our intervention. Just as the remedy for an acute infection like bronchitis is very different than the treatment for a chronic condition such as asthma, it is unlikely that the multifactorial, progressive process of cognitive aging can be “cured” with a short-term dose of cognitive training. Continued practice on challenging, engaging cognitive tasks may be required to minimize age-related cognitive decline. Training programs that can successfully alter brain physiology as well as behavior are likely to be one important component of a mentally, physically, and socially active lifestyle that supports healthy cognitive aging.

6.6 Future directions and conclusions

There are a number of important questions raised by the studies performed for this thesis. It is clear that additional experiments will be required to determine the underlying source of age-related increases in baseline sensory processing. Importantly, our training program was able to successfully reduce cross-modal distraction through repeated practice at suppressing visual and auditory background noise. Future work to improve the training paradigm interface and adaptively alter task difficulty based on initial level of competence could potentially amplify training gains. Our training intervention also increased regional CBF at rest, suggesting that repeated stimulation of prefrontal cortical networks during training served to increase resting metabolism. Although we did not

observe clear training-induced alterations in functional activity, the CBF data indicate that future fMRI studies may want to use paradigms sensitive to activity in the inferior and medial prefrontal cortices in order to better characterize the neural effects of this training program. Other issues that could be addressed by extending the training duration, adding booster sessions, or incorporating longer follow-up intervals include an exploration of the best methods for promoting long-term maintenance of training gains and determining the cumulative effects or upper limits of continued training. Future studies might also include additional outcome measures to assess the effects of training on real-world activities such as balance and communication. Additionally, by altering the highly stringent age and health inclusion criteria of this study it might be possible to determine if the effects of training are modulated by the age, cognitive ability, or physical health of participants. Finally, it will be important to address the interaction of cognitive training with other variables that may influence brain health, such as exercise, diet, and pharmacological interventions, in order to determine how best to promote healthy brain aging for older adults.

REFERENCES

- Alain, C. and Woods, D. L. (1999). Age-related changes in processing auditory stimuli during visual attention: evidence for deficits in inhibitory control and sensory memory. *Psychol Aging* **14**(3): 507-19.
- Anderson, B. J., Li, X., Alcantara, A. A., Isaacs, K. R., Black, J. E., et al. (1994). Glial hypertrophy is associated with synaptogenesis following motor-skill learning, but not with angiogenesis following exercise. *Glia* **11**(1): 73-80.
- Andin, J., Hallbeck, M., Mohammed, A. H. and Marcusson, J. (2007). Influence of environmental enrichment on steady-state mRNA levels for EAAC1, AMPA1 and NMDA2A receptor subunits in rat hippocampus. *Brain Res* **1174**: 18-27.
- Andres, P., Guerrini, C., Phillips, L. H. and Perfect, T. J. (2008). Differential effects of aging on executive and automatic inhibition. *Dev Neuropsychol* **33**(2): 101-23.
- Baldi, E. and Bucherelli, C. (2005). The inverted "u-shaped" dose-effect relationships in learning and memory: modulation of arousal and consolidation. *Nonlinearity Biol Toxicol Med* **3**(1): 9-21.
- Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., et al. (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. *Jama* **288**(18): 2271-81.
- Ball, K., Edwards, J. D. and Ross, L. A. (2007). The impact of speed of processing training on cognitive and everyday functions. *J Gerontol B Psychol Sci Soc Sci* **62 Spec No 1**: 19-31.
- Bennett, E. L., Diamond, M. C., Krech, D. and Rosenzweig, M. R. (1964). Chemical And Anatomical Plasticity Brain. *Science* **146**: 610-9.
- Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., et al. (2006). Testing the limits of cognitive plasticity in older adults: application to attentional control. *Acta Psychol (Amst)* **123**(3): 261-78.
- Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., et al. (2008). Transfer effects in task-set cost and dual-task cost after dual-task training in older and younger adults: further evidence for cognitive plasticity in attentional control in late adulthood. *Exp Aging Res* **34**(3): 188-219.
- Black, J. E., Isaacs, K. R., Anderson, B. J., Alcantara, A. A. and Greenough, W. T. (1990). Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc Natl Acad Sci U S A* **87**(14): 5568-72.
- Black, J. E., Polinsky, M. and Greenough, W. T. (1989). Progressive failure of cerebral angiogenesis supporting neural plasticity in aging rats. *Neurobiol Aging* **10**(4): 353-8.
- Black, J. E., Sirevaag, A. M. and Greenough, W. T. (1987). Complex experience promotes capillary formation in young rat visual cortex. *Neurosci Lett* **83**(3): 351-5.
- Boyke, J., Driemeyer, J., Gaser, C., Buchel, C. and May, A. (2008). Training-induced brain structure changes in the elderly. *J Neurosci* **28**(28): 7031-5.
- Brady, M. J. and Kersten, D. (2003). Bootstrapped learning of novel objects. *J Vis* **3**(6): 413-22.

- Buckner, R. L., Andrews-Hanna, J. R. and Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* **1124**: 1-38.
- Bugos, J. A., Perlstein, W. M., McCrae, C. S., Brophy, T. S. and Bedenbaugh, P. H. (2007). Individualized piano instruction enhances executive functioning and working memory in older adults. *Aging Ment Health* **11**(4): 464-71.
- Bunce, D. J., Barrowclough, A. and Morris, I. (1996). The moderating influence of physical fitness on age gradients in vigilance and serial choice responding tasks. *Psychol Aging* **11**(4): 671-82.
- Burke, S. N. and Barnes, C. A. (2006). Neural plasticity in the ageing brain. *Nat Rev Neurosci* **7**(1): 30-40.
- Churchill, J. D., Galvez, R., Colcombe, S., Swain, R. A., Kramer, A. F., et al. (2002). Exercise, experience and the aging brain. *Neurobiol Aging* **23**(5): 941-55.
- Clariana, R. B. and Koul, R. (2006). The effects of different forms of feedback on fuzzy and verbatim memory of science principles. *Br J Educ Psychol* **76**(Pt 2): 259-70.
- Clopper, C. G. and Pisoni, D. B. (2004). Effects of talker variability on perceptual learning of dialects. *Lang Speech* **47**(Pt 3): 207-39.
- Colcombe, S. and Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci* **14**(2): 125-30.
- Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., et al. (2006). Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci* **61**(11): 1166-70.
- Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., et al. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A* **101**(9): 3316-21.
- Dahlin, E., Neely, A. S., Larsson, A., Backman, L. and Nyberg, L. (2008a). Transfer of learning after updating training mediated by the striatum. *Science* **320**(5882): 1510-2.
- Dahlin, E., Nyberg, L., Backman, L. and Neely, A. S. (2008b). Plasticity of executive functioning in young and older adults: Immediate training gains, transfer, and long-term maintenance. *Psychology and Aging* **23**(4): 720.
- Diamond, M. C., Ingham, C. A., Johnson, R. E., Bennett, E. L. and Rosenzweig, M. R. (1976). Effects of environment on morphology of rat cerebral cortex and hippocampus. *J Neurobiol* **7**(1): 75-85.
- Diamond, M. C., Johnson, R. E., Protti, A. M., Ott, C. and Kajisa, L. (1985). Plasticity in the 904-day-old male rat cerebral cortex. *Exp Neurol* **87**(2): 309-17.
- Dustman, R. E., Ruhling, R. O., Russell, E. M., Shearer, D. E., Bonekat, H. W., et al. (1984). Aerobic exercise training and improved neuropsychological function of older individuals. *Neurobiol Aging* **5**(1): 35-42.
- Edwards, J. D., Wadley, V. G., Vance, D. E., Wood, K., Roenker, D. L., et al. (2005). The impact of speed of processing training on cognitive and everyday performance. *Aging Ment Health* **9**(3): 262-71.
- Emery, C. F., Huppert, F. A. and Schein, R. L. (1995). Relationships among age, exercise, health, and cognitive function in a British sample. *Gerontologist* **35**(3): 378-85.

- Erickson, K. I., Colcombe, S. J., Wadhwa, R., Bherer, L., Peterson, M. S., et al. (2007). Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging* **28**(2): 272-83.
- Eysenck, M. W. (1976). Arousal, learning, and memory. *Psychol Bull* **83**(3): 389-404.
- Fields, R. D. (2005). Myelination: an overlooked mechanism of synaptic plasticity? *Neuroscientist* **11**(6): 528-31.
- Frankenhaeuser, M. and Gardell, B. (1976). Underload and overload in working life: outline of a multidisciplinary approach. *J Human Stress* **2**(3): 35-46.
- Gagne, J., Gelinas, S., Martinoli, M. G., Foster, T. C., Ohayon, M., et al. (1998). AMPA receptor properties in adult rat hippocampus following environmental enrichment. *Brain Res* **799**(1): 16-25.
- Gazzaley, A., Cooney, J. W., Rissman, J. and D'Esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging. *Nat. Neurosci.* **8**(10): 1298.
- Gelfo, F., De Bartolo, P., Giovine, A., Petrosini, L. and Leggio, M. G. (2009). Layer and regional effects of environmental enrichment on the pyramidal neuron morphology of the rat. *Neurobiol Learn Mem* **91**(4): 353-65.
- Goodman, J. S., Wood, R. E. and Hendrickx, M. (2004). Feedback specificity, exploration, and learning. *J Appl Psychol* **89**(2): 248-62.
- Grady, C. L., Springer, M. V., Hongwanishkul, D., McIntosh, A. R. and Winocur, G. (2006). Age-related changes in brain activity across the adult lifespan. *J Cogn Neurosci* **18**(2): 227-41.
- Green, C. S. and Bavelier, D. (2008). Exercising your brain: A review of human brain plasticity and training-induced learning. *Psychology and Aging* **23**(4): 692.
- Greicius, M. D. and Menon, V. (2004). Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. *J Cogn Neurosci* **16**(9): 1484-92.
- Gunther, V. K., Schafer, P., Holzner, B. J. and Kemmler, G. W. (2003). Long-term improvements in cognitive performance through computer-assisted cognitive training: a pilot study in a residential home for older people. *Aging Ment Health* **7**(3): 200-6.
- Hall, K. G. and Magill, R. A. (1995). Variability of Practice and Contextual Interference in Motor Skill Learning. *J Mot Behav* **27**(4): 299-309.
- Herzog, M. H. and Fahle, M. (1997). The role of feedback in learning a vernier discrimination task. *Vision Res* **37**(15): 2133-41.
- Hillman, C. H., Erickson, K. I. and Kramer, A. F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nat Rev Neurosci* **9**(1): 58-65.
- Hugenschmidt, C. E., Mozolic, J. L., Tan, H., Kraft, R. A. and Laurienti, P. J. (in press-a). Age-related increase in cross-sensory noise in resting and steady-state cerebral perfusion. *Brain Topography*.
- Hugenschmidt, C. E., Peiffer, A. M., McCoy, T. P., Hayasaka, S. and Laurienti, P. J. (in press-b). Preservation of crossmodal selective attention in healthy aging. *Experimental Brain Research*.
- Hultsch, D. F., Hertzog, C., Small, B. J. and Dixon, R. A. (1999). Use it or lose it: engaged lifestyle as a buffer of cognitive decline in aging? *Psychol Aging* **14**(2): 245-63.

- Ickes, B. R., Pham, T. M., Sanders, L. A., Albeck, D. S., Mohammed, A. H., et al. (2000). Long-term environmental enrichment leads to regional increases in neurotrophin levels in rat brain. *Exp Neurol* **164**(1): 45-52.
- Jennings, J., Webster, L., Kleykamp, B. and Dagenbach, D. (2005). Recollection Training and Transfer Effects in Older Adults: Successful Use of a Repetition-Lag Procedure. *Aging, Neuropsychology, and Cognition (Neuropsychology, Development and Cognition)* **12**(3): 278-298.
- Jones, R. E., Jr. (1968). Effects of delay of informative feedback, post-feedback interval, and feedback presentation mode on verbal paired-associates learning. *J Exp Psychol* **77**(1): 87-93.
- Jones, S., Nyberg, L., Sandblom, J., Stigsdotter Neely, A., Ingvar, M., et al. (2006). Cognitive and neural plasticity in aging: general and task-specific limitations. *Neurosci Biobehav Rev* **30**(6): 864-71.
- Jou, J. and Foreman, J. (2007). Transfer of learning in avoiding false memory: the roles of warning, immediate feedback, and incentive. *Q J Exp Psychol (Colchester)* **60**(6): 877-96.
- Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., et al. (1988). Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol* **23**(2): 138-44.
- Kempermann, G., Gast, D. and Gage, F. H. (2002). Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Ann Neurol* **52**(2): 135-43.
- Kempermann, G., Kuhn, H. G. and Gage, F. H. (1997). More hippocampal neurons in adult mice living in an enriched environment. *Nature* **386**(6624): 493-5.
- Kempermann, G., Kuhn, H. G. and Gage, F. H. (1998). Experience-induced neurogenesis in the senescent dentate gyrus. *J Neurosci* **18**(9): 3206-12.
- Kramer, A. F., Bherer, L., Colcombe, S. J., Dong, W. and Greenough, W. T. (2004). Environmental influences on cognitive and brain plasticity during aging. *J Gerontol A Biol Sci Med Sci* **59**(9): M940-57.
- Kramer, A. F., Hahn, S., Cohen, N. J., Banich, M. T., McAuley, E., et al. (1999). Ageing, fitness and neurocognitive function. *Nature* **400**(6743): 418-9.
- Krech, D., Rosenzweig, M. R. and Bennett, E. L. (1960). Effects of environmental complexity and training on brain chemistry. *J Comp Physiol Psychol* **53**: 509-19.
- Laurienti, P. J., Kraft, R. A., Maldjian, J. A., Burdette, J. H. and Wallace, M. T. (2004). Semantic congruence is a critical factor in multisensory behavioral performance. *Exp Brain Res* **158**(4): 405-14.
- Leggio, M. G., Mandolesi, L., Federico, F., Spirito, F., Ricci, B., et al. (2005). Environmental enrichment promotes improved spatial abilities and enhanced dendritic growth in the rat. *Behav Brain Res* **163**(1): 78-90.
- Li, C. S., Yan, P., Bergquist, K. L. and Sinha, R. (2007). Greater activation of the "default" brain regions predicts stop signal errors. *Neuroimage* **38**(3): 640-8.
- Linkenhoker, B. A. and Knudsen, E. I. (2002). Incremental training increases the plasticity of the auditory space map in adult barn owls. *Nature* **419**(6904): 293-6.
- Lustig, C., Snyder, A. Z., Bhakta, M., O'Brien, K. C., McAvoy, M., et al. (2003). Functional deactivations: change with age and dementia of the Alzheimer type. *Proc.Natl.Acad.Sci.U.S.A* **100**(24): 14504.

- Mahncke, H. W., Connor, B. B., Appelman, J., Ahsanuddin, O. N., Hardy, J. L., et al. (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proc Natl Acad Sci U S A* **103**(33): 12523-8.
- Markham, J. A. and Greenough, W. T. (2004). Experience-driven brain plasticity: beyond the synapse. *Neuron Glia Biol* **1**(4): 351-363.
- McDougall, G. J., Jr. (1999). Cognitive interventions among older adults. *Annu Rev Nurs Res* **17**: 219-40.
- McKiernan, K. A., D'Angelo, B. R., Kaufman, J. N. and Binder, J. R. (2006). Interrupting the "stream of consciousness": an fMRI investigation. *Neuroimage* **29**(4): 1185-91.
- Mora, F., Segovia, G. and del Arco, A. (2007). Aging, plasticity and environmental enrichment: structural changes and neurotransmitter dynamics in several areas of the brain. *Brain Res Rev* **55**(1): 78-88.
- Mozolic, J. L., Hugenschmidt, C. E., Peiffer, A. M. and Laurienti, P. J. (2008). Modality-specific selective attention attenuates multisensory integration. *Exp Brain Res* **184**(1): 39-52.
- Murtha, S., Pappas, B. A. and Raman, S. (1990). Neonatal and adult forebrain norepinephrine depletion and the behavioral and cortical thickening effects of enriched/impoverished environment. *Behav Brain Res* **39**(3): 249-61.
- Naka, F., Narita, N., Okado, N. and Narita, M. (2005). Modification of AMPA receptor properties following environmental enrichment. *Brain Dev* **27**(4): 275-8.
- Nichols, J. A., Jakkamsetti, V. P., Salgado, H., Dinh, L., Kilgard, M. P., et al. (2007). Environmental enrichment selectively increases glutamatergic responses in layer II/III of the auditory cortex of the rat. *Neuroscience* **145**(3): 832-40.
- Nyberg, L., Sandblom, J., Jones, S., Neely, A. S., Petersson, K. M., et al. (2003). Neural correlates of training-related memory improvement in adulthood and aging. *Proc Natl Acad Sci U S A* **100**(23): 13728-33.
- Olson, A. K., Eadie, B. D., Ernst, C. and Christie, B. R. (2006). Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. *Hippocampus* **16**(3): 250-60.
- Oswald, W. D., Rupperecht, R., Gunzelmann, T. and Tritt, K. (1996). The SIMA-project: effects of 1 year cognitive and psychomotor training on cognitive abilities of the elderly. *Behav Brain Res* **78**(1): 67-72.
- Persson, J., Lustig, C., Nelson, J. K. and Reuter-Lorenz, P. A. (2007). Age differences in deactivation: a link to cognitive control? *J Cogn Neurosci* **19**(6): 1021-32.
- Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., et al. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A* **98**(2): 676-82.
- Rampon, C., Jiang, C. H., Dong, H., Tang, Y. P., Lockhart, D. J., et al. (2000). Effects of environmental enrichment on gene expression in the brain. *Proc Natl Acad Sci U S A* **97**(23): 12880-4.
- Rosenzweig, M. R. and Bennett, E. L. (1996). Psychobiology of plasticity: effects of training and experience on brain and behavior. *Behav Brain Res* **78**(1): 57-65.

- Rosenzweig, M. R., Krech, D., Bennett, E. L. and Diamond, M. C. (1962). Effects of environmental complexity and training on brain chemistry and anatomy: a replication and extension. *J Comp Physiol Psychol* **55**: 429-37.
- Rowe, G., Valderrama, S., Hasher, L. and Lenartowicz, A. (2006). Attentional disregulation: a benefit for implicit memory. *Psychol Aging* **21**(4): 826-30.
- Scarmeas, N. and Stern, Y. (2003). Cognitive reserve and lifestyle. *J Clin Exp Neuropsychol* **25**(5): 625-33.
- Schooler, C., Mulatu, M. S. and Oates, G. (1999). The continuing effects of substantively complex work on the intellectual functioning of older workers. *Psychol Aging* **14**(3): 483-506.
- Schmidt, R. A. and Bjork, R. A. (1992). NEW CONCEPTUALIZATIONS OF PRACTICE: Common Principles in Three Paradigms Suggest New Concepts for Training. *Psychological Science* **3**(4): 207.
- Spirduso, W. W. (1975). Reaction and movement time as a function of age and physical activity level. *J Gerontol* **30**(4): 435-40.
- Stern, Y., Gurland, B., Tatemichi, T. K., Tang, M. X., Wilder, D., et al. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. *Jama* **271**(13): 1004-10.
- Stevens, W. D., Hasher, L., Chiew, K. S. and Grady, C. L. (2008). A neural mechanism underlying memory failure in older adults. *J Neurosci* **28**(48): 12820-4.
- Valenzuela, M. J., Breakspear, M. and Sachdev, P. (2007). Complex mental activity and the aging brain: molecular, cellular and cortical network mechanisms. *Brain Res Rev* **56**(1): 198-213.
- Valenzuela, M. J., Jones, M., Wen, W., Rae, C., Graham, S., et al. (2003). Memory training alters hippocampal neurochemistry in healthy elderly. *Neuroreport* **14**(10): 1333-7.
- Valenzuela, M. J. and Sachdev, P. (2006). Brain reserve and dementia: a systematic review. *Psychol Med* **36**(4): 441-54.
- van Praag, H., Christie, B. R., Sejnowski, T. J. and Gage, F. H. (1999). Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci U S A* **96**(23): 13427-31.
- van Praag, H., Shubert, T., Zhao, C. and Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *J Neurosci* **25**(38): 8680-5.
- Verhaeghen, P. and Cerella, J. (2002). Aging, executive control, and attention: a review of meta-analyses. *Neurosci Biobehav Rev* **26**(7): 849-57.
- Verhaeghen, P., Marcoen, A. and Goossens, L. (1992). Improving memory performance in the aged through mnemonic training: a meta-analytic study. *Psychol Aging* **7**(2): 242-51.
- Volkmar, F. R. and Greenough, W. T. (1972). Rearing complexity affects branching of dendrites in the visual cortex of the rat. *Science* **176**(42): 1445-7.
- Vygotsky, L. S. (1978). Mind and society: The development of higher psychological processes. Cambridge, MA, Harvard University Press.
- Weissman, D. H., Roberts, K. C., Visscher, K. M. and Woldorff, M. G. (2006). The neural bases of momentary lapses in attention. *Nat Neurosci* **9**(7): 971-8.
- Whalley, L. J., Deary, I. J., Appleton, C. L. and Starr, J. M. (2004). Cognitive reserve and the neurobiology of cognitive aging. *Ageing Res Rev* **3**(4): 369-82.

- Wiesel, T. N. and Hubel, D. H. (1963). Single-Cell Responses In Striate Cortex Of Kittens Deprived Of Vision In One Eye. *J Neurophysiol* **26**: 1003-17.
- Wiesel, T. N. and Hubel, D. H. (1965). Extent of recovery from the effects of visual deprivation in kittens. *J Neurophysiol* **28**(6): 1060-72.
- Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., et al. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *Jama* **296**(23): 2805-14.
- Wolf, S. A., Kronenberg, G., Lehmann, K., Blankenship, A., Overall, R., et al. (2006). Cognitive and physical activity differently modulate disease progression in the amyloid precursor protein (APP)-23 model of Alzheimer's disease. *Biol Psychiatry* **60**(12): 1314-23.
- Wulf, G., Schmidt, R. A. and Deubel, H. (1993). Reduced feedback frequency enhances generalized motor program learning but not parameterization learning. *J Exp Psychol Learn Mem Cogn* **19**(5): 1134-50.
- Zhu, J., Apparsundaram, S., Bardo, M. T. and Dwoskin, L. P. (2005). Environmental enrichment decreases cell surface expression of the dopamine transporter in rat medial prefrontal cortex. *J Neurochem* **93**(6): 1434-43.

SCHOLASTIC VITA

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University of Mary Washington
Fredericksburg, Virginia, 1999-2003
B.S., Biology and Psychology

**GRADUATE
STUDY:**

Wake Forest University Graduate School of Arts and
Sciences, Winston-Salem, North Carolina, 2004-2009
Ph.D., Neuroscience

SCHOLASTIC AND PROFESSIONAL EXPERIENCE

Ruth L. Kirschstein National Research Service Award - National Institute on
Aging, Pre-doctoral Fellowship

Teaching Assistant, Introduction to Neuroscience, Wake Forest University, 2008

Teaching Assistant, Neuroanatomy, Wake Forest University Graduate School of
Arts and Sciences, 2008

HONORS AND AWARDS

George Sacher Student Research Award, Gerontological Society of America 2008

Poster Award, WFU Graduate Student Research Day 2008

Student Travel Scholarship, Aging and Speech Communication Conference 2007

Student Travel Award, Human Brain Mapping Conference 2007

OTHER ACADEMIC AND PROFESSIONAL SERVICE

Invited lecture, Central Piedmont Community College Lifelong Learning Institute

Brain Awareness Council, science education outreach program

Ad hoc reviewer for *Experimental Brain Research* and *Brain Research*

PUBLICATIONS

Book chapter

Mozolic, JL, Hugenschmidt, CE, Peiffer, AM, Laurienti, PJ. (*in review*) Multisensory integration and aging, in Frontiers in the neural bases of multisensory processes, Wallace, M, Murray, M, Simon, S, Nicolelis, M, *Eds*.

Research articles

Mozolic, JL, Hayasaka, S, Laurienti, PJ. (*in review*). A cognitive training intervention increases resting cerebral blood flow in healthy older adults. *Human Brain Mapping*.

Mozolic, JL, Long, AB, Morgan, AR, Rawley-Payne, M, Laurienti, PJ. (*in press*). A cognitive training intervention improves modality-specific attention in a randomized controlled trial of healthy older adults. *Neurobiology of Aging*.

Hugenschmidt, CE, **Mozolic, JL**, Tan, H, Kraft, RA, Laurienti, PJ. (*in press*). Age-related increase in cross-sensory noise in resting and steady-state cerebral perfusion. *Brain Topography*.

Hugenschmidt, CE, **Mozolic, JL**, Laurienti, PJ. (2009). Suppression of multisensory integration by modality-specific attention in aging. *Neuroreport*, 20(4):349-353.

Mozolic, JL, Joyner, D, Hugenschmidt, CE, Peiffer, AM, Kraft, RA, Maldjian, JA, Laurienti, PJ. (2008). Cross-modal deactivations during modality-specific selective attention. *BMC Neurology*, 8:35.

Mozolic, JL, Hugenschmidt, CE, Peiffer, AM, Laurienti, PJ. (2008). Modality-specific selective attention attenuates multisensory integration. *Experimental Brain Research*, 184(1):39-52.

Peiffer, AM, **Mozolic, JL**, Hugenschmidt, CE & Laurienti, PJ. (2007). Age-related multisensory enhancement in a simple audiovisual detection task. *Neuroreport*, 18:1077-1081.

Abstracts

Mozolic, JL, Morgan, AR, Laurienti, PJ. Cognitive training impacts brain function and structure of healthy older adults in a randomized controlled trial. Abstract No. 1315, Washington, D.C.: GSA 2008.

Mozolic, JL, Morgan, AR, Laurienti, PJ. Cognitive training impacts functional brain activity and cerebral blood flow of healthy older adults in a randomized controlled trial. Abstract No. 60, Melbourne, Australia: HBM 2008.

Mozolic, JL, Morgan, AR, Laurienti, PJ. BFIT: Evaluating the behavioral and neural effects of a cognitive training program in older adults. Charlotte, NC: CBTC 2007.

Mozolic, JL, Morgan, AR, Long, AB, Laurienti, PJ. Brain Fitness in Older Adults: A randomized controlled trial of the effects of attention training in older adults. Bloomington, IN: ASC 2007.

Mozolic, JL, Rawley-Payne, M, Long, AB, Laurienti, PJ. Brain Fitness in Older Adults: A randomized controlled trial of the effects of attention training in older adults. Abstract No. 53, Chicago IL: HBM 2007.

Peiffer, AM, **Mozolic, JL,** Hugenschmidt, CE & Laurienti, PJ. Age-related multisensory enhancement occurs with simple audiovisual detection task. Program No. 137.4 2006. *Abstract Viewer/Itinerary Planner*. Atlanta, GA: SFN 2006. Online.