THE EFFECTS OF AGING ON CROSS-MODAL ATTENTION

BY

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LIST OF ABBREVIATIONS

3DSPGR-IR: 3 dimensional spoiled gradient – inversion recovery
AC/PC: Anterior commissure/posterior commissure
ANOVA: Analysis of variance
AUDIT: Alcohol use disorders identification test
BOLD: Blood-oxygen level dependent
CBF: Cerebral blood flow
CES-D: Centers for epidemiological studies depression scale
CDF: Cumulative distribution function
C-FOCI: C-shaped frequency offset corrected inversion
DMN: Default mode network
EEG: Electroencephalogram
EPI: Echo-planar imaging
ERP: Event-related potential
FAIR: Flow sensitive alternating inversion recovery
FDR: False discovery rate
FEF: Frontal eye fields
fMRI: Functional magnetic resonance imaging
FWHM: Full-width half-maximum
ICA: Independent component analysis
LED: Light-emitting diode
MEG: Magnetoencephalogram
MMN: Mismatch negativity
<table>
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<tr>
<td>MMSE</td>
<td>Mini-mental state examination</td>
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<td>MSE</td>
<td>Modality shift effect</td>
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<tr>
<td>OEF</td>
<td>Oxygen extraction fraction</td>
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<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>PFC</td>
<td>Prefrontal cortex</td>
</tr>
<tr>
<td>Q2TIPS</td>
<td>QUantitative imaging of perfusion using single subtraction with thin slice TI$_1$ periodic saturation (also called QUIPSS II TIPS)</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>RT</td>
<td>Reaction time</td>
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<tr>
<td>SEM</td>
<td>Standard error of the mean</td>
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<td>SEP</td>
<td>Sensory evoked potential</td>
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<tr>
<td>SNR</td>
<td>Signal-to-noise ratio</td>
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<tr>
<td>TPJ</td>
<td>Temporoparietal junction</td>
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<td>VBM</td>
<td>Voxel-based morphometry</td>
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<td>VSS</td>
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THE EFFECTS OF AGING ON CROSS-MODAL ATTENTION

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

ABSTRACT

Healthy aging is accompanied by declining sensory function in all five senses and subtle deficits in higher order cognition. Among the age-related changes that have been observed is an increase in multisensory integration. In the young brain, multisensory integration is governed by a combination of stimulus characteristics (spatial location, timing, and intensity) and higher-order cognitive constraints (semantic congruence, attention). Given previous research suggesting that executive functioning and attention might be impaired in healthy aging, it was hypothesized that increased integration resulted from a failure to properly restrict incoming sensory information with cross-modal attention.

Behavioral testing comparing reaction times and accuracy during voluntary and involuntary attentional tasks demonstrated that older adults maintained the ability to successfully engage cross-modal attention. Therefore, another behavioral experiment was undertaken to investigate the ability of older adults to restrict multisensory processing using cross-modal attention. The amount of multisensory integration while participants divided their attention across vision and hearing was compared to that when they attended selectively to vision or hearing. Greater multisensory integration was observed with aging in all attentional conditions, suggesting that older adults were processing more to-be-ignored stimuli than younger adults. However, older adults were able to attenuate multisensory integration equivalently to younger adults, supporting the findings from the first study that cross-modal attentional mechanisms are functional in healthy aging. The
reason for increased integration during selective attention appeared to be that there was an overall increase in the amount of sensory information processed in all conditions. This suggests that the reason for increased multisensory integration with aging is not due to a failure of attention, but rather greater sensory processing at baseline.

A functional neuroimaging study was undertaken to investigate the neural mechanisms of a baseline shift in sensory processing. Average quantitative perfusion maps were used to assess functional brain activity in older and younger adults for resting state and visual steady-state conditions. Previous research shows that cross-modal attention acts primarily by suppressing processing of stimuli in the unattended modality. Therefore, relative activity in auditory and visual cortices was examined, as well as the ratio of visual to auditory activity. Results of the imaging experiment supported behavioral observations. Older adults showed relatively greater auditory activity than younger adults at resting baseline. While participants in both age groups showed expected task-related reductions during the visual condition, older adults still exhibited greater activity to background auditory stimuli.

Finally, it was hypothesized that the observed baseline increase in processing of unattended auditory stimuli was due to increased activity in the default mode network. Evidence did not support this hypothesis. The default mode was found to have lower resting activity in older adults than younger adults, and default mode activity did not correlate with auditory activity. However, the observation of reduced metabolic activity in the default mode network is novel and important in its own right, as is the suggestion from the data that the default mode network may become decoupled during visual tasks in healthy aging adults.
CHAPTER I

INTRODUCTION

Christina E. Hugenschmidt and Paul J. Laurienti
A 20 year-old man sits in a crowded subway car reading a newspaper. Although his hearing is good, he is focused on the text in front of him and could not tell you about the conversations going on around him. In fact, he is ignoring many other sensory stimuli that are not relevant to the task at hand. Could a healthy 70 year-old person do the same thing? This is the fundamental question this thesis seeks to answer by investigating how the aging brain processes stimuli from multiple senses and engages selective attention.

1.1 Multisensory Integration

The brain interfaces with the environment through different sources of energy: light, sound waves, physical energy, and chemical odorants and tastants. In addition to clear benefits, this wealth of information faces the brain with distinct challenges of how, when, and if this information should be combined to best form a functional approximation of the surrounding world. Our experiences inform us that the brain has solved this problem to a useful enough degree, and over the past thirty years, research in models ranging from the moth to the human has investigated the neural and behavioral characteristics of interactions between the senses in multiple brain regions (Menzel and Barth, 2005; Meredith and Stein, 1986b; Schroeder and Foxe, 2002; Skals, et al., 2005; Stein, et al., 1993; Wallace, et al., 1992, 1993, 1998; Wallace, et al., 1996).

1.1.1 Modulating Multisensory Integration

Data from neural recordings in animals and human psychophysical experiments show that stimuli that engage multiple senses (cross-modal stimuli) result in gains in the form of increased neuronal action potential output, faster onset of neuronal firing, faster
reaction times and improved accuracy under certain circumstances (Diederich and Colonius, 2004; Forster, et al., 2002; Giard and Peronnet, 1999; Hughes, et al., 1994; Lovelace, et al., 2003; Meredith and Stein, 1983; Rowland, et al., 2007; Schroger and Widmann, 1998; Stein and Meredith, 1993; Stein and Wallace, 1996; Wallace, et al., 1998). Such gains are examples of a positive interaction or dependency between the sensory channels, where more information results in better performance of the system. Sensory inputs can also be dependent on one another in a negative way, where the presence of information from additional sensory channels actually interferes with behavioral functioning, or depresses the firing of neurons (Hu and Woollacott, 1994a, 1994b; Jiang and Stein, 2003; Kadunce, et al., 1997; Laurienti, et al., 2004).

Of course, cross-modal stimulation is frequently present and information from the different senses does not interact, as in the subway example above. There are many sounds occurring at the same time the man is reading, but he is not combining the noises around him with the text he reads. Both subcortical “bottom-up” and cortically-mediated “top-down” processes contribute to the outcome of which sensory inputs are combined and which are processed independently.

1.1.2 Bottom-up Modulation

From a bottom-up perspective, physical characteristics of cross-modal stimuli such as their location, temporal coincidence, and intensity govern whether or not they are likely to be combined (Kadunce, et al., 1997; Stein, et al., 1988; Stein and Meredith, 1993; Wallace, et al., 1996). If two stimuli occur at the same location or close together in time, they are more likely to be combined (Meredith, et al., 1987; Meredith and Stein,
This makes intuitive sense from an environmental standpoint – two stimuli that are coincident in space and/or time are likely to emanate from the same source. Stimuli are also most likely to be combined as they individually become less effective, a phenomenon known as the principle of inverse effectiveness (Meredith and Stein, 1986c). This makes intuitive sense - detection or discrimination of an ambiguous stimulus could be improved with additional information from another sensory modality. Thus, if one stimulus is difficult to resolve, the brain is more likely to combine information from other sensory modalities (Hairston, et al., 2003; Stein and Meredith, 1993; Stein and Stanford, 2008; Stevenson, et al., 2007).

1.1.3 Top-down Modulation

In addition to basic stimulus characteristics, cortically dependent processes such as semantic congruence and attention also modulate multisensory integration (Alsius, et al., 2005; Laurienti, et al., 2004; Mozolic, et al., 2008a; Talsma, et al., 2007; Talsma and Woldorff, 2005; van Atteveldt, et al., 2007). For instance, Laurienti and colleagues (2004) demonstrated behavioral gains when cross-modal stimuli were semantically congruent (e.g., a blue circle and the word “blue” being spoken), but slowed reaction times and increased errors to incongruent pairs of stimuli (e.g., a blue circle and the word “green” being spoken). The spatial location and temporal onset of the paired stimuli were the same, but their meaning determined the behavioral outcome.

Multisensory interactions can also be modulated by endogenous attentional mechanism as has been demonstrated recently by multiple laboratories (Alsius, et al., 2005; Degerman, et al., 2007; Johnson and Zatorre, 2005; Mozolic, et al., 2008a; Talsma,
The ability of modality-specific selective attention to restrict multisensory integration in young healthy adults was demonstrated by Mozolic and colleagues (2008). In this experiment, subjects were asked to discriminate whether they detected a red or a blue target. Targets could be visual only (a colored circle), auditory only (the words “red” or “blue” being spoken), or cross-modal (e.g., a blue circle and the word “blue” being spoken). Before each target was presented, subjects were cued to attend selectively to their sense of vision, selectively to their sense of hearing, or to divide their attention and attend to vision and hearing at the same time. On divided attention trials, participants demonstrated a positive interaction between the senses; their performance was significantly speeded to multisensory stimuli (Figure 1, adapted from Mozolic et al., 2008). However, on trials where they were directed to selectively attend, participants no longer benefited from the presence of multisensory stimuli. Similarly, Talsma and Doty (2007) found event-related potential (ERP) evidence of multisensory enhancements when attention was directed simultaneously to vision and hearing, but not when only one sensory channel was attended. These studies clearly show that the same stimuli can be integrated or not based on the engagement of cross-modal selective attention.

1.2 Cross-modal Attention

Multisensory integration emphasizes salient events by combining information from different sensory channels (Stein and Meredith, 1993). Attention, on the other hand, trains a “spotlight” on relevant stimuli while suppressing extraneous information.
The difference in response probability between multisensory trials and race model predictions during divided attention (orange solid curve), selective auditory attention (green dotted curve), and selective visual attention (blue dashed curve) illustrates that significant multisensory enhancements are only present under divided attention conditions (shaded bar, 356–408 ms) (Mozolic, et al., 2008a).

(Chawla, et al., 1999; Kastner and Ungerleider, 2000, 2001; Kawashima, et al., 1995; Pinski, et al., 2004; Posner and Driver, 1992; Roland, 1982). Attentional resources can be deployed voluntarily (endogenously), such as the young man on the subway choosing to limit his processing to the visual stimulus of his paper. Attention can also be captured involuntarily (exogenously) by particularly salient stimuli (Corbetta and Shulman, 2002; Kincade, et al., 2005). For instance, the man reading on the subway would likely be distracted if an alarm went off in the subway car regardless of his voluntary concentration. A person’s overall attentional state is a balance of both attentional processes that results in the volitional suppression of some inputs but automatic processing of others.

Endogenous attention can restrict processing along several different dimensions (Corbetta, et al., 1991), the best explored being spatial location (Brefczynski and DeYoe, 1999; Desimone and Duncan, 1995; Kastner and Ungerleider, 2000, 2001). In a spatial attention task, stimuli that are presented in the attended location result in enhanced neural responses (Kastner and Ungerleider, 2001) and improved behavioral performance (Posner, et al., 1980). Conversely, stimuli presented outside of the region of attention produce suppressed neural responses (Kastner and Ungerleider, 2001) and poor behavioral performance (Posner and Driver, 1992). This central enhancement and surrounding suppression is the origin of the analogy of the attentional spotlight, implying attention works like a beam of light focused on the attended area in space. The benefits of such an attentional mechanism are fairly obvious. When one wants to process information in a specific location the signal is enhanced and the surrounding noise is suppressed.
Exogenous attention is the ability of attention to be captured by salient stimuli in the environment. The ability for an external event to capture attention is important ecologically as it can focus attention on potentially consequential environmental events. While the young man in the opening scenario is quite effective at suppressing background noise, if a group of noisy teenagers entered the train, his attention might be captured and he would look to see who boarded the train despite the fact that he was focused on his reading. If an auditory stimulus captures exogenous auditory attention, it not only conveys environmental benefits, but also facilitates processing of subsequent auditory stimuli at the expense of other sensory modalities (Spence and Driver, 1997). For example, processing of an auditory stimulus following the boarding of the teenagers will be speeded because attention is already directed to the auditory modality.

It has been well-demonstrated that processing can be restricted based on sensory modality (Spence and Driver, 1997; Spence, et al., 2001), a phenomenon termed either modality-specific or cross-modal attention. In this thesis, both terms will be used interchangeably. The neural mechanism underlying modality-specific attention appears to be more heavily weighted toward suppressing neural activity in brain regions processing the unattended sense(s) with minor enhancements in neural activity for the cortices serving the attended modality (Fox, et al., 2005; Ghatan, et al., 1998; Johnson and Zatorre, 2005; Kawashima, et al., 1995; Mozolic, et al., 2008b; Roland, 1982).

1.3 The effects of aging on multisensory interactions

Normal aging is accompanied by declining function in all five sensory systems (Cerf-Ducastel and Murphy, 2003; Cienkowski and Carney, 2002; Enrietto, et al., 1999;
Mordi and Ciuffreda, 2004; Ostroff, et al., 2003; Schmolesky, et al., 2000). Changes in peripheral sense organs, (e.g., lens changes such as cataracts, loss of hair cells in the cochlea), and in the central nervous system both contribute to perceptual degradation evidenced in poorer discrimination of sights, sounds, smells, tastes, and somatosensory discrimination of objects. Interestingly, at the same time perception in individual senses declines, integration between sensory channels increases (Laurienti, et al., 2006; Strupp, et al., 1999). In fact, this effect is so powerful that older adults actually respond faster than younger adults to cross-modal stimuli in a simple response time task (Peiffer, et al., 2007) (Figure 2 adapted from Peiffer et al. 2007). However, this increase in multisensory integration is not a fountain of youth. Unpublished data from our laboratory show that older adults are more slowed when cross-modal stimuli are semantically incongruent. The implications of this finding are twofold: 1) there can be negative consequences for unrestrained interactions between the senses and 2) older adults do not restrict multisensory interactions as much as younger adults.

The mechanisms of multisensory integration described above offer several potential reasons for increasing multisensory interactions with age. From a bottom-up perspective, aging-induced sensory deficits in discrimination and detection thresholds might alter interactions between the senses [for review see (Timiras, 2003)]. One consequence of sensory degradation is that more environmental stimuli are less effective for older than for younger adults. Therefore, older adults may integrate more based on the principle of inverse effectiveness (Stein and Meredith, 1993). Although stimulus characteristics likely have a considerable effect on integration in older adults, there is also
Response Time averages for sensory conditions presented in a simple detection task. Multisensory responses were significantly faster than either visual or auditory responses for younger and older adults (+). While no main effect of age group was found, a significant interaction was seen between sensory condition and age group indicating that older adults were actually faster than young adults on multisensory trials but not on unisensory trials (*). Error bars indicate standard error of the mean. Adapted from (Peiffer, et al., 2007).
evidence that higher-order cognitive functions, including attention, may decline with age, suggesting another mechanism for increased integration in older adults.

1.4 The effects of aging on modality-specific attention

Findings about the effects of healthy aging on attention are far from uniform. It appears that for every study that finds age-related changes in attention, there is another that does not. Several studies have observed that healthy older adults can benefit from voluntary attention (Ballesteros, et al., 2008; Madden and Langley, 2003; Madden, et al., 2004; Verhaeghen and Cerella, 2002), although other studies have found age-related deficits (Allen, et al., 1994; Milham, et al., 2002; West, 2004). Research on exogenous processing has reported reasonably consistent findings that older adults process more extraneous information than younger adults within sensory systems (Alain and Woods, 1999a; Andres, et al., 2006; Dywan, et al., 1998; Fabiani, et al., 2006; Healey, et al., 2008; Yang and Hasher, 2007). However, none of these studies explicitly explore the effects of aging on cross-modal attention.

Research about the effects of aging on modality-specific attention is limited. Poliakoff and colleagues (2006) tested the effects of age and spatial modulation on cross-modal attention. Older adults were differentially affected by visual distractors in a tactile discrimination task, committing more errors than younger participants. However, there was no significant Distractor x Age interaction in reaction times, suggesting that older adults were not differentially slowed by the presence of distractors. This is noteworthy as most studies of cross-modal selective attention report and observe effects in reaction times (Spence and Driver, 1997; Spence, et al., 2001). In addition, it should be noted that
data were heavily cleaned in this study. Reaction times greater than 1500 ms were discarded, and then outliers were cleaned from the reduced data set. Moreover, 10 older adults were omitted from the final analysis for low accuracy, but no younger adults were dropped (Poliakoff, et al., 2006). Overall, results from this study are interesting and suggest that age-related differences in modality-specific attention may exist under certain circumstances, but further research is warranted.

Behavioral evidence using tasks such as visual search with distractors (Allen, et al., 1994; Plude, et al., 1994) indicates that attention in older adults is more influenced by stimulus properties than in young adults, a concept supported by studies of event-related potentials (ERPs). Mismatch negativity (MMN) represents higher-order processes evoked to deviant stimuli in oddball tasks. In the auditory modality, it has been found that older adults demonstrate smaller MMNs to unattended stimuli than younger adults (Chao and Knight, 1997; Tales, et al., 2002; Valeriani, et al., 2003; Woods, 1992), indicating that irrelevant stimuli are processed to the same extent as relevant stimuli. Sensory evoked potential (SEPs) reflect the response in sensory cortex to sensory stimulation. In contrast to MMN, SEPs to task irrelevant or background stimuli in sensory cortices are enhanced in the elderly when compared to younger adults (Alain and Woods, 1999b; Chao and Knight, 1997; Valeriani, et al., 2003). These data suggest that older adults process irrelevant stimuli more than younger adults because they do not effectively filter unwanted stimuli. While these studies suggest age-related limitations in exogenous attention, this topic is only beginning to be explored, and functional brain imaging of exogenous attention in the elderly is all but nonexistent.
The studies discussed above suggest that there are age-related changes in the processing of cross-modal distractors. However, the reason for the observed differences is not clear. Older adults might be more distracted because they never properly instantiate top-down voluntary selective attention. That is, they might be constantly in a state of divided attention and never effectively suppress potentially distracting information, thereby increasing processing of distractors. Alternatively, bottom-up changes in stimulus processing could increase the influence of exogenous attentional capture. The studies included in this thesis were aimed at determining the effects of aging on modality-specific attention and the potential underlying neural mechanisms. To this end, a series of behavioral and neuroimaging studies were undertaken. First, a behavioral experiment tested cross-modal attention in younger and older adults using a cued attention paradigm (Chapter 2). This was followed by another behavioral experiment comparing multisensory integration during selective attention between older and younger participants (Chapter 3). Finally, a functional brain imaging experiment was undertaken to examine the neural correlates of the behavioral findings (Chapters 4 & 5).
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CHAPTER II

PRESERVATION OF CROSSMODAL SELECTIVE ATTENTION
IN HEALTHY AGING

Christina E. Hugenschmidt, Ann M. Peiffer, Thomas P. McCoy, Satoru Hayasaka, and
Paul J. Laurienti

The following manuscript is under review at Experimental Brain Research, 2008. Stylistic variations are due to the requirements of the journal. Christina E. Hugenschmidt performed the experiments and prepared the manuscript. Dr. Ann M. Peiffer performed the experiments. Thomas P. McCoy acted in an advisory capacity for performance of Cox proportional hazards analysis. Dr. Satoru Hayasaka acted in an advisory capacity for statistical analysis of capacity analyses. Dr. Paul J. Laurienti acted in an advisory and editorial capacity.
Abstract

The goal of the present study was to determine if older adults benefited from attention to a specific sensory modality in a voluntary attention task and evidenced changes in voluntary or involuntary attention when compared to younger adults. Suppressing and enhancing effects of voluntary attention were assessed using two cued forced-choice tasks, one that asked participants to localize and one that asked them to categorize visual and auditory targets. Involuntary attention was assessed using the same tasks, but with no attentional cues.

The effects of attention were evaluated using traditional comparisons of means and Cox proportional hazards models. All analyses showed that older adults benefited behaviorally from selective attention in both visual and auditory conditions, including robust suppressive effects of attention. Of note, the performance of the older adults was commensurate with that of younger adults in almost all analyses, suggesting that older adults can successfully engage crossmodal attention processes.

Keywords: aging, crossmodal, elderly, human, proportional hazards, selective attention
2.1. Introduction

Attention can be thought of as the ability to restrict processing to only the most important or salient stimuli in the environment, and different kinds of attention have been identified based on what stimulus characteristics are used to restrict processing. Crossmodal attention is the ability to restrict processing based on sensory modality, that is, the ability to focus selectively on what you are seeing and ignore stimuli from other senses (Spence and Driver 1997; Spence et al. 2001). The ability to ignore has both voluntary and involuntary components. A person could be more distractible because s/he is less effective at suppressing potential distractors with endogenous (voluntary) attention, or because changes in exogenous (involuntary) attention, stimulus processing, or baseline cognitive state make him/her more vulnerable to distraction.

Most research on aging and attention has focused on attention within one modality, such as visual attention during a visual search task (Lavie and Cox 1997; Maylor and Lavie 1998; Madden et al. 2002; Madden and Langley 2003; Madden et al. 2004) [for review see (Plude et al. 1994; Groth and Allen 2000)]. Little research has addressed the effects of aging on crossmodal selective attention. Poliakoff and colleagues (2006) have one of the only studies directly assessing crossmodal selective attention and aging. Their study examined reaction times and error rates for young, young-old, and old-old participants in a visual task with tactile distractors and a tactile task with visual distractors. They observed that older adults were more slowed and committed more errors than younger adults during a tactile task with visual distractors. Importantly, this suggests that crossmodal attention is impaired in older adults under certain task conditions. As mentioned above, this increase in distractibility when people are instructed to attend
could occur if older adults did not engage voluntary selective attention, exhibited changes in stimulus processing or exogenous capture, or had a change in baseline state. The present study aimed to address the question of whether or not older adults can successfully instantiate crossmodal selective attention and to examine potential age-related effects on exogenous attentional pull.

Spence, Driver, and colleagues’ (Spence and Driver 1997; Spence et al. 2001) thorough exploration of potential caveats in the careful design of crossmodal paradigms provided the basis for these experiments. Healthy older and younger adults completed cued and uncued versions of a task where they were required to identify the spatial location of a visual or auditory target, closely following Spence and Driver’s (1997) design. In addition, participants performed cued and uncued versions of a non-spatial task in which they were required to categorize visual or auditory targets. It was hypothesized that younger adults would better engage voluntary attention, therefore exhibiting greater effects of endogenous attention than older adults, but older adults would be more influenced by involuntary attentional capture than younger subjects.

2.2 Methods

2.2.1 Subjects

A total of 26 younger adults and 26 older adults were tested. Results from 25 younger and 24 older adults are reported for the endogenous tasks. Data were excluded for participants that did not complete all paradigms (one older adult), did not follow instructions (one older adult), or were greater than 3 standard deviations from the group
mean in 3 of the 4 tasks (one younger adult). In the cued spatial task, one additional older subject was excluded for having cost and benefit values well greater than 3 standard deviations from the other subjects. In the exogenous paradigms, three younger participants were excluded because of an error in data acquisition, for a total of 23 younger and 24 older subjects. Major subject characteristics are listed in Table 2.1.

As this was a study of healthy aging, participants were excluded for evidence of dementia, considered to be a score of greater than 2.5 standard deviations from the mean for their age and education on the mini-mental state examination (MMSE) (Bravo and Herbert 1997), as well as self-reported diagnoses or medications consistent with psychiatric disorders, neurological problems, head injuries, stroke, or diabetes. Potential participants were further screened for evidence of alcoholism with the Alcohol Use Disorders Identification Test (Bohn et al. 1995). Participants who reported a diagnosis of depression were allowed to participate if they had been receiving treatment for 3 months or longer and were currently non-symptomatic as assessed using the Center for Epidemiological Studies Depression Scale (CES-D) (Haringsma et al. 2004). In addition, participants 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), audioscope (Welch Allyn, Skaneateles Falls, NY), or audiologists at the Wake Forest University Department of Speech and Hearing.
<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Education (years)</th>
<th>Right handed</th>
<th>MME</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger</td>
<td>28.3 (5.9)</td>
<td>16.1 (2.6)</td>
<td>n = 23</td>
<td>28.8 (1.5)</td>
<td>n = 13</td>
</tr>
<tr>
<td>Older</td>
<td>67.9 (3.5)</td>
<td>14.8 (2.6)</td>
<td>n = 22</td>
<td>28.5 (1.4)</td>
<td>n = 11</td>
</tr>
</tbody>
</table>

Means are listed with standard deviations in parentheses. MME = Mini-mental state exam
2.2.2 Design

Participants completed spatial and non-spatial tasks testing endogenous and exogenous attention, for a total of 4 tasks (spatial – endogenous, spatial – exogenous, non-spatial – endogenous, non-spatial – exogenous). Subjects completed the experiments over the course of two visits, spatial tasks on one day and non-spatial on another. The order of spatial versus non-spatial tasks was randomized across subjects. Within the spatial and non-spatial tasks, the order of presentation of endogenous and exogenous tasks was randomized. All experiments were completed in a sound and light attenuated booth (Whisper Room, Morristown, PA, USA). All stimuli were presented and reaction time and accuracy data collected using E-Prime stimulus presentation software (Psychology Software Tools, Pittsburgh, PA, USA). Reported reaction times are from correct responses only. Each participant’s reaction time data were cleaned for outliers by removing responses that were more than 3 standard deviations from that participant’s mean on the task.

2.2.3 Stimuli for spatial tasks

Spatial tasks were based on paradigms developed by Spence, Driver, and colleagues (Spence and Driver 1997; Spence et al. 2001) to test crossmodal attention in younger adults. Participants faced an array of 4 speakers and 4 red light emitting diodes (LEDs) arranged at the corners of an imaginary rectangle where speakers and LEDs were located 52° right and left of fixation and 18° above and below midline (Figure 2.1). Participants were instructed to press the right button if they saw or heard a target in one of the two locations on their right and the left button if they saw or heard a target from
the left locations. Auditory targets were 150 ms white noise stimuli (five 20 ms white noise bursts separated by 10 ms gaps) from one speaker, and visual targets were a 50 ms illumination of one of the 4 red LEDs. A 5 cm long row of 5 LEDs was located at the center of the display. A blue central LED served as fixation. The fixation LED remained illuminated throughout the task, and subjects were instructed to remain focused on the fixation. The fixation LED was flanked by two green LEDs whose illumination served as the cue to attend to the auditory sense. The green LEDs were in turn flanked by two yellow LEDs whose illumination directed participants to attend to their sense of vision. Illumination of both yellow and green LEDs served as a divided attention cue. Participants were seated 45 cm from fixation with fixation at eye level.

2.2.4 Stimuli for Non-spatial Tasks

The non-spatial task was designed to closely replicate the crossmodal attention demands of the spatial task, but with a design that did not use spatial location as a target. During non-spatial tasks, participants were seated with their chin in a comfortably adjusted chin rest 52.1 cm from a 17 inch LG 915FT+ monitor run by a Dell PC computer and were instructed to maintain fixation on a black fixation cross located at the center of the screen at all times (Figure 2.1). Visual targets were black silhouettes of animals presented for 250ms against a white screen above or below fixation. Auditory targets were 250ms clips of animal sounds (edited for length using Goldwave software, www.goldwave.com) presented through speakers flanking the monitor with volume adjusted to be clearly audible. During the task, participants indicated with a button press
On the left is a schematic representation of the spatial task, where colored circles represent light emitting diodes (LEDs) and black squares indicate speaker position. On the right is an example of the non-spatial task, illustrated with one of the visual farm animal targets. Both examples show visual targets, but auditory targets were presented with equal frequency.
indicate they saw or heard a zoo animal and the other half pressed the right button. An attentional cue was presented prior to the presentation of the target. The attentional cue consisted of two black and white pictures, one located to the left of fixation and one to the right, and an auditory cue. The visual attention cue was two eyes and the word “see” being spoken, the auditory cue was two ears and the word “hear”, and one ear and one eye with the word “both” spoken directed subjects to divide their attention between the visual and auditory modalities.

2.2.5 Endogenous Design

The endogenous tasks were a cued spatial task and a cued non-spatial task. The timeline for the two cued tasks was identical except for the duration of the targets (Figure 2.1). Each trial began with a delay whose length varied randomly between 500-700 ms. The delay was followed by presentation of an attentional cue for 750 ms. After another delay that randomly varied between 400 and 700 ms, the target was presented, and participants had 2000 ms in which to make a response. Participants completed a practice block of 24 trials, which they could repeat if necessary, and then 7 blocks of 60 trials each. In each block, 40 trials were validly cued, 10 were invalidly cued, and 10 were preceded by a divided attention cue, for a total 420 trials of 280 valid trials, 70 invalid trials, and 70 neutral trials. Subjects were informed during the instructions that the cues would not always be correct, but were correct about 80% of the time (valid and neutral trials), and that they should pay attention to the cued sense.
2.2.6 Exogenous Design

The exogenous paradigms were identical to the endogenous tasks except they contained no cues. Each trial began with a delay period that randomly varied in duration between 500 and 700 ms. The target was presented after the delay, and again participants had 2000 ms in which to make a response. Participants completed a practice block of 24 trials, and then 4 blocks with 80 trials each. Trials could either be “same” trials or “switch” trials. In same trials, the sensory modality of the target matched the sensory modality of the preceding target, e.g., a visual target preceded by a visual target. In switch trials, the sensory modality of the target was different from the sensory modality of the preceding trial, e.g., a visual target preceded by an auditory target. Overall, there were a total of 79 same and 79 switch trials in each modality.

The measure of interest in the exogenous tasks was the modality shift effect (MSE) (Cohen and Rist 1992; Spence and Driver 1997). The modality shift effect captures the slowing that occurs when a person switches processing from one sensory modality to the other. The MSE is believed to be completely exogenous and is calculated by determining the difference between reaction time on same and switch trials. Because the only difference between the targets in the same and switch trials is the sensory modality of the trial preceding them, the MSE is thought to index the exogenous pull of the preceding sensory modality. Therefore, the MSE calculated on visual trials would reflect the exogenous influence of the auditory modality on the visual, and vice versa.
2.3 Analysis methods

Two different analysis methods were used to investigate potential age-related differences in attentional effects. Mean reaction times were compared, as these are most commonly used in the literature and provide fundamental and valuable information about the central tendencies of the data. In addition, Cox proportional hazards modeling was performed as a means to capture relationships between conditions using a semi-parametric design with the potential to be more sensitive to age-related differences in the data. The Cox proportional hazards analysis is described below.

2.3.1 Measures of central tendency

Previous research has observed speeding on validly cued trials (benefit) and slowing on invalidly cued trials (cost) relative to divided attention trials, as discussed in detail by Spence and Driver (Spence and Driver 1997; Spence et al. 2001). For the endogenous tasks, the measures of interest were these attentional effects (benefit and cost). The benefit is determined by calculating the difference between average response times to neutrally and validly cued trials (neutral – valid), and cost is the difference between neutrally and invalidly cued trials (invalid – neutral). Visual and auditory reaction times and attentional effects were explored in separate repeated measures analyses of variance (ANOVAs) using SPSS (SPSS Inc., Chicago, IL, USA), as attentional effects were not assumed to be the same between modalities. As such, comparisons between the auditory and visual modalities are not explored within this paper. Reaction times in the cued task were examined in ANOVAs of Cue Condition (valid, invalid, neutral) x Age and cost and benefit were tested in ANOVAs of
Attentional Effects (cost, benefit) x Age. For the exogenous tasks, repeated measures ANOVAs were performed separately on visual and auditory reaction times to test the effects of Condition (same, switch) x Age. The effects of age on the MSE were examined using a two-sample t-test.

2.3.2 Proportional hazards analyses

Proportional hazards analyses are most commonly used to evaluate survival data (or any time-to-event outcomes) in epidemiological and medical studies, but also can be useful in comparing conditions in psychophysical experiments as they allow reaction time data to be modeled similarly to multiple regression (Wenger and Gibson 2004). In addition, they result in a hazard ratio, which has a straightforward interpretation as an increase or decrease in the occurrence of an event under the experimental condition compared to the control condition. S-plus (www.insightful.com) was used for Cox proportional hazards analysis. The Cox proportional hazards model used in this analysis compares two conditions, assuming their hazard functions share the same shape over time and are therefore parallel (i.e., “proportional” hazards). If the hazard functions of the two group distributions being compared are not parallel, this fundamental assumption of the model has been violated and corrective procedures must be undertaken. In this case, log-log plots and the addition of time-dependent interactions in the regression model indicated that older and younger adults had different baseline hazard functions. Therefore, the model stratified older and younger adults to correct for the non-parallel baseline hazards (Kleinbaum 1996; Therneau and Grambsch 2000). In addition, the fact that each person had multiple reaction times was accounted for by using the “cluster”
command in S-plus to explicitly incorporate the correlation of repeated measures in the estimates resulting from the modeling (Therneau and Grambsch 2000).

2.4 Results

Over all four task types, accuracy was quite high for both groups (young = 98.3%, older 97.9%). Each condition had accuracy above 96% for both younger and older participants, and there were no significant differences in accuracy between groups on any task as tested with a two-sample t-test.

2.4.1 Endogenous spatial task

Reaction times for each condition and each age group are reported in Table 2.2. Graphs of Attentional Effects for both the spatial and non-spatial task are shown in Figure 2.2. In the ANOVA for reaction times to visual targets (Cue Condition x Age), there was a main effect of Age (F (1, 46) = 9.5, p < 0.01) reflecting that younger adults were significantly faster than older adults in all three cue conditions. There was also a main effect of Cue Condition (F (2, 92) = 12.5, p < 0.01), but the interaction between condition and age was not significant, indicating that differences between cue conditions did not vary by age group. A separate ANOVA examining Attentional Effects (cost and benefit) x Age to visual targets showed a main effect of Attentional Effects (F (1, 46) = 12.6, p < 0.01), reflecting that benefit was larger than cost to visual targets. However, no main effect of Age or interaction between Attentional Effects and Age was observed.

Results for the auditory modality in the spatial task were similar. There was a main effect of Age in the ANOVA for reaction times to auditory targets (F (1, 46) = 7.7,
p < 0.01) due to the fact that older participants were slower than younger participants in all three cue conditions. A main effect of Cue Condition was also observed (F (2, 92) = 10.8, p < 0.01) but the interaction between Cue Condition and Age was not significant. Analysis of cost and benefit to auditory targets showed no significant results in main effects of Age, Attentional Effects, or interaction between them.

Cost and benefit were also analyzed using the Cox proportional hazards method (Table 2.3). Both older and younger adults showed benefits of attention to visual targets when valid and neutrally cued trials were compared. Younger adults performance was enhanced 11% and older adults 13%. Both groups also showed attentional cost when visual targets were preceded by an auditory cue, with younger adults being slowed by 4% and older adults 11%. No significant difference was found between older and younger adults for the speeding to visual targets, but a trend toward a significant difference was present for visual cost (p=0.061). In response to auditory targets, younger adults showed a benefit of 7% and older adults 6%. Cost was slightly larger for both groups with a decrease in performance 11% for younger adults and 16% for older adults. Neither cost nor benefit to auditory targets differed significantly between older and younger adults.
TABLE 2.2 Reaction times and attentional effects to cued tasks.

<table>
<thead>
<tr>
<th></th>
<th>Valid</th>
<th>Neutral</th>
<th>Invalid</th>
<th>Benefit</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPATIAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visual target</strong></td>
<td>Younger</td>
<td>416.9 (70.2)</td>
<td>433.7 (76.9)</td>
<td>437.9 (80.3)</td>
<td>16.8 (20.8)</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>486.5 (74.9)</td>
<td>504.6 (78.9)</td>
<td>497.3 (76.7)</td>
<td>18.0 (22.6)</td>
</tr>
<tr>
<td><strong>Auditory target</strong></td>
<td>Younger</td>
<td>425.8 (87.2)</td>
<td>433.4 (95.6)</td>
<td>451.6 (114.3)</td>
<td>7.6 (25.0)</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>504.5 (104.7)</td>
<td>519.0 (108.6)</td>
<td>530.4 (108.0)</td>
<td>14.5 (40.5)</td>
</tr>
<tr>
<td><strong>NON-SPATIAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visual target</strong></td>
<td>Younger</td>
<td>658.6 (100.5)</td>
<td>666.4 (102.9)</td>
<td>733.3 (152.4)</td>
<td>7.8 (23.6)</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>691.5 (82.1)</td>
<td>700.1 (93.2)</td>
<td>762.8 (135.2)</td>
<td>8.6 (26.8)</td>
</tr>
<tr>
<td><strong>Auditory target</strong></td>
<td>Younger</td>
<td>810.2 (168.7)</td>
<td>834.2 (172.1)</td>
<td>902 (194.1)</td>
<td>24 (56.1)</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>863.2 (134.5)</td>
<td>895.3 (154.4)</td>
<td>947.3 (174.3)</td>
<td>32.1 (58.1)</td>
</tr>
</tbody>
</table>

Mean reaction times are reported in milliseconds with standard deviation in parentheses for the spatial and non-spatial cued tasks for each age group.
Attentional effects (cost and benefit) are shown in milliseconds. Error bars represent standard error of the mean (sem).

FIGURE 2.2 Results of spatial and non-spatial endogenous attention tasks.
Results show a percentage effect of attention for each age group. Attentional effects were detected for older and younger adults in all conditions, but no significant differences were observed between younger and older adults.

TABLE 2.3 Proportional hazards results for all conditions.

<table>
<thead>
<tr>
<th></th>
<th>Spatial</th>
<th>Non-spatial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Visual Target</td>
<td>Benefit</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Cost</td>
<td>4%</td>
</tr>
<tr>
<td>Auditory Target</td>
<td>Benefit</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Cost</td>
<td>11%</td>
</tr>
</tbody>
</table>
2.4.2 Endogenous non-spatial task

The ANOVA for visual reaction times in the non-spatial task reflected a main effect of Cue Condition \( (F (2, 94) = 41.7, p < 0.01) \), but no main effect of Age or interaction between Age and Cue Condition was detected. An ANOVA examining Attention Effects x Age for visual targets revealed a main effect of Attention, \( (F (1, 47) = 26.5, p < 0.01) \) reflecting the fact that cost was much larger than benefit to visual targets for both older and younger adults. No other significant effects were observed. Results for auditory targets in the non-spatial task were similar. An ANOVA of Cue Condition x Age demonstrated a main effect of Cue Condition \( (F (2, 94) = 38.6, p < 0.01) \), but no effect of Age or an interaction between Cue Condition and Age. Comparison of attentional effects revealed a main effect of Attention \( (F (1, 47) = 4.8, p < 0.05) \), reflecting that cost was larger than benefit for both older and younger adults, but no main effect of Age or an interaction between Age and Attentional Effect.

Proportional hazards analysis showed no differences between the age groups. Both younger and older adults displayed an attentional benefit to visual targets in the non-spatial task of approximately 7% and attentional cost approximately 30%. This reiterates the results of the comparison of means, which showed small but significant benefits, more robust costs, and no difference between older and younger participants. In response to auditory targets, younger adults showed benefit of approximately 11% and older approximately 7%. Auditory cost was more disparate, although the difference between the groups was still non-significant \( (p=0.15) \). Younger adults showed suppression of approximately 10% and older adults 18%.
2.4.3 Exogenous spatial task

Reaction times and MSEs for both uncued tasks are reported in Table 2.4. The ANOVA of Condition (same/switch) x Age for visual targets demonstrated main effects of both Condition (F (1, 45) = 105.5, p < 0.01) and Age (F (1, 45) = 8.4, p < 0.01) but no interaction between the two. The MSE for visual targets did not show a difference between younger and older adults (t = -1.3, p > 0.10). The outcomes for auditory targets were the same. A main effect of both Condition (F (1, 45) = 51.4, p < 0.01) and Age (F (1, 45) = 9.8, p < 0.01) was observed, and comparison of the auditory MSE showed no effect of age group (t = -1.1, p > 0.20). Using Cox proportional hazards analysis, younger adults demonstrated a 26.9% difference between same and switch trials for visual targets, which was not significantly different from the 27.4% difference observed in older adults. In response to auditory targets, younger adults exhibited a 12.0% difference and older adults 10.9%, which again did not differ significantly with age.

2.4.4 Exogenous non-spatial task

A main effect of Condition (same/switch) was found for both visual (F (1, 45) = 29.7, p < 0.01) and auditory (F (1, 45) = 19.8, p < 0.01) targets in the non-spatial task. No main effects of Age or interaction of Condition and Age were observed in either modality. As in the spatial task, no significant age difference was demonstrated for visual (t = -0.97, p > 0.3) or auditory (t = 0.54, p > 0.5) MSEs. However, proportional hazards analysis did suggest a trend for an age difference in the auditory MSE, where younger adults showed a 16.9% effect of switching modalities while older adults showed a 22.5% effect, a difference that trended toward significance (p=0.06, z = -1.90). The visual MSE
TABLE 2.4 Reaction times and modality shift effect for uncued tasks.

<table>
<thead>
<tr>
<th></th>
<th>SPATIAL</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Same</td>
<td>Switch</td>
<td>MSE</td>
</tr>
<tr>
<td>Visual Younger</td>
<td>394.4 (59.1)</td>
<td>422.6 (66.0)</td>
<td>28.2 (21.8)</td>
</tr>
<tr>
<td>Older</td>
<td>457.0 (87.8)</td>
<td>495.9 (101.7)</td>
<td>38.9 (23.0)</td>
</tr>
<tr>
<td>Auditory Younger</td>
<td>417.5 (71.8)</td>
<td>435.1 (67.4)</td>
<td>17.6 (16.0)</td>
</tr>
<tr>
<td>Older</td>
<td>498.1 (110.3)</td>
<td>522.4 (111.1)</td>
<td>24.3 (23.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>NON-SPATIAL</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Younger</td>
<td>625.0 (105.4)</td>
<td>648.1 (115.1)</td>
<td>23.2 (31.0)</td>
</tr>
<tr>
<td>Older</td>
<td>655.9 (96.5)</td>
<td>682.7 (101.5)</td>
<td>31.4 (26.9)</td>
</tr>
<tr>
<td>Auditory Younger</td>
<td>788.8 (145.3)</td>
<td>829.6 (153.6)</td>
<td>40.9 (59.5)</td>
</tr>
<tr>
<td>Older</td>
<td>884.7 (176.4)</td>
<td>915.1 (191.8)</td>
<td>32.2 (49.0)</td>
</tr>
</tbody>
</table>

Mean reaction times are reported in milliseconds with standard deviation in parentheses for older and younger adults for both spatial and non-spatial tasks.
was not significantly different in the proportional hazard analysis. In this comparison, a 16.0% effect was observed in younger and 13.1% in older adults.

### 2.5 Discussion

Previous work showing that older adults are more influenced by crossmodal distractors than younger adults (Alain and Woods 1999; Poliakoff et al. 2006) led to our hypothesis that older adults would fail to instantiate voluntary crossmodal selective attention and their involuntary attention would be more easily captured than younger adults. However, our results do not support these hypotheses. The findings of these experiments are remarkably consistent across different tasks, different sensory modalities, different kinds of attention, and different analyses: attentional effects were observed in older adults and were not different from those observed in younger adults. Importantly, this suggests that the ability to engage crossmodal selective attention is preserved with aging, in spite of the fact that older adults are differentially affected by crossmodal distractors.

#### 2.5.1 Endogenous tasks

Two tasks were used to test crossmodal attention, a spatial task and a non-spatial task. Results from both paradigms are quite similar to the results Spence and Driver observed in the spatial task most similar to the one performed here (Spence and Driver 1997). In the cued spatial task, benefit was larger than cost for both age groups in response to visual targets, but cost was larger than benefit to auditory targets. Both traditional and proportional hazards results suggest that visual attention caused larger
attentional effects than auditory attention for both younger and older participants in the spatial task. Attentional cost and benefit were also observed for both age groups in the non-spatial task, with the magnitude of cost being larger than that of benefit.

One interesting difference between the tasks is that in the non-spatial task, benefit is larger for the auditory than the visual modality. Findings from our spatial task as well as others (Spence and Driver 1997) show larger benefit for the visual modality. This difference in results could be due to the relative dominance of the visual modality in spatial localization, the more complex nature of the categorization task, or the use of crossmodal cues in the non-spatial task. This spatial task was meant to closely parallel previous studies, where visual cues are used to cue both auditory and visual attention (Spence and Driver 1997; Spence et al. 2001). The authors cite previous literature showing that the modality shift effect primarily affects target rather than non-target stimuli. However, it seems possible that switching from a valid visual cue to an auditory target could have the effect of minimizing speeding associated with benefit. Using a cue with an auditory component might therefore result in larger auditory benefit. Future studies will be needed to investigate these potential differences further and replicate these results using this or other non-spatial tasks.

2.5.2 Exogenous tasks

To our knowledge, this is the first investigation of the MSE in healthy aging adults, but event-related potential (ERP) and behavioral studies of attentional capture by distracting information have largely shown that older adults process more extraneous information than their younger counterparts (Alain and Woods 1999; Andres et al. 2006;
Healey et al. 2008). Given this information, we hypothesized that the MSE would be larger for older adults. Findings from our studies of exogenous attention were less conclusive than those from the cued tasks, in that there was a trend for significance in the Cox proportional hazards analysis for the auditory MSE in the non-spatial task. Nevertheless, the fact remains that these results do not convincingly support our hypothesis that older adults are more influenced by exogenous attentional pull than younger adults. This suggests that older adults are not more influenced by exogenous attentional pull, in spite of the fact that they process more distracting information.

2.5.3 Does paying attention mean not distracted?

To put this question another way, could a 75 year-old ignore background sounds like noise on the subway while reading or people talking while he drives as well as a 20 year-old? The results from this study would suggest yes – an older man is not more susceptible to the exogenous pull of stimuli and is able to effectively engage crossmodal attention. However, studies of crossmodal distractors suggest this is not the case. The study of attention in aging is rife with apparent conflict such as that embodied in this paper: some cued attentional studies suggest that older adults successfully engage and benefit from attention (Bahramali et al. 1999; Groth and Allen 2000; Verhaeghen and Cerella 2002; Madden et al. 2004; Ballesteros et al. 2008), while a host of other research indicates that the ability to inhibit responses to distracting stimuli in both the visual and auditory modalities decreases with age (Folk and Lincourt 1996; Alain and Woods 1999; Groth and Allen 2000; Gaeta et al. 2001; Tales et al. 2002; McCarley et al. 2004; Fabiani et al. 2006; Rowe et al. 2006; Yang and Hasher 2007) and older adults exhaust their
attentional capacity at lower task load than their younger counterparts (Maylor and Lavie 1998).

The resolution of this apparent conflict may lie in the way that attention is tested. Selective attention (crossmodal or unimodal) is defined as a relative measure, commonly as increases or decreases in reaction time or accuracy when compared to a control condition, often divided attention. This means that if significant differences are noted between selective and divided attention, participants are able to instantiate selective attention. In the present study, older and younger adults were both able to engage selective attention relative to divided attention. However, these findings do not necessarily mean that resistance to distractibility is equivalent across different age groups. Older adults could be more distractible, but still show a relative improvement due to selective attention. In fact, increased distractibility and decreased attentional capacity might be expected when selective attention is fully engaged if older adults had a higher sensory load at baseline. In this situation, older adults would work harder at all levels of processing to attain the same behavioral results as younger adults.

2.5.4 Limitations and future directions

The results of this study combined with previous findings suggest that baseline processing load may be altered in older adults. However, no tests of baseline functioning were directly undertaken here, and participants were not tested in any tasks with distractors, which would allow direct comparison of attentional functioning and distractor processing in the same subjects. Future studies using functional neuroimaging techniques are needed to directly assess the impact of distractors and baseline sensory functioning on
attentional performance in aging adults. In addition, research on a healthy aging population is necessary to characterize behavior in the absence of disease, but it must be acknowledged that the results of studies based on people who are highly successful at aging may not apply broadly to the aging population.

Acknowledgements

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Disclosure statement

The authors report no actual or potential conflicts of interest relating to this research.
REFERENCE LIST


CHAPTER III

SUPPRESSION OF MULTISENSORY INTEGRATION BY MODALITY-SPECIFIC ATTENTION IN AGING

Christina E. Hugenschmidt, Jennifer L. Mozolic, and Paul J. Laurienti

A revised version of the following manuscript is in press at Neuroreport, 2008 and is printed here with permission. Stylistic variations are due to requirements of the journal. Christina E. Hugenschmidt performed the experiments and prepared the manuscript. Jennifer L. Mozolic performed the experiments and analyzed data. Dr. Paul J. Laurienti acted in an advisory and editorial capacity.
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.

Keywords: aging, attention; cross-modal; elderly; multisensory integration; selective attention
3.1 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; Mozolic, et al., 2008; Talsma, et al., 2007; Talsma and Woldorff, 2005). 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; Mozolic, et al., 2008; Talsma, et al., 2007; Talsma and Woldorff, 2005). 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 (Mozolic, et al., 2008; Talsma, et al., 2007). 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.

### 3.2 Methods

#### 3.2.1 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.

3.2.2 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. Stimulus presentation and response collection were controlled by E-prime software (PST, Pittsburg, PA, USA; www.pstnet.com). 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. 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. an auditory attention cue always contained an auditory component. Incorrect
cues as used in Chapter 2 were never presented in this experiment. The 7 cue-target trial
types are listed in Table 3.1. 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 Age x 2 Attention Cue x 2 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.

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). 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 were
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. 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, the area under each subjects’ difference curves was calculated. These area values were then averaged across participants in each age group, and group differences in integration were assessed using a 2 Age x 3 Attention Cue mixed model ANOVA.

### 3.3 Results

#### 3.3.1 Accuracy

Accuracy was very high in all conditions (Table 3.1). A 2 Age x 2 Attention Cue x 2 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
TABLE 3.1 Mean accuracy and reaction time data for each attentional condition.

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

Means are presented with standard deviations in parentheses.
the fact that older and younger adults showed slightly improved accuracy to multisensory targets.

3.3.2 Reaction time

Average reaction times are reported in Table 3.1. A 2 Age x 2 Attention Cue x 2 Target ANOVA analyzing reaction 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 reaction 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, along with Target x Group (F (1, 39) = 5.21, p < 0.03) and Attention x Target (F (1, 39) = 4.42, p < 0.05) interactions.

3.3.3 Race model comparisons

Positive deflections in the difference curves shown in Figure 3.1 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
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.

FIGURE 3.1 Age-related increases in multisensory integration illustrated in race model difference curves and mean area under the curve.
of 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 3.1 C). A 2 Age x 3 Attention Cue ANOVA comparing divided and selective auditory attention 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.

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 both vision and hearing, 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.

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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CHAPTER IV

AGE-RELATED INCREASE IN CROSS-MODAL NOISE IN RESTING AND STEADY-STATE CEREBRAL PERFUSION

Christina E. Hugenschmidt, Jennifer L. Mozolic, Huan Tan, Robert A. Kraft,
and Paul J. Laurienti

Christina E. Hugenschmidt performed the experiments and prepared the manuscript. Jennifer L. Mozolic performed the experiments. Huan Tan and Dr. Robert A. Kraft programmed pulse sequences and calculated cerebral blood flow maps. Dr. Robert A. Kraft assisted with preparing the portion of the manuscript detailing cerebral perfusion methods. Dr. Paul J. Laurienti acted in an advisory and editorial capacity.
Abstract

Behavioral research indicates that aging is accompanied by maintenance of voluntary attentional function in many situations, but increased influence of distractors. One hypothesis for this apparent conflict is that older adults process more sensory information than younger adults at baseline. Therefore, even when sensory activity is successfully modulated by attention, there is still a net increase in processing of irrelevant stimuli. This hypothesis was tested by comparing average functional brain activity in auditory cortex using quantitative perfusion imaging during resting state and steady-state visual conditions. It was observed that older adults demonstrated greater processing of task-irrelevant auditory background noise than younger adults in both conditions. Auditory activity was attenuated relative to rest during a visually engaging task for both older and younger participants, but older adults continued to show greater auditory processing than their younger counterparts.
4.1 Introduction

Behavioral research on the effects of aging on cross-modal attention presents an apparent paradox in the aging brain – older adults are able engage selective attention as effectively as younger adults (Chapter 2), yet at the same time are more influenced by unattended stimuli (Chapter 3). Chapter 3’s behavioral experiment using integration of to-be-ignored cross-modal stimuli as an index of background processing presented in Chapter 3 offers a potential explanation for this conflict. In that study, it was observed that not only was processing of unattended stimuli increased during selective attention, but it was also increased in the divided attention referent condition. Selective attention resulted in attenuation of processing of unattended stimuli in older and younger adults, but did not compensate for the overall increase of background processing in older adults. The present study is concerned with investigating the neural underpinnings of enhanced processing of background stimuli in healthy older adults.

Several positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies indicate that the neural mechanism of cross-modal attention is a reciprocal relationship between sensory modalities with slightly enhanced processing in the attended modality and suppressed processing in the unattended modality (Ghatan, et al., 1998; Johnson and Zatorre, 2005; Kawashima, et al., 1995; Mozolic, et al., 2008b; Roland, 1982; Weissman, et al., 2004), similar to the “spotlight” of visual attention. That is, the relevant signal in the attended modality is increased and noise (irrelevant information) from an unattended modality is decreased. In general, the amount of deactivation in the unattended modality is greater than the increase of activity in the attended modality, highlighting the importance of cross-modal deactivations. Research
thus far shows robust decreases in activity of auditory cortex during both visual
stimulation with low attentional load (Laurienti, et al., 2002) and attention alone in the
absence of visual stimulation (Mozolic, et al., 2008b), suggesting both bottom-up and
top-down contributions to cross-modal deactivations. The bulk of neuroimaging research
on cross-modal attention has focused on the relationship between the visual and auditory
senses, partly due to the relative dominance of these senses and because of
methodological difficulties in presenting olfactory, gustatory, and tactile stimuli in the
scanner environment. Nevertheless, there is evidence that cross-modal deactivations are a
fundamental aspect of modality-specific attention regardless of the sensory modality
(Kawashima, et al., 1995).

The behavioral studies mentioned above suggest clear hypotheses for the effects
of healthy aging on the neural mechanisms of cross modal attention. Older adults should
be able to attentionally modulate processing in sensory cortices, but still show relatively
increased processing of ignored stimuli when compared to younger adults.

Conceptualizing attention as a mechanism to enhance the signal to noise ratio (SNR) of
the attended modality, this would mean that older adults would show increased cross-
modal noise. The ability to investigate this hypothesis with fMRI is limited by
methodological constraints. Areas of neural activity in fMRI paradigms are determined
relative to some referent condition since absolute measures cannot be obtained. The
behavioral studies mentioned above suggest that older adults will successfully modulate
neural activity in sensory cortices during a task, but show increased processing of
background stimuli in both the task and referent condition. This suggests that the
difference of interest in this study, a baseline increase in sensory processing, would not
be evident in a traditional fMRI paradigm. In fact, results from a low level attentional task in our laboratory bear this out. Age has no differential effect on activity in unisensory cortices in older adults (Peiffer, et al., 2007).

Quantitative perfusion imaging is similar to blood oxygen level dependent (BOLD) fMRI in that it uses the paramagnetic properties of blood to image neural activity through blood flow changes in the brain. Unlike fMRI, though, perfusion imaging yields quantitative maps of cerebral blood flow (CBF), meaning that comparison with a referent condition is not necessary. Perfusion imaging has not supplanted traditional fMRI because as a dynamic measure it has lower signal and poorer time resolution. However, the technique has excellent signal as a steady-state technique that measures average blood flow over several minutes. Therefore, the present study investigated the effects of aging on processing of background auditory stimuli by comparing average CBF during steady-state resting and a visual conditions. It was hypothesized that older adults would show greater proportional auditory activity at rest than younger adults. It was also hypothesized that task-related attenuation of auditory activity during the visual steady-state condition for both age groups due to cross-modal suppression of activity. However, auditory activity was hypothesized to still be greater in older adults secondary to changes in baseline processing.

In addition to auditory activity, the relationship between activity in auditory and visual cortices was of interest as a metric of cross-modal noise. It was hypothesized that older adults would show reduced cross-modal SNR resulting from increased noise assessed as the ratio of auditory to visual activity.
4.2 Methods

4.2.1 Subjects

Data were collected on 20 young (mean age = 26.9 ± 5.8, 9 women) and 20 older (mean age = 73.3 ± 6.4, 11 women) volunteers. As this was a study of healthy aging, potential participants were excluded for a self-reported history or medications consistent with dementia, neurological disease, psychiatric disorders, stroke, head injury, or diabetes. Participants were also excluded for evidence of dementia, defined as a Mini-Mental State Examination (MMSE) score more than 2.5 standard deviations from their age and education adjusted mean (Bravo and Herbert, 1997), or alcoholism as assessed with the Alcohol Use Disorders Identification Test (AUDIT) (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. 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.
4.2.2 Study design

Data for this study were collected over three visits: a screening visit, a behavioral visit and an imaging visit. In the course of the imaging visit, a high-resolution T1-weighted anatomical image was collected, followed by two perfusion and three fMRI scans. The order of perfusion and fMRI scans was randomized across subjects, with the constraint that the two perfusion scans were completed together. Data from the perfusion portion of the imaging visit are reported here. During a resting state perfusion scan, participants viewed a grey fixation cross on a black background. During a visual steady-state perfusion scan they watched a color video clip with no sound. Edited video clips were extracted from the documentary Of Penguins and Men, a special feature describing the making of the film March of the Penguins (2005, Warner Bros. Entertainment, Inc.). Film clips were edited using Ulead VideoStudio software (www.ulead.com) and presented using Presentation software (Neurobehavioral Systems, Albany, CA, USA; www.neurobs.com). Participants were told that they should carefully attend to the video as they would be given a quiz on its content following the scan. Following the imaging session, all participants completed a follow-up questionnaire where they provided subjective feedback about their alertness, described any strategies they used during scanning, and answered questions about the content of the videos they viewed. All stimuli were presented through MRI compatible goggles (Resonance Technology, Inc., Northridge, CA) with an integrated infrared eye tracker used to ensure that subjects kept their eyes open throughout the experiment.
4.2.3 MRI acquisition

All images were acquired in a 1.5T echo speed horizon LX General Electric Scanner with a neurovascular head coil (GE Medical Systems, Milwaukee, WI). High resolution T1-weighted images were acquired with a multi-slice spoiled gradient inversion recovery (3DSPGR-IR) protocol with the following parameters: phase = 256, frequency = 192; 128 contiguous slices, 1.5 mm thick; in-plane resolution 0.938 x 0.938 mm; TE=1.9 ms; TI=600 ms.

Cerebral blood flow was measured with QUantitative Imaging of Perfusion using Single Subtraction with Thin Slice TI1 Periodic Saturation: QUIPSS II TIPS, also known as Q2TIPS (Luh, et al., 1999) with Flow-sensitive Alternative Inversion Recovery (FAIR) encoding (Kim and Tsekos, 1997). Images were acquired with a single shot gradient echo Echo Planar Imaging (EPI) sequence (Mansfield, 1977). Blood was tagged using a C-shaped Frequency Offset Corrected Inversion (C-FOCI) pulse ($\beta$=1361, $\mu$=6) (Ordidge, et al., 1996) to improve perfusion sensitivity by minimizing slice imperfections (Frank, et al., 1997; Yongbi, et al., 1999). Very Selective Suppression (VSS) pulses (Tran, et al., 2000) were applied every 25 msec between 800 ms (TI1) and 1200 msec (TI1s) to minimize the uncertainty of the transit time of the labeled blood to the imaging slice (Wong, et al., 1998). Three VSS pulses were also applied immediately before and after the inversion pulses to suppress tissue signal in the imaging plane. Immediately after the EPI 90 degree excitation RF pulse, a bipolar diffusion gradient with an equivalent $b$ value of 5.25 mm$^2$/sec was used to suppress intra-arterial spins (Yang, et al., 1998). Additional parameters of interest for the Q2TIPS-FAIR-EPI sequence used in this experiment are as follows: TE = 30.4 msec, TR = 3000 sec, TI = 2000 msec, bandwidth =
62.5 kHz, flip angle = 90 degrees, field of view = 240 mm (frequency) x 240 mm (phase), and an acquisition matrix of 64 (frequency) x 40 (phase).

The total duration of the Q2TIPS-FAIR sequence was 8 minutes 36 seconds. The first 36 seconds were used to achieve steady state and consisted of a 6 second quiescent delay that ensured spins were at thermal equilibrium prior to scanning, followed by 8 volume acquisitions. After the initial 6 seconds, a single-shot EPI proton density ($M_0$) image was acquired. The initial 36 seconds were followed by 82 alternating slice-selective and non-selective radiofrequency inversion pulses (label/control pairs). Twelve contiguous 8-mm thick slices were acquired inferior to superior and aligned parallel to the anterior commissure/posterior commissure (AC/PC) line. Slices were placed to ensure full coverage of the occipital cortex. For most subjects, there were 4 slices below and 8 slices above the AC/PC line.

4.2.4 Computation of cerebral blood flow

Perfusion data were preprocessed using SPM5 software (Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab (The Mathworks, Inc., Sherborn, MA, USA) (Maldjian, et al., 2008). The reconstructed control and label images were motion corrected separately with a six-parameter rigid body transformation. After motion correction, control/label images were pair-wise subtracted, yielding difference images. The difference images were averaged and quantitative perfusion maps were calculated from Equation 1:

$$ CBF = \frac{\Delta M(TI_2)}{2M_{0,blood}T_1\alpha TI_1q_p(T_{1,tissue}, T_{1,blood}, TI_2)} e^{\left(\frac{TI_2}{T_{1,blood}}\right)} $$ (1)
In this equation, cerebral blood flow (CBF) is calculated where $\Delta M(TI_2)$ is the mean difference in the signal intensity between the label and control images, $\alpha$ is tagging efficiency, $TI_1$ is the time duration of the tagging bolus, $TI_2$ is the inversion time of each slice, $M_{0,blood}$ is the equilibrium magnetization of blood, $T_{1,blood}$ is the longitudinal relaxation time of blood, and $q_p$ is a correction factor that accounts for the difference between the $T_1$ of blood and the $T_1$ of brain tissue (Wong, et al., 1998). For this study, the correction factor $q_p$ was assumed to be unity, which is a reasonable approximation when the $T_1$ of blood and the $T_1$ of brain tissue are similar. Based upon the literature the $T_1$ of blood was assumed to be 1200ms at 1.5T (Simonetti, et al., 1996). The inversion efficiency was measured to be 0.95 from prior experiments in our laboratory (data not shown). The mean signal of white matter ($M_{0,white\ matter}$) was calculated from thresholded tissue maps and was used to approximate the $M_{0,blood}$ (Wong, et al., 1998). Tissue probability maps were created using an SPM99 automated segmentation of the $T_1$-weighted anatomical scan. The high-resolution $T_1$-weighted anatomical image was coregistered to the $M_0$ image and this transformation was applied to the tissue probability maps. The coregistered white matter probability maps were thresholded at 81% probability to create a white matter mask. Absolute quantitative CBF maps (ml/100 g tissue/min) were calculated using equation 1 according to the General Kinetic Model (Buxton, et al., 1998).

4.2.5 Data analysis

Region of interest (ROI) analyses were completed to investigate a priori hypotheses. Two ROIs were selected using Wake Forest University’s Pickatlas tool
(Maldjian, et al., 2003) and assessed statistically using SPSS (SPSS Inc., Chicago, IL, USA). Activity in auditory cortex was evaluated using regions of auditory cortex identified as both responsive to an auditory stimulus and modulated by visual attention in healthy young adults in a previous experiment in our laboratory (Fig. 4.1). An ROI in visual cortex was identified from a previous study where 60 young, middle-aged, and older adults viewed a flashing checkerboard (Peiffer, et al., 2007). The peak activity from the right side of occipital cortex was selected and a 5mm ROI was generated using the Pickatlas tool ($x = 32$ $y = -92$ $z = 10$). It is important to evaluate the CBF measures relative to the whole brain mean as previous studies have shown an overall decrease in cortical perfusion in older adults (Bentourkia, et al., 2000; Marchal, et al., 1992; Meltzer, et al., 2000; Pantano, et al., 1984; Takahashi, et al., 2005; Van Laere and Dierckx, 2001). Each subject’s ROI activity was normalized by dividing the average ROI CBF value by their average grey matter CBF value to account for global changes in CBF. Mean gray matter CBF values were calculated by averaging the perfusion values from all the voxels contained in a gray matter mask determined from the coregistered tissue probability map by thresholding at 51% probability. These normalized CBF values for each ROI during the rest and visual engagement conditions were compared between age groups using a 2

Age x 2 Condition repeated measures ANOVA. Average grey matter CBF values are also reported. These were calculated by averaging the CBF values within the grey matter mask.
The ROI to analyze auditory cortical activity was taken from a previous investigation of cross-modal attention in healthy younger adults. In this study, 19 normal volunteers completed a mixed event-related/block design. The block portion of the design consisted of four runs with 6 30 s blocks of a 2 Hz alternating checkerboard interspersed with 30 s blocks of fixation. In two runs, participants were asked to identify with a button press either a blue or red square embedded pseudorandomly within the flashing checkerboard (visual event-related task). In the other two runs, subjects had to differentiate two sounds that occurred while the flashing checkerboard was presented (auditory event-related task). Areas of auditory responsive cortex were identified using the time course of the auditory event-related task. These regions were then used to mask regions of significant cross-modal deactivation due to visual attention. The regions identified through this analysis as being responsive to auditory stimuli and visual attention were then used to create the mask for this study.

FIGURE 4.1 Location of auditory cortex ROI.
4.3 Results

Overall grey matter perfusion during resting state was observed to be significantly greater in younger adults (mean = 66.972 ± 14.4) than older adults (mean = 48.95 ± 12.3) using a two-sample t-test (t = 4.26, p < 0.01), replicating findings from previous studies. Average grey matter perfusion was also greater in younger adults (mean = 68.81 ± 16.1) than older adults (mean = 52.98 ± 13.2) during the steady-state visual condition as evaluated with a two-sample t-test (t = 3.40, p < 0.01). To control for these global differences in the regional analyses, each subject’s data was normalized to their corresponding global gray matter perfusion.

A 2 Age x 2 Condition repeated measures ANOVA was performed on average CBF in the auditory cortex ROI. Significant main effects were observed for both Age (F (1, 38) = 5.13, p < 0.03) and Condition (F (1, 38) = 5.26, p < 0.03). Older adults had higher levels of normalized perfusion in auditory cortex in both conditions than younger adults, and both age groups had greater perfusion of auditory cortex in the resting condition than the active condition (Fig. 4.2A). No interaction of Age and Condition was observed (F (1, 38) < 0.01, p > 0.90), suggesting that both study populations effectively suppressed activity in auditory cortex during visual engagement.

Average CBF in the visual ROI was compared using a 2 Age x 2 Condition repeated measures ANOVA. The main effect of Condition (F (1, 38) = 78.57, p < 0.01) and the main effect of Age (F (1, 38) = 16.56, p < 0.01) were both significant. There was a trend toward significance in the interaction between Age and Condition (F (1, 38) = 3.70, p > 0.06), reflecting that the older adults showed a slightly larger increase between rest and visual conditions than younger adults. These results demonstrate that both older and
Results from ROI analysis in older adults are shown in black and younger adults in grey. (A) Normalized average CBF values within the auditory ROI show significantly greater activity in older adults than younger adults during the rest condition. Engagement in a visual task reduced perfusion for both groups, but average values were still greater in older adults. (B) Normalized average CBF values within the visual ROI showed greater activity in younger adults than older adults at rest. Both age groups show increases in activity in response to the visual stimulus. The older adults have a slightly larger increase than younger adults, although the interaction between age and condition did not reach significance. (C) Cross-modal SNR was calculated by taking a ratio of the visual to auditory ROIs. Younger adults have significantly higher SNR during both resting and visual stimulation conditions. Error bars show standard error of the mean.

FIGURE 4.2 Steady-state activity for rest and visual engagement.
younger participants showed significantly increased activity in visual cortex during the visual condition, but that younger adults had greater visual perfusion than older adults in both conditions (Fig. 4.2B).

In addition to perfusion of unisensory cortices, the perfusion ratio between visual and auditory cortices was also evaluated. As both of the study conditions were visual in nature, a low level visual task of fixation and visual engagement during the viewing of a movie, no auditory information was task relevant. Therefore, all auditory processing can be considered “noise” in relation to the visual tasks. The ratio of visual to auditory perfusion was evaluated as a measure of this cross-modal noise. A 2 Age x 2 Condition repeated measures ANOVA was used to evaluate the ratios. Significant main effects were again observed for both Age (F (1, 38) = 6.11, p < 0.02) and Condition (F (1, 38) = 129.53, p < 0.01), reflecting the fact that older adults had a lower SNR than their younger counterparts in both conditions, and that SNR was higher during the active task for both age groups (Fig. 4.2C). The interaction of Age and Condition did not reach significance (F (1, 38) = 1.95, p > 0.10). Thus, both groups effectively increased the SNR during visual processing but the older adults had a greater level of cross-modal noise across conditions.

4.4 Discussion

As hypothesized, older adults showed relatively greater auditory activity than younger adults to background auditory stimuli during resting state and a visual steady-state condition. In addition, this auditory activity was attenuated when participants viewed an engaging visual stimulus, but the reduction in auditory activity did not vary by
age group. Interestingly, older adults also evidenced a decrease in cross-modal SNR, reflecting that increased auditory background activity was not accompanied by a correspondingly larger task-related enhancement in visual cortex.

These important findings suggest a neural mechanism for the behavioral observation that older adults are more distracted by background auditory stimuli than younger adults, in spite of the fact that they are able to successfully instantiate selective attention. The previous study (Chapter 3) noted that even after older adults suppressed background stimuli as much as younger adults, these stimuli were still eliciting responses in the form of multisensory interactions. The increase in multisensory integration during selective attention seemed to be a result of increased integration during divided attention that was not fully compensated for. The results of the present study demonstrate that older adults show increased activity in auditory cortex at rest. Auditory activity is suppressed by engagement in a visual task, as would be expected from previous research on cross-modal deactivations (Johnson and Zatorre, 2005; Kawashima, et al., 1995; Laurienti, et al., 2002; Mozolic, et al., 2008a), but older adults continue to show greater auditory activity than younger adults.

The results of this study are straightforward regarding the processing of background auditory stimuli during resting state and an engaging visual task. However, it is not clear if the reverse relationship is true, or if the findings will generalize to other pairings of cross-modal stimuli, for instance vision and touch. Most studies that have investigated the effects of unattended or distractor stimuli in aging have either used unimodal paradigms (Healey, et al., 2008; Yang and Hasher, 2007) or examined the effects of auditory stimuli on visual processing (Alain and Woods, 1999; Fabiani, et al.,
The idea that auditory stimuli may be particularly potent distractors (Parmentier, 2008) has some ecological validity. It is generally accepted that humans are visually dominant animals and that we negotiate our world visually. However, the visual system does not allow monitoring of all regions of the environment. In contrast, the auditory system provides lower spatial resolution, but allows 360 degree monitoring of the world. In this way, the auditory system may act preferentially to orient the visual modality. However, results from unimodal visual studies (Healey, et al., 2008; Rowe, et al., 2006; Yang and Hasher, 2007) do show enhanced processing of background stimuli, which indicates that increased baseline processing of sensory stimuli as a source of distraction may be a general finding across modalities. Future research will be needed to resolve this question.

One potential caveat in interpreting this study is the use of cross-modal SNR as a measure. To our knowledge, a ratio of sensory cortical activity has not been used before. Directly comparing activity in two different cortices would be uninterpretable, as there is no reason to assume that the relationships between cortical activity and perception are equivalent between modalities. However, comparing the ratio of activity across tasks and age groups reveals meaningful information about the relationship between the auditory and visual modalities. Prior research on cross-modal attention makes a reliable prediction that during visual stimulation relative to eyes open fixation activity in the visual cortex should increase and activity in the auditory cortex should decrease, and indeed, this is the pattern that was observed. The important finding is that this relationship between the unisensory systems is different between the young and older adults.
Future studies will be needed to investigate the specificity of these findings to the visual and auditory systems. In addition, the older subjects in this experiment are very healthy, with good sensory functioning and low prevalence of disease. As such, they are part of a population considered to be successful agers, and the findings from this study may not be representative of the entire spectrum of aging.
REFERENCES


CHAPTER V

DECREASED FUNCTIONAL ACTIVITY IN THE DEFAULT MODE NETWORK AT REST IN HEALTHY AGING ADULTS

Christina E. Hugenschmidt, Jennifer L. Mozolic, Huan Tan, Robert A. Kraft,
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Christina E. Hugenschmidt performed the experiments and prepared the manuscript. Jennifer L. Mozolic performed the experiments. Huan Tan and Dr. Robert A. Kraft programmed pulse sequences and calculated cerebral blood flow maps. Dr. Robert A. Kraft assisted with preparing the portion of the manuscript detailing cerebral perfusion methods. Dr. Paul J. Laurienti acted in an advisory and editorial capacity.
Abstract

Previous studies have shown cross-modal distractors are increasingly influential in healthy aging, but that at the same time, functioning of cross-modal attention is preserved. Further, greater distraction may be due to a baseline increase in processing of background stimuli that is not fully compensated for by attentional suppression. However, the reason for this baseline increase is not known. The default mode network (DMN) has been hypothesized to act as an attentional filter that monitors the environment when one is not engaged in a task. It has been observed that the DMN network is less suppressed during tasks in older adults than younger adults. Therefore, it was hypothesized that increased activity of this attentional filter both at rest and during a visually engaging task might explain the increase in background sensory processing. Quantitative cerebral perfusion imaging was used to compare the neural activity in visual, auditory, and default mode brain regions at rest and during a steady-state visual condition. An overall age-related decrease in perfusion of the default mode network was observed at rest. Results from the visual steady-state scan were mixed, and indicated that the default mode network became decoupled during visual stimulation in the older adults. The hypothesized linear relationship between DMN activity and processing of background auditory information was not observed, suggesting either that changes in the DMN do not underlie a baseline increase in background sensory processing or a more complex relationship exists between the DMN and sensory processing.
5.1 Introduction

Behavioral and neuroimaging investigations in Chapters 3 and 4 suggest that increased cross-modal distractibility in older adults is not caused by a failure of attention, but by a fundamental alteration in baseline sensory noise. The behavioral experiment reported in Chapter 3 used multisensory integration as an indirect measure of processing of unattended stimuli. It was noted that older adults showed a proportional increase in integration under all attention conditions. Older adults were able to modulate multisensory integration with cross-modal attention, but still showed more integration than younger adults. In addition, an experiment using quantitative perfusion imaging in Chapter 4 demonstrated increased processing of background auditory stimuli not just during visual attention-demanding tasks, but even in a resting state when no task was being performed. This leaves the question, what might cause a change in sensory processing at rest?

The resting state in which increased sensory processing was observed, being quietly awake viewing a fixation cross, is a very well characterized state that has been investigated in functional neuroimaging studies for over 10 years (see Buckner 2008 for review). The hallmark of the resting state is activity of the default mode network (DMN), a group of brain regions including the posterior cingulate, anterior cingulate, and parietal cortices that is more active during resting state than almost any task state. The exact function of the DMN is not known, but it has been hypothesized to act as an attentional filter that monitors the external environment, integrates this information into a self-referenced representation of the world, and orients attention accordingly (Buckner, et al., 2008; Raichle, et al., 2001; Shulman, et al., 2007). Lack of suppression of the DMN
during tasks is linked with lapses of attention (Weissman, et al., 2006), increased error commission (Li, et al., 2007), and intrusion of task-unrelated thoughts (McKiernan, et al., 2006). Interestingly, healthy aging is also associated with a reduced suppression of activity of the DMN during tasks (Grady, et al., 2006; Lustig, et al., 2003; Persson, et al., 2007). It has been hypothesized that failure to suppress the DMN is related to increased distractibility in older adults (Damoiseaux, et al., 2008; Grady, et al., 2006; Lustig, et al., 2003; Persson, et al., 2007).

The present study investigated the association between activity of the DMN and processing of background auditory stimuli in healthy older adults. Since previous studies showed that older adults could successfully engage attention, suggesting that failures of voluntary attentional suppression do not underlie increased distraction, it was hypothesized that the observed increase in processing of background auditory stimuli could be explained by a failure to attenuate monitoring of the environment during tasks by the DMN. Therefore, older adults would show greater relative activity of the DMN than younger adults both at rest and during visual engagement. Moreover, if this were true, increased activity of the DMN would be correlated with increased auditory activity.

One challenge in investigating the DMN is that it is most active at rest. Since functional magnetic resonance imaging (fMRI) studies reflect changes in neural activity relative to a baseline referent condition, they typically investigate the behavior of the network when it is suppressed. Resting state fMRI scans can be interrogated without use of a referent condition using functional connectivity analyses or blind-source separation techniques such as independent component analysis (Calhoun and Adali, 2006; Cordes, et al., 2001). However, these techniques predominantly reflect temporal correlations
between network regions rather than magnitude of network activity. Quantitative perfusion imaging is a method that is similar to blood oxygen level dependent (BOLD) fMRI in that it indexes neural activity through changes in blood flow (Aguirre, et al., 2002; Wang, et al., 2003). Unlike fMRI, though, perfusion imaging generates quantitative maps of cerebral blood flow (CBF), meaning that activity can be assessed without using a referent condition. The present study investigated the effects of aging on DMN activity at rest and during a visual steady-state task using voxel-wise analysis of CBF maps. In addition, the relationship between the DMN and activity in sensory cortices was evaluated in regions of interest.

5.2 Methods

5.2.1 Subjects

Resting state data were collected on 29 young (mean age = 27.0 ± 6.3, 16 women) and 28 older (mean age = 73.3 ± 6.1, 15 women) participants. Visual steady state data were collected on a subset of 20 young (mean age = 26.9 ± 5.8, 9 women) and 20 older (mean age = 73.3 ± 6.4, 11 women) volunteers. Voxel-wise resting state analyses include all 29 younger and 28 older subjects. Region of interest (ROI) analyses use only subjects who have both visual and resting state data. As this was a study of healthy aging, potential participants were excluded for a self-reported history or medications consistent with dementia, neurological disease, psychiatric disorders, stroke, head injury, or diabetes. Participants were also excluded for evidence of dementia, defined as a Mini-Mental State Examination (MMSE) score more than 2.5 standard deviations from their age and education adjusted mean (Bravo and Herbert, 1997), or alcoholism as assessed
with the Alcohol Use Disorders Identification Test (AUDIT) (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. 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.

5.2.2 Study design

Data for this study were collected over three visits: a screening visit, a behavioral visit and an imaging visit. In the course of the imaging visit, a high-resolution T1-weighted anatomical image was collected, followed by two perfusion and three fMRI scans. The order of perfusion and fMRI scans was randomized across subjects, with the constraint that the two perfusion scans were completed together. Data from the perfusion portion of the imaging visit are reported here. During the resting state perfusion scan, participants viewed a grey fixation cross on a black background. During the visual steady-state perfusion scan they watched a color video clip with no sound. Edited video clips were extracted from the documentary Of Penguins and Men, a special feature describing the making of the film March of the Penguins (2005, Warner Bros.
Entertainment, Inc.). Film clips were edited using Ulead VideoStudio software (www.ulead.com) and presented using Presentation software (Neurobehavioral Systems, Albany, CA, USA; www.neurobs.com). Participants were told that they should carefully attend to the video as they would be given a quiz on its content following the scan. Following the imaging session, all participants completed a follow-up questionnaire where they provided subjective feedback about their alertness, described any strategies they used during scanning, and answered questions about the content of the videos they viewed. All stimuli were presented through MRI compatible goggles (Resonance Technology, Inc., Northridge, CA) with an integrated infrared eye tracker used to ensure that subjects kept their eyes open throughout the experiment.

5.2.3 MRI acquisition

All images were acquired in a 1.5T echo speed horizon LX General Electric Scanner with a neurovascular head coil (GE Medical Systems, Milwaukee, WI). High resolution $T_1$-weighted images were acquired with a multi-slice spoiled gradient inversion recovery (3DSPGR-IR) protocol with the following parameters: phase = 256, frequency = 192; 128 contiguous slices, 1.5 mm thick; in-plane resolution 0.938 x 0.938 mm; TE=1.9 ms; TI=600 ms.

Cerebral blood flow was measured with QUantitative Imaging of Perfusion using Single Subtraction with Thin Slice TI$_1$ Periodic Saturation: QUIPSS II TIPS, also known as Q2TIPS (Luh, et al., 1999) with Flow-sensitive Alternative Inversion Recovery (FAIR) encoding (Kim and Tsekos, 1997). Images were acquired with a single shot gradient echo Echo Planar Imaging (EPI) sequence (Mansfield, 1977). Blood was tagged
using a C-shaped Frequency Offset Corrected Inversion (C-FOCI) pulse ($\beta=1361$, $\mu=6$) (Ordidge, et al., 1996) to improve perfusion sensitivity by minimizing slice imperfections (Frank, et al., 1997; Yongbi, et al., 1999). Very Selective Suppression (VSS) pulses (Tran, et al., 2000) were applied every 25 ms between 800 ms ($T_{I1}$) and 1200 ms ($T_{I1s}$) to minimize the uncertainty of the transit time of the labeled blood to the imaging slice (Wong, et al., 1998). Three VSS pulses were also applied immediately before and after the inversion pulses to suppress tissue signal in the imaging plane. Immediately after the EPI 90 degree excitation RF pulse, a bipolar diffusion gradient with an equivalent $b$ value of 5.25 mm$^2$/sec was used to suppress intraarterial spins (Yang, et al., 1998). Additional parameters of interest for the Q2TIPS-FAIR-EPI sequence used in this experiment are as follows: $TE = 30.4$ ms, $TR = 3000$ sec, $TI = 2000$ ms, bandwidth = 62.5 kHz, flip angle = 90 degrees, field of view = 240 mm (frequency) x 240 mm (phase), and an acquisition matrix of 64 (frequency) x 40 (phase).

The total duration of the Q2TIPS-FAIR sequence was 8 minutes 36 seconds. The first 36 seconds were used to achieve steady state and consisted of a 6 s quiescent delay that ensured spins were at thermal equilibrium prior to scanning, followed by 8 volume acquisitions. After the initial 6 seconds, a single-shot EPI proton density ($M_0$) image was acquired. The initial 36 seconds were followed by 82 alternating slice-selective and non-selective radiofrequency inversion pulses (label/control pairs). Twelve contiguous 8-mm thick slices were acquired inferior to superior and aligned parallel to the anterior commissure/posterior commissure (AC/PC) line. Slices were placed to ensure full coverage of the occipital cortex. For most subjects, there were four slices below and 8 slices above the AC/PC line.
5.2.4 Computation of cerebral blood flow

Perfusion data were preprocessed using SPM5 software (Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab (The Mathworks, Inc., Sherborn, MA, USA). The reconstructed control and label images were motion corrected separately with a six-parameter rigid body transformation. After motion correction, control/label images were pair-wise subtracted, yielding difference images. The difference images were averaged and quantitative perfusion maps were calculated from Equation 1:

\[
CBF = \frac{\Delta M(TI_2)}{2M_{0,\text{blood}}\alpha T1_q p(T1,\text{tissue},T1,\text{blood},TI_2)} e^{\left(\frac{TI_2}{T1,\text{blood}}\right)}
\]

In this equation, cerebral blood flow (CBF) is calculated where \(\Delta M(TI_2)\) is the mean difference in the signal intensity between the label and control images, \(\alpha\) is tagging efficiency, \(T1\) is the time duration of the tagging bolus, \(TI_2\) is the inversion time of each slice, \(M_{0,\text{blood}}\) is the equilibrium magnetization of blood, \(T1,\text{blood}\) is the longitudinal relaxation time of blood, and \(q p\) is a correction factor that accounts for the difference between the \(T1\) of blood and the \(T1\) of brain tissue (Wong, et al., 1998). For this study, the correction factor \(q p\) was assumed to be unity, which is a reasonable approximation when the \(T1\) of blood and the \(T1\) of brain tissue are similar. Based upon the literature the \(T1\) of blood was assumed to be 1200ms at 1.5T (Simonetti, et al., 1996). The inversion efficiency was measured to be 0.95 from prior experiments in our laboratory (data not shown). The mean signal of white matter (\(M_{0,\text{white matter}}\)) was calculated from thresholded tissue maps and was used to approximate the \(M_{0,\text{blood}}\) (Wong, et al., 1998). Tissue
probability maps were created using an SPM99 automated segmentation of the T₁-weighted anatomical scan. The high-resolution T₁-weighted anatomical image was coregistered to the M₀ image and this transformation was applied to the tissue probability maps. The coregistered white matter probability maps were thresholded at 81% probability to create a white matter mask. Absolute quantitative CBF maps (ml/100 g tissue/min) are calculated using equation 1 according to the General Kinetic Model (Buxton, et al., 1998).

5.2.5 Analysis of perfusion data

Voxel-wise age group comparisons of CBF maps were computed using SPM5. Images were globally normalized using proportional scaling of the mean to account for global age-related decreases in cerebral perfusion. The need for this global normalization is illustrated in Figure 5.1, where average CBF maps for younger and older participants are displayed. Voxel-wise analyses were completed separately on CBF maps from the resting state and active visual engagement. Average grey matter values from the modulated voxel-based morphometry (VBM) analysis (Ashburner and Friston, 2005) were included as covariates to account for any effects of age-related atrophy on CBF. Significance was evaluated using a threshold of p < 0.05 corrected for multiple comparisons using false discovery rate (FDR) as implemented in SPM5.

In addition to voxel-wise analyses, region of interest (ROI) analyses were completed to investigate *a priori* hypotheses. Two ROIs were selected using Wake Forest University’s Pickatlas tool (Maldjian, et al., 2003) and assessed statistically using SPSS (SPSS Inc., Chicago, IL, USA). Activity in the DMN was identified using a mask of
regions deactivated during simple visual and auditory tasks in young, middle-aged, and older adults in a previous experiment in our laboratory (Fig. 5.2). Activity in auditory cortex was evaluated using regions of auditory cortex identified as both responsive to an auditory stimulus and modulated by visual attention in healthy young adults in a previous experiment in our laboratory. Each subject’s ROI activity was normalized by dividing the average ROI CBF value by their average grey matter CBF value to account for global changes in CBF. These normalized CBF values for each ROI during the rest and visual engagement conditions were compared between age groups using a $2^{\text{Age}} \times 2^{\text{Condition}}$ repeated measures ANOVA.

A global grey matter covariate was calculated using the segment function implements in SPM5. Briefly, each subject’s high resolution structural image was normalized to the MNI template by segmenting it with prior probability maps after an affine transformation, normalizing the grey matter segment, and applying the parameters from this normalization to the high resolution T1-weighted image. Jacobian determinants calculated from the normalization into study-specific template space were applied on a voxel-wise basis, producing modulated maps representing tissue volume. All images were resampled to 2 x 2 x 2 mm and smoothed with an 8 x 8 x 8 mm full-width half-maximum (FWHM) isotropic Gaussian smoothing kernel. Average values from these smoothed, modulated grey matter segments were used as a covariate in the voxel-wise analyses to account for possible effects of atrophy on cerebral perfusion.
Global decreases in cerebral perfusion are clearly evident in older adults. Two axial slices are shown for each subject population. The upper image (left) is from $Z = 40$. The lower slice (right) is from $Z = 0$. 

FIGURE 5.1 Average quantitative cerebral blood flow maps for younger and older adults.
In order to evaluate average CBF values within the entire DMN, a mask was created showing deactivations during two runs of a simple visual task and two runs of a simple auditory task in 60 subjects (Peiffer, et al., 2007).
5.3 Results

5.3.1 Voxel-wise analyses

Age group comparison of resting state CBF maps revealed that older adults showed significantly less perfusion in several regions \((T = 2.62, p < 0.05)\) (Fig. 5.3). These regions included medial prefrontal cortex dorsal to the anterior cingulate (MNI peak: \(x = 0\), \(y = 36\), \(z = 30\); \(T = 4.74\)) and posterior medial cortex primarily in the precuneus but extending down into the posterior cingulate (MNI peak: \(x = 0\), \(y = -44\), \(z = 40\); \(T = 5.88\)). Two areas of age-related decreases in perfusion were noted in right (MNI peak: \(x = 28\), \(y = -68\), \(z = 45\); \(T = 5.81\)) and left (MNI peak: \(x = -40\), \(y = -48\), \(z = 55\); \(T = 5.69\)) parietal cortex. The lower aspect of these regions of significance was at the border of parietal and occipital cortices, and they extended into superior parietal lobule. That is, after accounting for global decreases in CBF with age, voxel-wise maps indicated that perfusion in regions associated with the DMN were differentially affected by aging during rest. In addition, decreased perfusion was observed in right (MNI peak: \(x = 56\), \(y = 16\), \(z = 30\); \(T = 4.75\)) and left (MNI peak: \(x = -44\), \(y = 12\), \(z = 40\); \(T = 4.86\)) dorsal prefrontal cortex on the dorsal aspect of the middle frontal gyrus extending to the precentral gyrus in the region of the frontal eye fields. These regions are not typically considered to be part of the DMN.

During visual engagement, younger adults showed greater perfusion than older adults bilaterally in parietal cortex and dorsal prefrontal cortex \((T = 3.9, p < 0.05)\) (Fig. 5.4). The areas of parietal cortex showing greater perfusion in younger adults during
Results of the voxel-wise analysis comparing resting CBF of older and younger adults after correcting for global decreases in perfusion. Younger adults showed significantly greater activity in several regions associated with the default mode network, including medial prefrontal regions, posterior cingulate, and bilateral parietal regions. Increased activity in younger adults was also noted in bilateral dorsolateral prefrontal cortex. The sagittal image is taken from midline to show the medial prefrontal and posterior cingulate/precuneus regions. The axial slices are from Z = 30, 40, 50, and 60 from top left to bottom right.
Regions of age-related decrease in perfusion during visual stimulation varied slightly from those observed at rest. Parietal regions continued to show greater perfusion in younger adults than older, as did regions of dorsolateral prefrontal cortex. However, age-related decreases in perfusion were not noted in the posterior cingulate or medial prefrontal cortices. The axial slices are from $Z = 30$, 40, 50, and 60 from top left to bottom right. No sagittal image is shown because there were no significant differences identified in the medial prefrontal or posterior cingulate/precuneus regions.
visual engagement were more extensive on the right (MNI peak: $x = 32$, $y = -72$, $z = 50$; $T = 5.30$) than the left (MNI peak: $x = -36$, $y = -56$, $z = 55$; $T = 5.40$) and overlapped with those identified at rest. Both peaks were located in superior parietal lobule. Three significant regions of decreased activity in older adults were noted in the left dorsolateral prefrontal cortex in inferior frontal gyrus (MNI peak: $x = -48$, $y = 12$, $z = 30$; $T = 5.56$), and the middle frontal gyrus (MNI peak: $x = -32$, $y = 44$, $z = 35$; $T = 5.37$; MNI peak: $x = -48$, $y = 44$, $z = 20$; $T = 5.04$) and two in the right middle frontal gyrus (MNI peak: $x = 52$, $y = 20$, $z = 35$; $T = 5.22$; MNI peak: $x = 32$, $y = 36$, $z = 40$; $T = 4.78$).

5.3.2 Region of interest analyses

Analyses of the auditory cortex ROI have been reported previously (Chapter 4) but are included here for ease of interpretation. A $2^{\text{Age}} \times 2^{\text{Condition}}$ repeated measures ANOVA was performed on average CBF in the auditory cortex ROI. Significant main effects were observed for both Age ($F(1, 38) = 5.13$, $p < 0.03$) and Condition ($F(1, 38) = 5.26$, $p < 0.03$). Older adults had higher levels of normalized activity in auditory cortex in both conditions than younger adults, and both age groups had greater activity of auditory cortex in the resting condition than the active condition (Fig. 5.5 A). No interaction of Age and Condition was observed ($F(1, 38) < 0.01$, $p > 0.90$), suggesting that the modulation of activity by condition was not significantly affected by age.

Perfusion in the DMN was also compared in a $2^{\text{Age}} \times 2^{\text{Condition}}$ repeated measures ANOVA. Significant main effects were observed for Age ($F(1, 38) = 6.29$, $p < 0.02$) and Condition ($F(1, 38) = 6.24$, $p < 0.02$), but no interaction between the two was seen ($F(1, 38) = 1.02$, $p > 0.30$). Older adults had significantly less activity in the DMN than
Grey lines represent younger adults and black lines represent older adults. Results of ROI analyses in the auditory cortex were reported previously, but are shown again for ease of comparison. Older adults showed greater relative activity in auditory cortex than younger adults. In contrast, perfusion in an ROI of the entire default mode network showed a relative decrease in older adults, both at rest and during visual stimulation. Default mode activity was decreased during the visual task in both age groups. Error bars represent standard error of the mean. The error bars on the default mode graph are encapsulated with the symbols.
younger adults in both conditions. In addition, the DMN showed lower CBF during the visual condition than the rest condition in both age groups (Fig. 5.5 B). However, the interaction between age and condition was not significant, suggesting that the decrease due to condition did not vary between younger and older adults.

If decreased DMN activity is linked to increased auditory activity, this relationship should be evident in a correlation between auditory and DMN activity. In order to test the relationship between default mode suppression and increased activity in auditory cortex, average CBF from the DMN and auditory ROIs were correlated for younger and older adults separately for both the resting and visual engagement scans. No significant relationships were observed between activity in the auditory cortex and the DMN during the resting state in younger (F (1, 19) = 0.20, p > 0.6, r² = 0.01) or older (F (1, 19) = 2.47, p > 0.1, r² = 0.12). The results were similar during visual stimulation, where no significant relationships were observed for younger (F (1, 19) = 2.16, p > 0.10, r² = 0.11) or older participants (F (1, 19) = 0.05, p > 0.80, r² = 0.003).

5.4 Discussion

The initial hypotheses for this study were that older adults would show relatively greater activity in the DMN both at rest and during a visually engaging task than younger adults, and this increase would correlate with increased activity in auditory cortex. However, results of voxel-wise analyses revealed that the DMN actually showed decreased activity in older adults at rest. Moreover, no straightforward linear relationship was observed between DMN and auditory cortical activity.
Two important observations arise from these findings. First, the noted decrease in DMN activity at rest suggests an alternative interpretation of fMRI findings that older adults suppress the DMN less than younger adults during visual tasks (Grady, et al., 2006; Lustig, et al., 2003; Persson, et al., 2007). This result has been interpreted as a failure of suppression (Grady, et al., 2006; Persson, et al., 2007). However, older adults may show a smaller relative decrease in DMN activity because the network was already less active at rest. That is, the network is less turned off during tasks because it was less turned on to begin with. Secondly, during the visual condition, voxel-wise comparisons showed that only parietal areas showed lower activity in older than younger adults, rather than the entire DMN. Closer examination of the data suggests that different regions of the DMN are affected differently by involvement in a task. Post hoc ROI analyses were completed on the posterior cingulate, medial prefrontal region, and left parietal regions identified as showing lower activity in older adults at rest (Fig. 5.6). All regions showed decreased activity in older adults at rest. However, they were modulated differently by engagement in a task and the regional variations in modulation help clarify voxel-wise results.

The posterior cingulate region showed decreased activity during the visual condition in younger adults, but no modulation by visual engagement in older adults. The result of this is that during the visual condition, there is no longer a significant difference between age groups. Although older adults had less activity at rest, they did not decrease activity with the visual task. In contrast, younger adults decreased activity to almost the resting levels of older adults.
Although an ROI of the entire DMN shows that the network decreases activity during visual engagement in younger and older adults, the network decouples older adults.

FIGURE 5.6 Regions of the default mode network are suppressed differently during visual stimulation in older adults.
In contrast, the parietal cortex and medial prefrontal regions that showed decreased activity during both resting and visual conditions in older adults also showed task-related decreases for both groups. Since older adults exhibited lower activity in these regions at rest and during visual stimulation, the age-related difference observed at rest was maintained in the visual condition.

Together, these data suggest that there is overall decreased metabolism in default mode regions in healthy older adults at rest, and that in older adults, these regions may become decoupled during a task. The initial hypothesis that auditory activity would correlate with default mode activity was clearly not supported. However, it is possible that age-related fragmentation of the network is more meaningful for brain function and behavior than its overall metabolic activity. In this case, some measure of the coherence or coupling might explain an increase in background auditory noise better than overall magnitude of activity.

While the present study makes important observations about the behavior of auditory activity to background stimuli and functioning of the DMN in healthy older adults, there are also limitations to the study that leave open avenues for future studies. For instance, using average CBF maps provides good signal to noise to test hypotheses about average signal changes in a steady-state paradigm, but does not yield the timecourse information necessary to examine decoupling of the DMN network. Furthermore, even if timecourse information were available, there is no single metric to quantify fragmentation of the network to correlate with other variables, such as activity to a background stimulus. Future research can address these questions by using higher field strength and/or cardiac and respiratory monitoring to boost the SNR of the perfusion
method, enabling the use of task-based studies with meaningful timecourse information. In addition, future research can quantify the property of coherence in a meaningful way and relate this to overall activity. A final limitation in applying these findings to the general public is that the older subjects in this experiment are very healthy and part of a population considered to be successful agers. As such, the findings from this study may not be representative of the entire spectrum of aging, which is associated with increased disease burden.
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CHAPTER VI

DISCUSSION

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6.1 Summary of findings

To put all of the findings from this thesis in perspective, let us return to the question posed in the introduction: A 20 year-old man sits in a crowded subway car reading a newspaper. Although his hearing is good, he could not tell you about the conversations going on around him. *Could a healthy 70 year-old person do the same thing?* The experiments in this thesis indicate that no, he could not, but not for the reasons that have typically been espoused in the literature and popular press, and not for the reasons initially hypothesized.

The original hypothesis of this thesis was that older adults are more distractible because of a failure of selective attention. In this model, aging-related increases in multisensory integration occur because older adults maintain a constant state of divided attention instead of suppressing competing sensory information with selective attention. However, the experiments presented in Chapters 2 and 3 demonstrated that older adults benefit behaviorally from selective attention in much the same way as younger adults.

The observations from these experiments led to a new hypothesis: that older adults are more distractible than younger adults because of a baseline increase in noise. Because cross-modal sensory processing is the focus of this work, noise means increased sensory processing in an unattended modality. This concept can be expressed very simplistically using the analogy of traffic on a highway. Too much traffic on the road slows the pace of travel. Attention can be thought of as redirecting unwanted traffic so that vehicles can move efficiently down the highway. Using this analogy, older adults begin with more cars on the highway. When the same number of vehicles is redirected from the young and older roads, the older highway will still be more crowded and will
move more slowly. The important point is that the failure is not in the redirection of traffic – that works equally well on each road. The older adults move more slowly because of an initially higher traffic load.

To take this analogy further, full traffic volume is analogous to divided attention, and reducing the traffic volume on the main road is like selective attention. The reason a difference was not observed between older and younger adults in the first set of experiments is that the study evaluated the difference between divided and selective attention. That is, the amount of redirected traffic was compared and it was observed that both roads redirected the same number of cars. Attention was functional in both groups.

In the second experiment, multisensory integration of unattended stimuli was evaluated as an indirect measure of background sensory processing. It was noted that older adults had increased multisensory integration under both selective and divided attention conditions relative to younger adults. Interestingly, participants in both age groups were able to reduce multisensory integration with selective attention, but older adults still showed increased integration. To put this in terms of the traffic analogy, redirection of cars was measured along with an indirect measure of traffic volume, like speed. Here, it was again observed that the same number of cars was redirected – attentional function was intact in both groups. But it was also demonstrated that cars on the older road moved more slowly after they had redirected the same number of vehicles, suggesting their traffic load was increased.

The goal of the final set of experiments was to directly examine the amount of background sensory processing. To this end, quantitative perfusion imaging was used to detect the magnitude of neural activity in auditory cortex during a well-defined baseline
state and a steady-state visual task. Greater activity was observed in older adults’ auditory cortex both during the resting state and after task-related reductions in auditory activity. In other words, traffic volume was higher for older adults even though they redirected the same number of cars as younger adults because they began with more vehicles on the road.

In short, the data presented here suggest that the older man on the subway would likely be more distracted than the younger man, but not because he cannot pay attention. Rather, he is more distracted because there are fundamental differences in his brain functioning at baseline that continue during tasks and result in increased processing of background auditory stimuli.

6.2 A brief review of attention

The study of attention dates back at least to William James, who established one of the two first psychology laboratories in existence in the late 1800s at Harvard University. The present understanding of attention has arisen from years of accumulated psychophysical and neurophysiological research, particularly in the branches of cognitive psychology and neuroscience. Broadly, attention can be conceived of as a balance between endogenous direction of attention to a chosen feature and exogenous capture of attention by particularly salient or behaviorally relevant stimuli in the environment. Exogenous attention functions as an alerting mechanism that causes a shift of voluntary attention to particularly relevant stimuli and is typically thought of as a “bottom-up” process, dominated by stimulus characteristics. In contrast, endogenous attention is conceived of at “top-down,” meaning that it is under conscious cognitive control and uses
higher-order cognitive functions such as memory to inform stimulus processing (Corbetta and Shulman, 2002).

Current evidence suggests that endogenous attention is served by a dorsal attentional network comprised of dorsal frontal regions, such as the frontal eye fields (FEF), dorsolateral prefrontal cortex (PFC), and superior parietal areas, and exogenous orienting relies on activity in the temporoparietal junction (TPJ) and ventral PFC (Corbetta, et al., 2000; Corbetta and Shulman, 2002; Serences, et al., 2005; Shulman, et al., 2003). During endogenous attention, it is believed that the dorsal attentional system acts to increase the relative signal of the attended feature by increasing neural activity in the cortices associated with the attended feature and decreasing neural activity in competing regions (Kastner and Ungerleider, 2000; Posner and Driver, 1992; Serences, et al., 2004). This function has been likened to a “spotlight” of attention, an analogy that dates back to at least 1968 [as referenced in (Posner, et al., 1980)]. This “spotlight” seems to be a general mechanism of attention that applies to processing of a spatial location, color, speed, or modality (Corbetta, et al., 1991; Kawashima, et al., 1995; Roland, 1982; Serences, et al., 2004).

Behaviorally, attentional enhancement and suppression are tested using cued attention tasks (Posner, et al., 1980). In these paradigms, it is expected that correct cueing will result in faster reaction times. In contrast, incorrect cueing is expected to slow reaction times since this situation requires that attention be shifted to a feature that has been suppressed. For example, in a task where subjects are cued to expect a target either to the right or left of fixation, a cue to attend to the right would result in increased activity in neurons representing the right region and decreased activity in neurons representing
the left. If the cue were incorrect and the target appeared to the left, the suppressed neurons would be required to respond, and the reaction time would be slower.

6.3 Cross-modal attention

Cross-modal attention seems to function with the same “spotlight” model as visual attention, only in this instance the spotlight is focused on a specific modality. Several studies have observed increased neural processing in cortices supporting the attended modality and decreased processing in competing modalities (Fox, et al., 2005; Ghatan, et al., 1998; Johnson and Zatorre, 2005; Kawashima, et al., 1995; Roland, 1982; Woodruff, et al., 1996). Studies from our laboratory show that these cross-modal deactivations can be induced by attention alone (Mozolic, et al., 2008b), but are more robust when the sensory stimulus is present (Laurienti, et al., 2002). Behaviorally, Driver, Spence and colleagues have shown definitively that cross-modal attention can speed reaction times to targets in the attended modality and slow responses to stimuli in the unattended modality (Spence and Driver, 1997; Spence, et al., 2001). Both behavioral and imaging studies suggest that suppression is greater than enhancement. Cross-modal attention is also important for its apparent role in modulating multisensory integration. Previous studies have shown that the McGurk effect, an audiovisual speech illusion, is attenuated under high attentional demand (Alsius, et al., 2005) and that selective attention to either the visual or auditory modality can suppress multisensory integration (Mozolic, et al., 2008a).
6.4 The effects of aging on attention

Reading any review paper on attention and aging shows that the literature is a morass of conflicting findings (Groth and Allen, 2000; Plude, et al., 1994). It seems that for every paper that says that aging is associated with attentional impairments, there is another reporting preservation of attention in older adults. One reason for this is that in spite of William James’ assertion that “Everyone knows what attention is,” there are several different kinds of attention, and operational definitions of attention vary across studies. Three main theories to explain aging-related attentional changes have arisen that have substantial bodies of research to support them: the theory of processing speed, limited attentional capacity, and reductions in inhibitory control.

6.4.1 General slowing of processing speed

One of the most reliable findings about age-related changes in processing is that reaction times are slowed in older adults to a variety of tasks, and that this slowing becomes more pronounced with increasing task complexity (Birren, et al., 1962; Brinley, et al., 1965; Cerella, 1985, 1994; Feldman and Reger, 1967; Nebes, 1978; Pierson and Montoye, 1958; Salthouse, 1988). This line of research has led to the theory of processing speed to explain cognitive deficits in older adults. According to this theory, older adults show generalized slowing on a variety of tasks, not just attention tasks. This slowing causes deficits in cognitive performance as older adults cannot complete cognitive processes in the necessary amount of time, cognitive processes may take so long that information is no longer available when it is needed, and timing between processes is negatively impacted (Salthouse, 1996). This concept is important when
interpreting attention literature because accounting for general slowing can negate age-related differences, suggesting that the age-related differences in attention in some studies may not actually be specific to attention, but rather better accounted for by general processing speed (Verhaeghen and Cerella, 2002). Stated another way, this line of research shows that attentional performance is functionally impaired in older adults in that they show performance deficits relative to younger adults. However, it is likely that attention itself works, and the observed decrements are general rather than localized to the attentional system.

Research on age-related slowing has found evidence that there are timing differences in the response of motor cortex that are most related to performance as tasks become more complex (Yordanova, et al., 2004). Another study has shown that older adults making visual saccades to a target have decreased peak velocity, slower reaction time, and reduced ability to inhibit saccades to a previous target (Sweeney, et al., 2001), again suggesting general slowing in the sensorimotor system. In short, the theory of processing speed suggests that older adults are slowed by general rather than attention-specific mechanisms, and that age-related alterations in neural activity are the cause of this slowing.

6.4.2 Reduced attentional capacity

The term capacity is used in many different contexts in aging literature (e.g., (Basak and Verhaeghen, 2003)), but here refers specifically to a theory proposed by Lavie and colleagues (Lavie, 2005; Lavie and Tsal, 1994; Maylor and Lavie, 1998) suggesting that processing of distractors is decreased as perceptual load increases (but see
Madden and Langley 2003). The task used to test this idea is a central display of letters flanked by larger distractor letters. During low task load, when there are only one or two letters in the central display, distractors are processed and impact performance. However, as set size of the central display increases, participants reach a point where perceptual load in the primary task is so great that they no longer process distractors. In this task, older adults are more distractible at smaller set sizes than younger adults, and reach their capacity at a smaller set size than younger adults. This has been interpreted as evidence that older adults have limited attentional capacity that is exhausted at lower perceptual load than younger adults. Two additional points about attentional capacity research are that ERP (Handy and Mangun, 2000; Handy, et al., 2001) studies show decreased neurophysiological activity to distractors as set size increases and distractor salience decreases, and that degradation of targets results in increased effects of distractors (Lavie and de Fockert, 2003). Although these findings are not in an older adult population, they do support Lavie’s theory.

6.4.3 Inhibitory deficits

Another line of research that has garnered support over the past twenty or so years is the idea that older adults show decreased attentional processing due to deficits in inhibitory control (Hasher and Zacks, 1988). Several behavioral tasks have been used to investigate this idea, including negative priming (Kieley and Hartley, 1997; Kramer, et al., 1994), visual search (Madden and Langley, 2003; Madden, et al., 2002; Madden, et al., 2004; Madden, et al., 2005) and distraction tasks (Lustig, et al., 2006; Murphy, et al., 1999; Rowe, et al., 2006).
Negative priming refers to tasks where a target and a distractor are presented on each trial. On some trials, the distractor from one trial becomes the target on the next. In this situation, it is anticipated that the response to the new target will be slowed, since it should have been suppressed in the previous trial. A decrease in this slowing would indicate that suppression (inhibition) of the distractor was weak. The effects of aging on negative priming are equivocal; several studies show no age-related changes in negative priming (e.g., (Kieley and Hartley, 1997; Kramer, et al., 1994)), while others show significant decreases in negative priming with age (Kane, et al., 1994; Kane, et al., 1997; May, et al., 1995) depending on the memory requirements of the task. Visual search tasks demonstrate reliable age-related slowing, but also show that attentional processes seem to be intact in older adults (Madden, et al., 2004; Madden, et al., 2005).

Research on distraction provides the greatest support for the inhibitory theory, and probably some of the most reliable findings in the attentional literature. Behavioral tasks show that older adults process more unattended background information than younger adults (Healey, et al., 2008; Rowe, et al., 2006; Yang and Hasher, 2007). This behavioral observation is also supported by event-related potential (ERP) research using the mismatch negativity (MMN) to examine processing of unattended stimuli. The mismatch negativity is typically computed using an oddball paradigm. In this task, a series of stimuli is presented where most of the stimuli are standards (the same stimulus repeated) and a smaller number are deviants. The mismatch negativity is a difference waveform computed by subtracting the response to the standard from the deviant. Older adults have consistently been found to have smaller mismatch negativities (Alain and Woods, 1999; Gaeta, et al., 2001; Kok, 2000; Tales, et al., 2002), suggesting that they are processing
standards and deviants equivalently. In addition to smaller MMN, larger sensory evoked potentials (SEPs) to background stimuli have been observed in older adults (Alain and Woods, 1999). Together, these pieces of evidence suggest that older adults are processing sensory information more than younger adults in all conditions and not differentiating between different kinds of background stimuli.

6.5 The effects of aging on cross-modal attention

Few studies have directly assessed the effects of aging on cross-modal attention. As mentioned above, in younger adults, one function of cross-modal attention is apparently to limit interactions between the senses. Increased multisensory interactions have been observed in older adults (Laurienti, et al., 2006; Strupp, et al., 1999), leading to the hypothesis that older adults might have deficits in cross-modal attention. One recent study addressed cross-modal attention in aging, but did so by examining cross-modal distraction (Poliakoff, et al., 2006). They found that older adults were more distracted by visual stimuli during a tactile task than younger adults in terms of error rates and interpreted this as a failure of selective attention. However, the results of the studies in Chapters 2 and 3 of this thesis suggest that older adults are in fact able to engage cross-modal attention. In Chapter 2, it was noted that older adults showed costs and benefits commensurate to younger adults in a cued attentional task, similar to findings in the visual attention literature suggesting that attentional mechanisms are functional in older adults (Langenecker and Nielson, 2003; Madden and Langley, 2003; Madden, et al., 2004). In chapter 3, multisensory integration was used as an indirect measure of the processing of to-be-ignored stimuli. Older adults showed increased processing of
unattended stimuli in the form of increased multisensory integration in all attentional conditions, a finding consonant with studies of cross-modal distraction (Alain and Woods, 1999; Fabiani, et al., 2006; Valeriani, et al., 2003). However, this study design also allowed for the determination that older adults actually modulated integration with cross-modal attention similarly to younger adults. The noted increase in multisensory integration during selective attention appeared to be due to an increase in the baseline divided attention condition.

**6.6 Attention, distraction, and aging**

One field of study not explicitly included in the discussion above are those interested in neural compensation. These studies, like the first study in this thesis, define attention as the ability to voluntarily demonstrate relative increases and decreases in processing, and tend to observe preservation of attention in older adults (Kok, 2000; Madden, et al., 2004). When examined using functional neuroimaging, results suggest that older adults show increased activity in the dorsal attentional network that correlates with task performance, suggesting that the increased activity is compensatory in nature (Buckner, 2004; Cabeza, et al., 2004; Evert, et al., 2003; Langenecker and Nielson, 2003; Logan, et al., 2002; Riis, et al., 2008; Velanova, et al., 2007). This also implicitly suggests that the attentional network is intact.

These findings contrast strongly with those examining the effectiveness of attentional suppression by indexing resistance to distraction discussed above. Importantly, these latter studies assume that distraction is a measure of attentional failure. Anecdotally, this would seem to be true. Most people would agree that they are more
easily distracted when they are not focused. This assumption also has neurobiological credence, as failure to suppress irrelevant stimuli with attention would result in increased processing of distractors. However, data from the second experiment in this thesis suggest that the processing of to-be-ignored stimuli and the ability to functionally engage attention can be dissociated. This in turn suggests that the behavioral effectiveness of attentional modulation is not solely dependent on the ability to pay attention, but also on the amount of information being processed. That is, the amount of work the attention network can do is affected by the sensory load on the system.

Results from experiments in this thesis suggest a mechanism that unites the disparate findings described above: a baseline increase in sensory processing that decreases the signal-to-noise ratio (SNR) in the older brain. Because most brain functions are predicated on sensory input, SNR decreases at the sensory level would propagate through other networks and functions. For instance, greater baseline sensory processing means a greater processing load and potentially slowed processing that is exacerbated as tasks become more complex as research on the theory of processing speed has observed. A baseline increase in sensory processing would increase perceptual load even at the lowest levels of processing, resulting in decreased attentional capacity, supporting Lavie’s observations of reduced attentional capacity with age. It would also mean that even when attentional mechanisms are functional, older adults would process more distracting information than younger adults, as inhibitory literature suggests they do.
6.7 The neurobiology of increased sensory noise

Why would a baseline increase in sensory processing constitute neurobiological noise? Attention is fundamentally a mechanism to increase the signal-to-noise ratio of an attended dimension by enhancing neural activity in relevant cortices and suppressing neural activity from competing processes. In modality-specific attention, this means enhancing activity in the cortical regions subserving the attended modality and suppressing activity in competing sensory channels. The relative signal is determined by the difference in activity between the two sensory channels. A baseline increase in sensory processing means that the same amount of suppression and enhancement results in a smaller difference in activity between the two sensory channels. Data from Chapter 4 clearly show that there is less difference in neural signal between visual and auditory cortices in older adults than in younger adults. Activity in visual cortex was slightly less and auditory activity was significantly greater in older adults than younger adults at baseline. Visual engagement boosted the activity in visual cortex and suppressed activity in auditory cortex as expected, but it did so proportionally in both age groups, meaning that the SNR was decreased both at rest and during the visual task for older adults.

This is illustrated with hypothetical data in Figure 6.1, and presents a simple mechanism to explain the relationship of increased baseline sensory processing and increased sensory processing during attention. Importantly, the relative change induced by attention is not altered. Therefore, methods that rely on a referent condition, such as cued attention tasks using divided attention as a baseline and fMRI, which also requires a baseline condition, would not detect changes in attention. In terms of Figure 6.1, this means comparing the difference between the blue and yellow bars in each condition. For
ease, this is illustrated as a separate difference graph to the right of each model. It is evident that under both normal sensory processing in younger adults (A) and conditions of increased auditory noise in older adults (B) the difference between selective and divided attention is the same. In contrast, methods evaluating processing of distractors as a metric of attention would see an age difference because they would essentially be comparing the yellow bar in young under selective attention (A) to the yellow bar in the older adult (B). However, such a study would not be able to see that the amount of attentional suppression (the difference bars) were the same for both age groups.
FIGURE 6.1 Hypothetical example of increased background sensory noise.

(A) Illustrates the amount of visual activity (blue) and auditory activity (yellow) under divided and selective attention conditions in younger adults. The difference between divided and selective attention for each modality is shown to the right. The difference in visual activity is enhancement of the attended modality (10 arbitrary units) and the difference in auditory activity is suppression of the unattended modality (30 arbitrary units). The SNR for younger adults is 60/25 or 2.4 in arbitrary units.

(B) In older adults, the amount of auditory activity is increased proportionally in the baseline divided attention state and in selective attention. Selective attention suppresses auditory activity by the same amount, as is evident in the difference graph, but overall, there is more auditory activity in panel B. This difference also impacts the SNR, which drops to 60/45 or 1.3 in arbitrary units.
One thing that is not clear from these experiments is the generalizability of these results. There is some evidence that the tactile modality may have more pull than visual or auditory senses (Spence, et al., 2001). However, it has also been suggested that the auditory modality may have more pull than the visual (Parmentier, 2008). Such imbalances in attentional pull have some ecological validity. It is generally accepted that the visual modality is dominant in humans, but the sense of sight is limited in the amount of the environment it can survey at one time. The sense of hearing has lower spatial resolution than sight, but has the advantage that it can monitor the environment in all directions at once. With this in mind, it would seem adaptive for the auditory modality to preferentially capture attention with the aim of focusing the sense of vision on behaviorally relevant stimuli in the environment. To extend this, the tactile modality might have an even stronger pull than the auditory, because by the time something in the environment is touching your skin, it likely requires a rapid response.

6.8 The effects of aging on the default mode network

A baseline increase in sensory noise provides a reasonable explanation for increased distraction in healthy older adults who effectively instantiate attention, but what might cause such a shift is not immediately clear. Further exploration of the baseline state may provide some insight. The resting state chosen as baseline in these experiments, eyes open viewing a fixation cross, was selected because it is particularly well-studied. This resting state and the network most active in it (the default mode network (DMN)) have garnered increasing attention in the research community since Raichle and colleagues suggested that it might constitute a true baseline state for the brain (Raichle, et al., 2001).
The reason for this hypothesis is the unique characteristic that the oxygen extraction fraction (OEF), or balance between oxygen supply and demand, is essentially uniform across the brain in the resting state. Once engaged in a task, whether sensory, motor, or cognitive, this homogenous OEF is disrupted and the region of increased brain activity becomes apparent.

From a cognitive standpoint, the DMN is thought to act as an attentional filter that monitors the external environment, integrates this information into a self-referenced representation of the world, and orients attention accordingly (Buckner, et al., 2008; Raichle, et al., 2001; Shulman, et al., 2007). It also seems important for the DMN to be suppressed during tasks. Increased DMN activity during tasks is associated with lapses of attention (Weissman, et al., 2006) and errors (Li, et al., 2007), while increasing task difficulty is correlated with increased suppression of the network (McKiernan, et al., 2003; Persson, et al., 2007). In this thesis it was hypothesized that the DMN might provide an explanation for increased baseline sensory processing in older adults. Previous research has observed that older adults do not suppress the DMN as much as younger adults (Grady, et al., 2006; Persson, et al., 2007). If the DMN is indeed responsible for monitoring the environment and shifting attention, increased activity in this network might correlate with increased processing of background stimuli.

Contrary to our hypothesis, voxel-wise analyses showed regional decreases in resting activity of the DMN. This observation is important for two reasons. First, it suggests a new interpretation of the observation that older adults suppress the DMN less than younger adults during task performance. Previously, it was thought that older adults exhibit slower and less accurate performance on memory and attention tasks because the
DMN was more active in older adults during tasks. The data presented here suggest instead that the magnitude of DMN suppression may be smaller in older adults because it was less active to start with. Secondly, this in turn suggests that if the DMN is related to cognitive decline in healthy older adults, it is likely because the network is too suppressed and not doing its function at rest rather than because the network is not being suppressed enough during tasks.

In designing these experiments, it was anticipated that the function of the DMN might be elucidated by demonstrating a relationship between increased processing of background auditory stimuli and increased metabolic activity in the DMN at rest. However, this simple relationship did not hold true. One reason the hypothesized relationship might not have been observed is that it is possible that the network commonly identified as the DMN is actually composed of sub-networks. The posterior cingulate is considered to be the “hub” of the default mode network. Other regions such as medial prefrontal cortex and hippocampus seem to be more variable, particularly in older adults. These sub-networks may have distinct purposes that correlate differently with cognitive functions such as attention and distraction. In addition, there is evidence within the data presented as well as from a previous study conducted in our laboratory that the DMN may become decoupled during tasks in older adults, and this decoupling may be modulated further by the type of task performed. It is possible that age-related changes in cognitive functioning have more to do with the integrity or coherence of the DMN than with its overall activity. The relationship between activity of the DMN at rest and decoupling of the network during tasks is not clear, and neither is the relationship between the integrity of the DMN and task performance. However, these interactions
may provide more insight into the function of the DMN, how it relates to age, and how it relates to distraction, particularly cross-modal distraction.

The finding of reduced activity in the DMN at rest raises an important point that is not often addressed in the literature: whatever function the DMN actually serves, it is an important part of normal brain functioning. For instance, PET and fMRI studies have shown that the DMN, particularly the posterior cingulate subregion, shows significantly decreased metabolic activity in Alzheimer’s disease. Arguably, if the DMN is simply a nuisance network that interferes with task performance when it is not suppressed, Alzheimer’s patients should show better task performance than healthy adults, which is decidedly untrue.

6.9 A potential role for the DMN

Raichle and colleagues (Raichle, et al., 2001) hypothesized that the resting state was a true baseline because in that state, the oxygen extraction fraction is virtually uniform across the brain. They also noted that the DMN is the most active network in the resting state. The resting state is characterized by a constellation of consistent “idle” rhythms that are associated with specific cortices – the mu rhythm in sensorimotor cortex, tau rhythm in temporal cortex, and alpha rhythm in occipital cortex (Hari and Salmelin, 1997). Immediately before an action or engagement with the environment, the rhythms desynchronize (Hari and Salmelin, 1997). If all the oscillators (in this case neurons) and their connections were identical, synchrony would be expected (Strogatz and Stewart, 1993). However, as even closely related groups of cortical neurons are quite heterogeneous, it is unlikely these resting oscillations would be maintained without being
driven by an external input. It is reasonable to hypothesize that the DMN is this input. It is the most active network at rest when resting activity is synchronous and it is suppressed during tasks when the rhythms are desynchronized (Hari and Salmelin, 1997; Raichle, et al., 2001). Lending further support to this association is the observation from simultaneous EEG and fMRI that desynchronizations in EEG are associated with task-related activations in fMRI (Ritter, et al., 2008). Furthermore, if the DMN functions to drive resting rhythms, it would actually be important for it to turn off during tasks to allow neurons to respond to incoming stimuli rather than remaining locked in synchronous activity, and activity of the DMN during tasks would be detrimental to performance, as has been noted (Li, et al., 2007; McKiernan, et al., 2006; Weissman, et al., 2006).

If the DMN is playing an active role in maintaining a true baseline state as the driving input for characteristic resting oscillations, the decrease in resting metabolic activity noted in Chapter 5 suggests that resting rhythms in older adults should be disrupted. In fact, older adults show a general decrease in the power of all resting rhythms and a concomitant loss of spatial specificity (Klimesch, 1996; Klimesch, 1999; Prichep, 2007; Rossini, et al., 2007). Put another way, resting oscillations in younger adults have a tight distribution with spatial and spectral specificity, while older adults have broader spatial distributions that have less power in the dominant frequency. That is, in the older brain is more spatially and spectrally homogenous, an idea supported by observed higher coherence between oscillations in different brain regions in older adults (Maurits, et al., 2006; Prichep, 2007).
A referent condition is important to the functioning of networks in the brain for the same reason it is important for individual neurons – it allows for a greater dynamic range of activity and therefore more transmission of information. Figure 6.2 illustrates conceptually how a tight distribution of activity in the referent condition facilitates detection of a simple visual stimulus. Imagine two visual neurons are oscillating at close to the same frequency at rest (Fig. 6.2A). A visual stimulus is presented that lies within the receptive field of one neuron and in the inhibitory surround of its neighbor. Because the two neurons began with very similar behavior at baseline, their responses to the incoming stimulus are quite distinct and have a high SNR. If the initial distribution of resting activity in the same population were broad (Fig. 6.2B), the baseline behavior of the two neurons would not necessarily be very similar. First, this means that the difference in activity between the two neurons compared to the population may be less. Secondly, it means that the responses of both neurons might now fall within the range of resting activity of the neuronal population so that the response to an external stimulus is not distinct. Both of these changes would reduce the SNR of the incoming visual signal. In addition, the resting frequency of the two neurons has the potential to be much more variable with a broad distribution. This means that in some cases, the resting activity of the neurons may be very far apart from one another in the distribution in a way to cause their active states to be very distinct from one another (they still may not be distinct from the resting activity of the population). However, it is equally possible that they may be very close together or be arranged so that their changes in activity bring them closer together in oscillatory frequency, making their active oscillatory states very similar.
In this model, oscillation frequency is on the x-axis and the amplitude of each curve represents the number of neurons oscillating at that frequency. The model shows two visual neurons, which are representative of populations of neurons. The dark circles show the neurons at rest and the bright circles show their behavior after being presented with a visual stimulus. The visual stimulus is in the receptive field of Neuron 1 (blue) and therefore increases its activity. However, the visual stimulus falls into the inhibitory surround of Neuron 2, resulting in a decrease of activity.

(A) Illustrates a tight distribution where most of the neurons in visual cortex are oscillating at their resting frequency, in this case, the $\alpha$ frequency observed at rest in visual cortex. When the visual stimulus is presented, Neuron 1 increases its firing rate while the activity of Neuron 2 is decreased. The changes in their activity create a clear difference from their previous behavior and in reference to the rest of the cell population. This difference is represented by the brackets.

(B) Illustrates the outcome of a broader baseline distribution of oscillatory frequencies. In this case, the amplitude of the distribution is lower and wider representing that fewer neurons are oscillating at each frequency. The magnitude of change in activity in response to a stimulus is the same for each neuron, but now the change in activity is barely different from the population distribution for Neuron 1 and still falls within the distribution of baseline activity for Neuron 2, lowering the SNR for the visual signal.
6.10 Future directions

Findings from these studies open new avenues for future research into the nature of cross-modal attention, distraction, and the default mode network in healthy aging adults. These lines of research have important implications for clinical applications, as they suggest relevant modifications for transmitting medical information to the elderly, such as discussing important issues in a distractor-free environment, and using multisensory educational materials to facilitate understanding and memory. In addition, mechanisms of multisensory integration and maintained attention provide potential avenues for clinical interventions, such as attention training to help maintain cognitive performance in aging.

As mentioned previously, research is needed to investigate the relationships between different sensory modalities both in cross-modal attention and distraction. To date, the studies of the relative weight and influence of modalities is sparse and the little that is there contains conflicting findings, even in younger adults. Until this work is done, the application of the current findings to other modalities cannot be assumed. Further investigation of age-related changes in cross-modal distraction and the interaction of this with attention networks would be facilitated by quantitative perfusion imaging of neural behavior during a cross-modal attention task. Because of limitations in the SNR of perfusion images, particularly in older adults, this would require accommodations to boost SNR, such as imaging at higher field strength and using equipment to monitor heart rate and respiratory fluctuations so that these effects could be accounted for during analysis.

In addition, while studies of the default mode network did not show the hypothesized simple linear relationship with background auditory stimuli, they did
generate new questions about the function of the default mode network in both younger and older adults. This data also suggested decoupling of the network during tasks in older adults. It will be interesting in the future to generate a metric to quantify this fragmentation so that it can be compared quantitatively across age groups and different tasks. It is possible that fragmentation of the network is a more relevant predictor of cognitive function than absolute magnitude of activity within the network. Finally, the hypothesis that the DMN actively sets a baseline state in the brain could be investigated in a range of future studies including further characterization of the relationships between neural oscillations and activity using combined EEG and fMRI, transcranial magnetic stimulation experiments, and animal studies.
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**ABSTRACTS**


