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Structural Integrity of Attention Networks in Cross-Modal Selective Attention Performance in Healthy Aging

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STRUCTURAL INTEGRITY OF ATTENTION NETWORKS IN CROSS-MODAL

SELECTIVE ATTENTION PERFORMANCE IN HEALTHY AGING

by

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ABSTRACT

STRUCTURAL INTEGRITY OF ATTENTION NETWORKS IN CROSS-MODAL
SELECTIVE ATTENTION PERFORMANCE IN HEALTHY AGING

by

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The influence of structural brain changes in healthy aging on cross-modal selective attention performance was investigated with structural MRI (T_1- and diffusion-weighted scans). Eighteen younger (M=26.1, SD=5.7) and 18 older (M=62.4, SD=4.9) healthy adults with normal hearing performed a reaction time (RT) cross-modal selective attention A/B/X task. Participants discriminated syllables presented in either visual or auditory modalities, with either randomized or fixed distraction presented simultaneously in the opposite modality. Within the older group only, RT was significantly slower during random (M=573.24, SE=33.66) compared to fixed (M=554.04, SE=33.53) distraction, $F(1,34)$=5.41, p=.026. Average gray matter thickness and white matter integrity were lower for older adults, all p<.05. Across the age range, lower average gray matter thickness in regions of the ventral (VAN), but not dorsal (DAN), attention network correlated with larger increases in RT related to distraction, all p<.05. Multiple regression revealed that white matter integrity did not predict RT distraction index (random-fixed), all p>.05. However, post-hoc adaptive lasso regressions demonstrated that FA of bilateral SLF predicted RT distraction index, Wald χ^2=3.88, p=.016. The present results indicate that structural integrity underlying both DAN and VAN may aid in cross-modal selective attention performance, suggesting that communication between the networks, likely via top-down modulation of bottom-up processes, may be crucial for optimal attention regulation.

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1. Introduction

The aim of the present study was to characterize the role of gray and white matter

structure of the dorsal and ventral aspects of the frontoparietal attention network (FPN) in

healthy younger and older adult age groups. The dual nature of maintaining attention to a task

(dorsal attention network: DAN) and monitoring for salient external events (ventral attention

network: VAN) is crucial in selective attention performance. Likewise, functional disconnection

associated with aging has been identified in brain regions implicated in both aspects of the FPN.

Furthermore, while cognitive decline in selective attention has been associated with aging, the

relationship of this decline to gray and white matter age-related changes needs better

clarification. Therefore, the current study examines a selective attention task that aims to

separate dorsal and ventral network components of attention for the purpose of better examining

attentional decline with advancing age.

1.1. Neural Correlates of Top-down and Bottom-up Attentional Control

Selective attention requires both the capacity to identify and attend to relevant stimuli, in

addition to the ability to recognize and filter irrelevant stimuli, in order to maintain focus in

pursuit of a desired goal. In a comprehensive review, Corbetta and Shulman (2002) propose

distinct yet collaborative frontoparietal processes engaged in attentional control. As a result of

extensive research evidence, the FPN has been parsed into dorsal top-down and ventral bottom-

up attention processing streams, both ultimately joining posterior parietal with prefrontal cortices

(Corbetta, Patel, & Shulman, 2008; Katsuki & Constantinidis, 2014; Bartolomeo, Thiebaut de

Schotten, & Chica, 2012; Vossel, Geng, & Fink, 2014; Kim, 2014; Shomstein, 2012). To date,

no prevailing consensus of whether endogenous and exogenous orienting of attention operate competitively or collaboratively for control (Pinto et al., 2013; Connor, Egeth, & Yantis, 2004; Corbetta et al., 2008; Chica, Bartolomeo, & Lupiáñez, 2013).

Top-down regulation refers to goal-oriented attention driven by voluntary, internal processes, and has been primarily attributed to dorsal attention network (DAN) function. Top-down attentional control relies on *a priori* knowledge of features related to expectations and current goals, and is largely endogenous in nature. The DAN is comprised of bilateral superior and middle frontal gyri (including the frontal eye fields), superior parietal lobule, and intraparietal sulcus (IPS; Corbetta & Shulman, 2002: Yantis 2008; Bartolomeo et al., 2012; Lückmann, Jacobs, & Sack, 2014; Shomstein, 2012), bound by connections via the Superior Longitudinal Fasciculus (SLF; Vossel et al., 2014; Ptak, 2012; Thiebaut de Schotten, et al., 2011). These dorsal regions have been shown to activate when anticipating location of stimuli, and the DAN has been widely implicated in cognitive control, goal-directed and task-relevant information processing (Corbetta & Shulman, 2002; Lückmann et al., 2014; Shomstein, 2012).

In contrast, bottom-up attentional processes are commanded exogenously, from environmental stimuli bearing salience to the observer. Hence, attentional processing for relevancy of unexpected, anomalous, or novel stimuli is predominantly linked to the ventral attention network (VAN). The VAN has been implicated both in the processing of unexpected or irrelevant stimuli in the context of tasks requiring the reorienting of attention (Vossel et al., 2014; Bennett et al., 2012; Corebetta & Shulman, 2002; Bartolomeo et al., 2012; Lückmann et al., 2014) and in ignoring salient but task-irrelevant distraction (Kim, 2014). The VAN encompasses inferior frontal gyri (IFG) and inferior parietal cortex, including angular and supramarginal gyri and the temporo-parietal junction (TPJ), and has been postulated to be right-

lateralized (Bennett et al., 2012; Corebetta & Shulman, 2002; Shomstein, 2012), although more recent work suggests that both hemispheres play a role in the VAN (Vossel et al., 2014). Integrity of the Inferior Longitudinal Fasciculus (ILF) has been associated with VAN function (Bennett et al., 2012). Specifically, Bennett and colleagues (2012) reveal that higher Fractional Anisotropy (FA) and lower Radial Diffusivity (RD), both indicative of greater white matter integrity, of bilateral ILF correlated with enhanced visual search performance across a wide age range of healthy individuals. Furthermore, lesions of the ILF have been related to spatial neglect, a deficit in ability to allocate attention to parts of visual space (Bird et al., 2006). Additional evidence proposes the Inferior Fronto-Occipital Fasciculus (IFOF) as a structural link among ventral frontoparietal regions in cases of spatial neglect (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007), as well as in a recent study of healthy individuals undergoing a visual attention paradigm (Chechlacz et al., 2015).

1.2. DAN and VAN Contributions to Cross-modal Selective Attention

Extensive research to uncover the neural substrates of selective attention performance have primarily focused on unimodal presentation. Particularly, broad investigation within the visual and auditory modalities has revealed significant involvement of frontoparietal brain regions during selective attention performance (Lückmann et al., 2014; Corbetta & Shulman, 2002; Cole et al., 2013; Vincent et al., 2008; Ptak, 2012; Bennett et al., 2012; Li et al., 2012; Makris et al., 2007; Almeida Montes et al., 2013; Kim, 2014).

Fewer studies have examined the involvement of these frontoparietal regions during cross-modal selective attention. Cross-modal selective attention tasks require participants to attend to one modality (e.g., auditory or visual) while competing, task-irrelevant information is presented in the opposite modality. Generally, it is more difficult to attend when competing

information is present even if that information is utterly irrelevant (Broadbent, 1956). Furthermore, task-irrelevant stimuli are associated with a mismatch negativity (Naatanen, 1992) that is involuntary yet susceptible to attentional manipulation under certain circumstances (Sabri et al., 2006). Sabri and colleagues in an ERP-fMRI study demonstrated that passive detection of task-irrelevant stimuli was associated with dorsal superior temporal gyrus (STG) activation while ventral STG was associated with involuntary shifts of attention to auditory task-irrelevant stimuli. These involuntary attention shifts occurred in the late selection phase of attention and were present only in more difficult tasks. Due to the association with frontocentral negativity at 200-400 ms, these late phase involuntary shifts in difficult attention tasks are likely modulated by top-down executive control. The top-down modulation and involuntary shifts of attention prompted by a cross-modal selective attention task may be associated with the cognitive impairment frequently displayed in healthy aging. Additionally, the involuntary and external, irrelevant nature of the distraction suggests a differential role on the dorsal and ventral aspects of the attention network. The mechanism by which the dorsal and ventral aspects of the FPN impact selective attention processing cross-modally warrant further exploration.

1.3. Attention Control and Structural Integrity Decline in Aging

Extant literature suggests that cortical disconnection, including decreased white matter integrity and cortical thinning, occurs with advancing age (Salat et al. 2004; McGinnis et al. 2011), coupled with cognitive decline, particularly in speed-related and attentional control tasks (Bennett & Madden, 2014; Salthouse, Fristo, & Rhee, 1996). Although processing speed typically declines with advancing age (Salthouse, 2000; Ferrer et al., 2013), Borghesani and colleagues (2013) found white matter integrity to be associated with higher-order cognitive functions beyond the contributions of processing speed decline in a large healthy aging sample.

Numerous studies have found older adults to display more widespread activation compared to younger adults (Reuter-Lorenz et al., 2000; Cabeza et al., 1997; McIntosh et al., 1999; Reuter-Lorenz & Cappell, 2008; Grady, 2008); and Daselaar and colleagues (2013) reveal that this over-recruitment in activation may compensate for diminished white matter integrity exhibited in older adults, underscoring the importance of structural integrity as it relates to functional and cognitive performance.

Prior research on selective attention in the visual modality demonstrates that although the ability to process task-relevant information remains largely intact, the ability to suppress task-irrelevant information declines with age (Geerligs et al., 2014). Additionally, Chou et al. (2013) demonstrated that older compared to younger adults displayed greater slowing of reaction time particularly during trials in which a salient singleton distractor was present. Thus, structural integrity of DAN and VAN is likely to be related to selective attention performance, especially when salient external distraction requires coordination of DAN and VAN activity. Since effective communication between these two networks is important in dynamic attentional control (Vossel et al., 2014), attempting to disentangle the role of the DAN and VAN requires a task that can reflect the maintenance of goal-directed attention in the face of salient but task-irrelevant distraction. Furthermore, the task must be sufficiently difficult to distinguish healthy aged from healthy younger controls.

1.4. Aims and Hypotheses

The present study aimed to disentangle the relative involvement of DAN and VAN structure in predicting selective attention performance in healthy aging. In order to broaden understanding of the implications structure may have on selective attention, both gray and white matter integrity were explored. The dynamic interchange of both the top-down endogenous cues

processed via the DAN and bottom-up exogenous input through the VAN are essential to adequate selective attention. Although the DAN and VAN function in concert, rather than completely independent of one another (Vossel et al., 2014; Connor et al., 2004), it is important to understand the contribution of the structural components of the two networks, and how these structures may differ in healthy aging. The present study aimed to investigate selective attention performance among a sample of older and younger healthy adults, and to examine the relationship between selective attention performance that distinguishes DAN and VAN processes and structural brain changes resulting from healthy aging in gray matter regions and white matter pathways that underlie attention control. The following hypotheses were therefore delineated.

Hypothesis 1. Age will be associated with a high frequency hearing loss. Despite displaying normal hearing thresholds required for inclusion in the study, it is expected that older adults will exhibit a typical decline in high-frequency hearing thresholds relative to younger adults. However, as the cross-modal selective attention task (described below) does not employ unimodal presentation of relevant and competing irrelevant auditory stimuli but rather competing information is always presented in a contrasting modality (e.g. visual, when auditory is the attend modality), it is thus unlikely that a high frequency hearing difference between younger and older adults, especially if within normal limits, would impact performance on the cross-modal selective attention task (described below).

Hypotheses 2 & 3: The random distraction condition of the cross-modal selective attention task will be more difficult than the fixed distraction condition, yet older adults will be more affected than young by the random distraction condition. A cross-modal selective attention task with distraction manipulation was therefore employed, wherein participants discriminated syllables in either visual or auditory modalities, with either random or fixed distraction presented

simultaneously in the opposite modality. We expected both age groups to display slower reaction times in the more difficult random distraction condition due to the increasing need to suppress attention to irrelevant external information, which is less necessary when the distraction can be anticipated in the simpler fixed distraction condition. Additionally, we hypothesized that older adults would perform more poorly than younger adults on the random distraction condition relative to performance on the fixed distraction condition, indicative of an age-related deficit in ignoring task-irrelevant salient and unexpected information. A difference score of reaction time between random and fixed distraction index (RTDI) was subsequently calculated to account for relative individual participant ability to ignore unexpected external distraction and maintain goal-directed endogenous attention.

Hypothesis 4: Gray and white matter integrity will be less in older adults compared to younger adults. It is also expected that older adults will display lower structural integrity than younger adults in both cortical thickness of frontoparietal regions and the underlying white matter tracts.

Hypotheses 5 & 6: RTDI will be better predicted by VAN gray matter thickness and white matter integrity than by DAN gray and white matter structural features. We hypothesized that RTDI would correlate more robustly with average gray matter thickness of the VAN compared to DAN since this index is thought to reflect the ability to ignore external, task-irrelevant distraction. We also expected that white matter integrity, operationalized by Fractional Anisotropy (FA), of the Sagittal Stratum (SS: includes ILF and IFOF) compared to the SLF, would predict the RTDI, reflecting that functional disconnection of the VAN is more involved in the age-related attention deficits of ignoring external, task-irrelevant distraction.

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Hypothesis 7: Bilateral aspects of the VAN will relate to selective attention. Finally, we expected gray matter thickness of bilateral VAN regions and FA values of both left and right SS to be predictive of RTDI given more recent results that have called into question the right dominance of the VAN.

2. Methods

2.1. Participants

Eighteen younger ($M = 26.1$, $SD = 5.7$) and 18 older ($M = 62.4$, $SD = 4.9$) adults were recruited for participation via community advertisements. The study was approved by the Institutional Review Board of the Medical College of Wisconsin, and all participants provided written informed consent prior to participation. All participants were right handed healthy adults, free of any neurological, psychiatric, and major medical conditions, as well as contraindications for MRI. Participants exhibited normal or corrected-to-normal visual acuity, and audiometric testing was conducted in a sound-proof testing booth to ensure normal hearing (audiometric thresholds ≤ 25 dB HL 500 - 4,000 Hz). Participants were screened for signs of Mild Cognitive Impairment (MCI) via the Montreal Cognitive Assessment (scores ≥ 26; Nasreddine et al., 2005), and a general neuropsychological battery to measure overall cognitive functioning using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, Tierney, Mohr & Chase, 1998). The Wechsler Adult Intelligence Scale – Third edition (WAIS-III; Wechsler, 1997) Vocabulary and Matrix Reasoning subscales were administered to estimate intellectual functioning. Participant characteristics are presented in Table 1.

2.2. Measures

2.2.1. Cognitive Screen

The MoCA, a brief 10-minute clinical measure, was administered to verify that no signs of MCI were present, using cutoff scores ≥ 26 (sensitivity = .90, specificity = .87; Nasreddine et al., 2005). Overall cognitive function was further assessed via the RBANS, a screening tool also used clinically to detect cognitive impairment (Randolph, Tierney, Mohr & Chase, 1998). Consisting of 12 subtests, the RBANS evaluates the following five cognitive domains which comprise the Total Scale: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. No cognitive impairment was defined by a Total Scale cutoff score of 85, representative of 1 SD below the mean (sensitivity = 0.55, specificity = 0.80; Duff et al., 2010). General intellectual functioning was estimated from WAIS-III Vocabulary and Matrix Reasoning subscales (Wechsler, 1997) to ensure comparability between the older and younger adult groups.

2.2.2. Cross-Modal Selective Attention Measure

Participants completed a Cross-modal Selective Attention A/B/X task (Figure 1) during fMRI; task activation results are not within the scope of this study but are separately analyzed. Employing a Garner paradigm of interference (1978) across five runs, participants performed a two-alternative forced-choice A/B/X discrimination task based on CV syllables (/ba/, /da/, /be/, /de/, /bi/, /di/, /bo/, /do/, /bu/, or /du/). Participants were instructed to press button 1 with the right index finger if X matches A, or button 2 with the right middle finger if X matches B. Ten A/B/X trials constitute one block, with five blocks total per run. Each block provided initial visual instruction to cue the specific attentional modality; participants were instructed to make their choice based on either the visual identity (Attend Visual: AV) or the sound (Attend Auditory: AA) of the syllable, while ignoring the contrasting modality (Figure 2). The type of distraction via the task-irrelevant stimuli was manipulated to either be fixed or random within a trial.

Regardless of trial type, syllables in both modalities were always presented simultaneously, and the task-irrelevant distractor stimulus was always presented in the opposite attentional modality. Hence in each trial, participants are simultaneously presented with relevant and irrelevant stimuli cross-modally. Therefore, participants must simultaneously engage attention toward a predetermined goal (e.g. "Attend Auditory") while filtering irrelevant stimulus input from a contrary modality (e.g. visual). Participants viewed a fixation cross during all time points apart from the presentation of A, B or X stimuli. Stimulus duration for A, B and X was 200 ms, with an inter-stimulus-interval of 1000 ms between A and B, and 2000 ms between B and X. Participants were allotted 1800 ms to respond after presentation of stimulus X. Accuracy and reaction times (RT) were recorded for each response. Total trial length was 6000 ms, and each block contained 10 trials. The inter-trial interval was jittered at 2000, 4000, and 6000 ms. The task employed randomized presentation of blocks as well as the stimuli within each trial. Presented in a random order, each run contained one block of the following: AA-fixed, AV-fixed, AA-random, AV-random. To ensure participants understood the task, they completed a separate practice run prior to undergoing fMRI.

The Cross-modal Selective Attention A/B/X task was programmed and presented via in-line integration of E-Prime 1.0 software (Psychology Software Tools, Pittsburgh, PA). List generation and randomization were controlled using MATLAB (The MathWorks Inc., Natick, MA). The visual stimuli were projected through an Epson LCD video projector onto an angled mirror located just above the eyes. Auditory syllables were recorded from a male native English speaker, and normalized according to loudness. Sounds were delivered through MRI-compatible STAXSR-003 electrostatic ear inserts (STAX, Saitama Prefecture, Japan), which were combined

with a Bilsom over-the-ear muff providing approximately 23 dB of passive noise reduction (Bilsom, Sweden).

2.3. Procedures

2.3.1. MRI Acquisition

Whole brain imaging was acquired on a 3T GE MR750 scanner (GE Medical Systems, Milwaukee, WI) using a 32-channel head coil. Participants viewed a fixation cross during image acquisition to aid in gaze fixation and minimize head motion. High resolution T_1-weighted whole brain anatomical images were obtained using a 3-D spoiled gradient-echo sequence (SPGR) as a set of 180 contiguous axial slices (voxel dimensions = .938 mm ×.938 mm × 1.000 mm; TR = 8.2 ms; TE = 3.2 ms; flip angle = 12°; matrix size = 256 x 224; FOV = 240 mm; slice thickness = 1 mm). The diffusion-weighted data acquisition employed a twice-refocused spin-echo EPI pulse sequence (TR = 9300 ms; TE = 80.8 ms; flip angle = 90°; matrix size = 128 x 128; FOV = 256 mm; slice thickness = 2 mm), collecting a random sample of 60 gradient directions at b = 1000 s/mm^2, and five images acquired at b = 0 s/mm^2 for a total of 65 slices.

2.3.2. MRI Processing and Analysis

Anatomical images of individual participants were processed using Freesurfer 5.1.0 software (http://surfer.nmr.mgh.harvard.edu; Dale, Fischl & Sereno, 1999; Fischl, Sereno & Dale, 1999). Through a series of automated algorithms, Freesurfer segments each voxel of extracted brain tissue into white and gray matter and estimates surface meshes at the gray and white matter boundaries to submillimeter accuracy (Fischl & Dale, 2000; Fischl et al., 2002). Cortical thickness is calculated by the distance between the gray/white boundary and pial surface at any given point (Fischl & Dale, 2000). Cortical surface maps are subsequently registered to a spherical atlas based on cortical fold patterns, and the cerebral cortex is parcellated into

anatomical regions using the structural information of brain gyral and sulcal folding (Desikan et al., 2006). Using the Destrieux atlas (Fischl et al., 2004), mean gray matter thickness for regions comprising the DAN and VAN were extracted for analyses to assess potential relationships between network ROI cortical thickness and cross-modal selective attention performance.

Diffusion-weighted data will be processed using the FSL Diffusion Toolbox (FDT; www.fmrib.ox.ac.uk/fsl; Smith et al., 2004; Woolrich et al., 2009; Jenkinson et al., 2012) to correct image distortions caused by eddy current. The non-gradient-distorted $b = 0$ image for each participant was utilized as a reference image for extracting brain tissue and generating a binary whole brain mask via Brain Extraction Tool (BET) in FSL (Smith, 2002). DTIFIT applying the computed whole brain mask was conducted for diffusion tensor model fit at each voxel, ultimately yielding a voxelwise map of FA values for each participant. Cluster editing (rmm = 2; vmul = 0) and erosion (pv = 95) of the binary whole brain mask were completed, and the resulting eroded mask was applied to FA maps to remove edge effects. All image registration and alignment was executed in Advanced Normalization Tools (ANTs; http://stnava.github.io/ANTs). Prior to registration, anatomical images were skull stripped applying either BET in FSL or 3dskullstrip in AFNI in order to achieve the most accurate brain extraction for future alignment. Nonlinear multivariate alignment of the DTI to anatomical image utilized two cost functions simultaneously (20 x 30 x 5 iterations): mutual information for $b = 0$ brain and anatomical registration; cross-correlation for FA map and anatomical registration (Avants et al., 2011). Nonlinear alignment of anatomical images to an in-house template was achieved by implementing a cross-correlation similarity metric (30 x 105 x 22 iterations). The template was created using non-linear deformation in ANTs (Tustison et al., 2010) to compute the mean of 40 healthy adult brains not comprising the present study (age range = 18 − 70 years,

M = 42.4). Individual participant FA maps were resampled into template space at 1.0 x 1.0 x 1.0 mm³. Affine transformation was applied to align the MNI152 brain (T1; 1mm) provided in FSL to template space for later use of the Johns Hopkins University (JHU) white matter labels atlas (JHU-ICBM-labels-1mm; Mori et al., 2005; Wakana et al., 2007; Hua et al., 2008) available in FSL. The JHU white matter labels atlas includes 50 white matter tract labels created by hand segmentation of a standard-space average of diffusion MRI tensor maps from 81 subjects (age range = 18 – 59 years, *M* = 39; http://neuro.debian.net/pkgs/fsl-jhu-dti-whitematter-atlas.html), and was utilized as a mask to extract values for white matter tracts of interest from the template-aligned FA maps for each individual participant. From the extracted data, mean FA was calculated for bilateral SLF and bilateral SS, which incorporates both the ILF and IFOF.

2.3.3. Statistical Analyses

Potential variation in peripheral hearing abilities was assessed utilizing a repeated measures Analysis of Variance (ANOVA) consisting of a 2 (group: young vs. old) X 2 (ear: left vs. right) X 4 (frequency: 500, 1000, 2000, 4000 Hz) analysis.

In order to test the hypotheses investigating age group differential effects of distraction on attention in the Cross-modal Selective Attention A/B/X task, a repeated measures ANOVA employing a 2 (group: young vs. old) X 2 (condition: fixed vs. random) X 2 (modality: auditory vs. visual) analysis of RT was conducted. As we expected older adults to experience greater difficulty in the face of increased distraction, planned comparisons within each group were conducted to examine the specific impact of increased distraction on RT. A distraction index of RT (RTDI; [random – fixed]) was computed for performance comparison between conditions and utilized in subsequent analyses examining links between structural integrity and selective attention performance.

Network average gray matter thickness was computed by hemisphere and analyzed via repeated measures ANOVA applying a 2 (group: young vs. old) X 2 (network: VAN vs. DAN) X 2 (hemisphere: right vs. left) design to test for group differences. A repeated measures ANOVA of a 2 (group: young vs. old) X 2 (network: SS of VAN vs. SLF of DAN) X 2 (hemisphere: right vs. left) analysis of FA was conducted to evaluate whether white matter integrity was lower for older compared to younger adults.

To examine potential associations linking gray matter thickness and selective attention performance, Pearson correlation analyses across the age range were performed between RTDI and average gray matter thickness for regions comprising the DAN (bilateral superior and middle frontal gyri, superior parietal lobule, and intraparietal sulcus) and VAN (bilateral inferior frontal, angular, supramarginal gyri) separately. Structural correlations were subject to false discovery rate correction ($q = .05$) for multiple comparisons (Benjamini and Hochberg, 1995).

In order to assess whether white matter integrity predicts age-related differences in cross-modal selective attention performance, four multiple regression analyses to predict RTDI were conducted separately by network by hemisphere. For example, FA of the right SLF, age group, and the interaction term were entered simultaneously as predictors of RTDI for the DAN. Equivalent analyses were conducted separately for left SLF underlying the DAN, and for right and left SS to elucidate contributions of the VAN white matter structure on selective attention performance.

3. Results

3.1. Hearing Thresholds

Despite normal hearing thresholds among all participants, a repeated measures ANOVA consisting of a 2 (group: young vs. old) X 2 (ear: right vs. left) X 4 (frequency: 500, 1000, 2000,

4000 Hz) revealed a main effect of Group, $F(1,34) = 4.313$, $p = .045$, $\eta_p^2 = .113$, such that

younger adults displayed lower hearing thresholds ($M = 1.18$, $SE = 1.61$) compared to older

adults ($M = 5.90$, $SE = 1.61$). A significant Frequency by Group interaction was found,

$F(2.387, 81.163) = 9.448$, $p < .001$, $\eta_p^2 = .217$, such that the higher the frequency, the greater the

difference in hearing thresholds between age group (Figure 3). Specifically, hearing thresholds at

2000 Hz were significantly lower for younger ($M = -1.11$, $SE = 1.72$) compared to older adults

($M = 4.86$, $SE = 1.72$), $p = .019$. Hearing thresholds at 4000 Hz were also significantly lower for

younger ($M = -0.56$, $SE = 2.00$) compared to older adults ($M = 9.17$, $SE = 2.00$), $p = .002$.

3.2. Cross-Modal Selective Attention Performance

Repeated measures ANOVA of a 2 (group: young vs. old) X 2 (condition: fixed vs.

random) X 2 (modality: auditory vs. visual) analysis of RT revealed a main effect of task

condition, $F(1,34) = 4.80$, $p = .035$, $\eta_p^2 = .124$, such that RT was significantly faster in the fixed

($M = 552.19$, $SE = 23.71$) compared to random ($M = 564.98$, $SE = 23.80$) distraction condition.

Planned comparisons revealed that within the older group only, RT was significantly slower

during random ($M = 573.24$, $SE = 33.66$) compared to fixed ($M = 554.04$, $SE = 33.53$)

distraction, $F(1,34) = 5.41$, $p = .026$, $\eta_p^2 = .137$; this relationship was not apparent in the younger

group only, $p > .05$ (Figure 4).

3.3. Structural Integrity

Network average gray matter thickness was compared in a 2 (group: young vs. old) X 2

(network: VAN vs. DAN) X 2 (hemisphere: right vs. left) repeated measures ANOVA design

revealing a main effect of age group $F(1,34) = 20.94$, $p < .001$, $\eta_p^2 = .381$, displaying greater

thickness for younger ($M = 2.680$, $SE = .033$) compared to older adults ($M = 2.465$, $SE = .033$).

A main effect of network was also evident, $F(1,34) = 188.87$, $p < .001$, $\eta_p^2 = .847$, demonstrating

greater thickness of VAN regions ($M = 2.675$, $SE = .025$) compared to the DAN ($M = 2.470$, $SE = .024$). A main effect of hemisphere was marginally significant, $F(1,34) = 3.97$, $p = .054$, $\eta_p^2 = .105$, showing that right hemisphere ($M = 2.582$, $SE = .025$) was thicker than left ($M = 2.563$, $SE = .022$). An interaction of network by side was uncovered, $F(1,34) = 6.29$, $p = .017$, $\eta_p^2 = .156$, indicating that average thickness differed by hemisphere only for VAN regions with the right hemisphere ($M = 2.685$, $SE = .036$) displaying greater thickness than the left hemisphere ($M = 2.675$, $SE = .032$). No additional interactions were significant (Figure 5).

Repeated measures ANOVA of a 2 (group: young vs. old) X 2 (network: SS vs. SLF) X 2 (hemisphere: right vs. left) analysis of FA revealed a main effect of group, $F(1,34) = 11.20$, $p = .002$, $\eta_p^2 = .248$, such that FA was significantly higher for younger ($M = .4214$, $SE = .0036$) compared to older ($M = .4046$, $SE = .0036$) adults. A main effect of network was also displayed, $F(1,34) = 14.45$, $p = .001$, $\eta_p^2 = .298$, such that FA was significantly greater in the SS ($M = .4201$, $SE = .0030$) compared to SLF ($M = .4059$, $SE = .0033$). A main effect of hemisphere was also evident, $F(1,34) = 121.38$, $p < .001$, $\eta_p^2 = .781$, such that FA was significantly greater for the right ($M = .4242$, $SE = .0028$) compared to left ($M = .4017$, $SE = .0027$). No significant interactions were found (Figure 6).

3.4. Structural Integrity Relationships to Cross-modal Selective Attention Performance

Across the age range, average gray-matter thickness significantly correlated with RTDI scores in 7 of the 10 regions of the VAN (all $p < .05$), indicating that larger increases in RT related to distraction were associated with decreasing thickness (Table 2). However, this relationship was not observed for any regions of the DAN. All structural correlations were subject to false discovery rate (FDR) correction ($q = .05$) for multiple comparisons.

All four separate multiple regression analyses of FA of right and left SS and SLF yielded null results, indicating that neither hemisphere, network white matter integrity, age group, nor any interactions predicted RTDI, all $p > .05$.

3.5 Post-Hoc Analyses of Structural Integrity and Performance Relationships

Given the null prior results, gray and white matter adaptive lasso regression procedures were undertaken in order to deal better with small sample size and a relatively high number of predictors compared to sample size. The adaptive lasso technique is a regularized regression, which like ridge regression penalizes the size of the model coefficients. This biasing reduces prediction error by shrinking model coefficients, selecting predictors in a forward stepwise fashion. Since collinearity is a danger with lasso techniques it was determined in the present model that all predictors correlated lowly prior to running the adaptive lasso regressions. Additionally, all variables used in the analyses were determined to fit a normal distribution as either the single best-fit distribution or within two absolute AICc points of the best distribution, indicating that a normal distribution was equivalent to the best-fit. This applied in all cases except the gray matter right pars triangularis variable for which a Johnson-Su was the best fit, although the normal distribution passed the 'eye-ball' test.

Using four adaptive lasso regressions with age, lateralized gray matter VAN and DAN regions and all interactions, only two results were significant both in the left hemisphere. The left VAN region, pars triangularis, predicted the RTDI, explaining 22% of the variance, Wald $\chi^2 =$ 4.69, $p = .033$, 95% CI [-200, -10]. The left DAN region, superior frontal gyrus, predicted the RTDI, explaining 17% of the variance, Wald $\chi^2 = 5.29$, $p < .001$, 95% CI [-278, -22].

Using another four adaptive lasso regressions with age, lateralized white matter VAN and DAN tracts and all interactions, all four white matter tracts were significant predictors of RTDI,

all $p < .05$. In order to make the analysis more parsimonious, the right and left sides of each of the DAN and VAN tracts were collapsed and combined with age and the interaction of the VAN and DAN terms. The DAN-bilateral variable was the only significant term predicting the RTDI, explaining 12% of the variance, Wald $\chi^2 = 3.88$, $p = .016$, 95% CI [-1731, -4].

4. Discussion

The present study investigated the relationship between selective attention performance and the structural integrity of gray and white matter pathways that underlie attention control in a sample of healthy younger and older adults with normal hearing thresholds. Expected age differences were found on both the cross-modal selective attention task and the structural brain indices. However, the selective attention task did not relate as expected to the VAN and DAN structural indices, perhaps because the RTDI variable was not constructed in a manner best suited to index VAN processes. Results for each hypothesis are discussed in the following sections.

Hypothesis 1: Age will be associated with a high frequency hearing loss. Typical high frequency hearing difficulty was demonstrated in the older age group compared to the younger age group. While these differences were present, hearing was thought to be sufficient to not seriously affect performance on the selective attention task. Specifically, all participants exhibited hearing thresholds within normal limits, and all sounds presented during the cross-modal selective attention task were at dB levels amply detectable by all participants at any frequency. These results simply reflect that high frequency hearing loss is evident even among relatively young, healthy high functioning older adults.

Hypotheses 2 & 3: The random distraction condition of the cross-modal selective attention task will be more difficult than the fixed distraction condition, yet older adults will be

more affected than young by the random distraction condition. Both age groups exhibited slower reaction times during the random distraction condition compared to the fixed condition. The need to suppress attention to irrelevant external information is greater in the random condition in comparison to the fixed distraction condition during which the distracting information can be anticipated. As a result, the RTDI (RTrandom – RTfixed) reflects selective attention and was, therefore, thought to index functioning of the VAN where external distracting stimuli must be ignored, as in the Dosenbach et al. (2007) model where certain regions underlying the VAN function to maintain mental set in a stable fashion over time. This assumption, however, did not appear to be valid, as discussed further below, but was more consistent with a view of the DAN as the network that gates out attention to irrelevant external stimuli (Vossel, et al., 2014). Additionally, as expected, older adults performed more poorly on the random distraction condition relative to the fixed distraction condition, and this performance difference was not evident for the younger adults alone. These findings suggest an age-related deficit in ability to filter task-irrelevant, salient, unexpected information, consistent with current literature (Chou et al., 2013). The RTDI score calculated to account for individual participant capacity to ignore unexpected external distraction while maintaining goal-directed endogenous attention was used to link structure to performance in subsequent analyses.

Hypothesis 4: Gray and white matter integrity will be less in older adults compared to younger adults. Structural analyses broadly indicate that younger adults displayed greater integrity compared to older adults in both gray matter thickness and white matter integrity, underscoring decreased structural integrity of attention networks in healthy, even successfully, aged individuals. The cross-sectional design of the present investigation is one caveat to consider, as inferences of direct effects specifically due to lifespan changes are unable to be

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concluded since longitudinal data are not available. Yet, even in a relatively young, healthy older adult group with Above Average to Very Superior range general intellectual and cognitive function, lower integrity of both gray and white matter of the broad FPN was evident.

Hypotheses 5 & 6: RTDI will be better predicted by VAN gray matter thickness and white matter integrity than by DAN gray and white matter structural features. Contrary to the hypotheses, results were mixed regarding the relationship between VAN and DAN gray matter thickness and selective attention as reflected in RTDI. The simple zero-order correlations were consistent with the hypothesis in that only VAN regions were significantly related to RTDI. No DAN regions survived false discovery rate corrections for simple zero-order correlations, although the superior frontal gyrus region bilaterally was above .3, generally considered a sufficient effect size. However, when white matter integrity of the network tracts were entered into simultaneous regressions, no significant relationships were found. Since sample size was small and the number of predictor variables was high, post-hoc analyses were completed utilizing a more appropriate regression procedure given the design constraints. The relatively new procedure of adaptive lasso regressions are designed to handle the small sample size and low predictor to sample size ratio. Using such a procedure, only left pars triangularis (VAN) and superior frontal gyrus (DAN) thickness, and integrity of bilateral SLF were found to be unique predictors of selective attention ability.

Such a result is inconsistent with the notion that VAN processes are related to the RTDI selective attention operationalization. Specifically, the RTDI features a focus on maintaining attention to task in the face of distracting but irrelevant stimuli. The nature of that index seems to be more related to DAN function than VAN function in retrospect. An index that focuses more on detecting external stimuli that are unexpectedly task-relevant in the sense of signaling a need

to switch task set may have been a better index to use in detecting VAN processes. Therefore, a task that includes both rare and unpredictable stimuli that require a different response from the predominant task set, and rare and unpredictable stimuli that do not require a momentary shift in response may be necessary to index VAN function. Using such a task would be important before concluding that age-related differences do not occur in VAN functioning. Suggestions of this notion are consistent with findings that IFG is related to invalidly cued or deviant targets that followed regular occurring targets (Vossel, et al., 2014). This is consistent with the integration of Vossel et al. (2014) that left IFG tonically inhibits left TPJ while actively maintaining attention to an internally regulated mental set. In such a case, the VAN would potentially serve to detect relevant, but not irrelevant, external stimuli in order to help switch attention away from the internal set of the moment via activation of the TPJ. As such, extensive work implicates the VAN as critical in the reorienting of attention to relevant stimuli. Less support, however, has been demonstrated implicating the VAN in the ability to recognize stimuli as irrelevant and as a result effectively ignore it as irrelevant distraction, while in the pursuit of current goals.

Furthermore, others have purported that top-down control from the DAN modulates VAN activation (Shulman et al., 2003 & 2007), likely via communication hubs such as the IFG, TPJ and IPS (Serences & Yantis, 2007; Serences et al., 2005; Asplund, Todd, Snyder, & Marois, 2010; Shomstein, 2012; Shulman et al., 2009; Chica et al., 2013), to successfully filter and ignore task-irrelevant information in the service of attaining current attentional goals. Contrary to our expectation, the VAN may not function solely on its own to actively ignore irrelevant stimuli in the absence of the momentary signaling from the DAN. Although the reorienting of attention to exogenous stimuli has strong evidence from the literature as a VAN-specific function, yet the capacity to effectively ignore that salient distraction may rely on top-down modulatory signals

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from the DAN since determining whether salient distraction is irrelevant and should be ignored relies on awareness of current goals. Hence, collaboration among the two networks is not only important, but the VAN may be somewhat dependent on DAN modulation to achieve more complex functions such as effectively ignoring irrelevant salient information.

In support of the idea that VAN and DAN integration is important in selective attention, Bartolomeo and colleagues (2012) reviewed studies of visual neglect and described a subcomponent of the SLF, termed the SLF II. This region was hypothesized to connect the inferior parietal aspect of the VAN with the prefrontal cortical component of the DAN, thereby allowing a channel of communication between the two networks. Damage to the SLF II may result in disruption of attention function due to severing communication between VAN and DAN for effective attentional processing (Bartolomeo et al., 2012). Additionally, it has been hypothesized that areas of the IFG (e.g., inferior frontal junction), a core region of the VAN, may operate as the mediator signaling activation switches between DAN and VAN (Asplund et al., 2010; Shomstein, 2012); therefore, the varying network predictability results observed presently may be a consequence of the IFG as a key element to effective cross-modal selective attention performance by implementing DAN-VAN shifts. Moreover, competition among task-irrelevant stimuli that more closely resemble task-relevant stimuli (e.g. similar features) has been described to modulate IFG and TPJ activity (Serences et al., 2005; Shulman et al., 2007) suggesting involvement of these regions in complex attentional control. Others have also noted the right TPJ, a component of the VAN, as a site for attentional shifts as well, independent of expectation to reorient (Shulman et al., 2009; Chica et al., 2013), though conflicting results have been reported (see DiQuattro, Sawaki, & Geng, 2013). Yet, divergent evidence also suggests the involvement of the IPS, part of the DAN, in attentional shifting between networks (Shulman et

al. 2009; Serences & Yantis, 2007). These discrepancies seem to resolve under the view that parallel attention networks work in concert, perhaps under regulatory influence of the Default Mode Network (Poole et al., 2016; Gerlach, Spreng, Madore, & Schacter, 2014).

Hypothesis 7: Bilateral aspects of the VAN will relate to selective attention. Consistent with more recent work, bilateral frontal areas of the VAN were important in selective attention performance with little evidence for the sometimes postulated idea that the right hemisphere is more related to the ventral aspects of attention. Correlations showed that left and right inferior frontal regions related to the RTDI, indicating that greater thickness of both hemisphere regions were related to less decrement in reaction times due to distraction. Additionally, the adaptive lasso regressions revealed that greater integrity of bilateral white matter tracts predicted smaller increases in RT during increased distraction indicative of better performance. Importantly, the majority of studies reporting the VAN to be right-lateralized result from visuospatial attention paradigms. The cross-modal selective attention task employed in the current study does not include visuospatial, nor audiospatial, manipulation. Therefore, we do not refute that the attention capture feature of spatial position may be specific to right hemisphere VAN, but rather that when spatial dynamics are not involved, the role of the VAN may become more bilateral. Particularly in the case of speech stimuli, it is possible that more left hemisphere regions engage, as language processes are left-lateralized, thereby implicating bilateral VAN. Yet even in a visual search task, higher integrity of bilateral ILF underlying the VAN has been reported to correlate with better performance (Bennett et al., 2012).

Several limitations of the present study should be considered. Firstly, the small sample size likely minimizes the power to detect differences between the groups. The relatively limited age range and unusually high functioning sample characteristics of the older adults with Superior

to Very Superior intelligence render the results less generalizable to typical older adults. Further, the RTDI performance measure constructed may be indexing ability to maintain focus more than the ability to switch focus because relevant external stimuli are present, which may be the purpose of the VAN. Future tasks may be better aimed at comparing conditions that include task relevant vs. irrelevant external stimuli that signal the need to switch or maintain attentional focus in order to distinguish VAN and DAN processes. Finally, visual and auditory processes were not separated in the current methodology. The averaging between both modalities may have influenced the results since some studies suggest the DAN and VAN may not be entirely supramodal (Ruff et al., 2007). Ruff and colleagues (2007) further suggest a right lateralization for top-down influences that was not seen in the current results. The lack of strong lateralized findings may be attributable to averaging across modalities or reflect a lack of confirmation of the earlier findings. Further study looking separately at the attend-visual and attend-auditory conditions is necessary in order to determine the meaning of this inconsistency. Of note, the cross-modal selective attention task inherently involves a working memory component, and thus may implicate working memory circuitry; however, this concern seems unlikely since the working memory aspect of the task was held constant, unmanipulated among all conditions.

Despite the above limitations, current results compliment extant research (Vossel et al., 2014; Poole et al., 2016) regarding functional neural correlates of attention performance, as the present study investigated the relationships of structural foundations of the FPN and cross-modal selective attention performance in a sample of healthy younger and older adults. The present results extend support for the important role of FPN structural integrity in cross-modal selective attention performance, bolstering the collaborative network theory inferring that effective interchange between DAN and VAN may be crucial for optimal attention regulation in that top-

down regions modulate bottom-up processes to effectively ignore salient distraction. Future

research in a larger sample may consider specifically examining FPN gray and white matter

regions of overlap between the VAN and DAN to parse the specific contributions of these

regions to attention performance, regardless of their network classifications. Furthermore,

alterations in the task to better reflect differences in DAN and VAN processes will lead to greater

understanding of how the attention networks collaborate to maintain internal goal-directed

efforts while remaining flexible enough to be responsive to external events that signal a need to

switch mental sets effectively.

Table 1. Participant demographic characteristics.

|		Mean (SD)		t / x^2	p
		Young	**Old**		
	N (% female)	18 (72.2%)	18 (66.7%)	0.131	0.717
	Age	26.1 (5.7)	62.4 (4.9)	-20.42	<.001
	Years of Education	16.5 (2.1)	16.6 (2.3)	-0.19	.853
	WAIS-III Estimated IQ	128.1 (10.8)	126.4 (6.4)	0.55	.589
	MoCA	28.7 (1.2)	28.1 (1.1)	1.36	.182
RBANS	Immediate Memory	103.8 (14.9)	108.5 (14.0)	-0.97	.339
	Visuospatial Construction	101.2 (9.9)	101.9 (11.7)	-0.19	.855
	Language	109.1 (11.9)	110.7 (15.3)	-0.36	.718
	Attention	111.6 (13.3)	117.8 (12.8)	-1.43	.162
	Delayed Memory	101.3 (10.1)	107.8 (12.6)	-1.70	.098
	Total Scale	107.3 (12.3)	113.8 (13.9)	-1.47	.150

Note. MoCA = Montreal Cognitive Assessment; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; WAIS-III = Wechsler Adult Intelligence Scale – Third edition; Standard scores are reported for RBANS and WAIS-III.

Table 2. Pearson correlations of RTDI with gray matter thickness by network.

Network	ROI	Correlation (r)	
		Left	**Right**
DAN	Middle Frontal Gyrus	-.224	-.233
	Superior Frontal Gyrus	-.317	-.325
	Superior Parietal Gyrus	-.276	-.136
	Intraparietal Sulcus	-.027	-.194
VAN	IFG: pars opercularis	**-.424***	**-.393***
	IFG: pars orbitalis	**-.355***	**-.455***
	IFG: pars triangularis	**-.414***	**-.407***
	Angular Gyrus	-0.143	-0.238
	Supramarginal Gyrus	-0.241	**-.393***

Note. ***** denotes significance at *p* < .05 after FDR correction (*q* = .05). IFG = Inferior Frontal Gyrus.

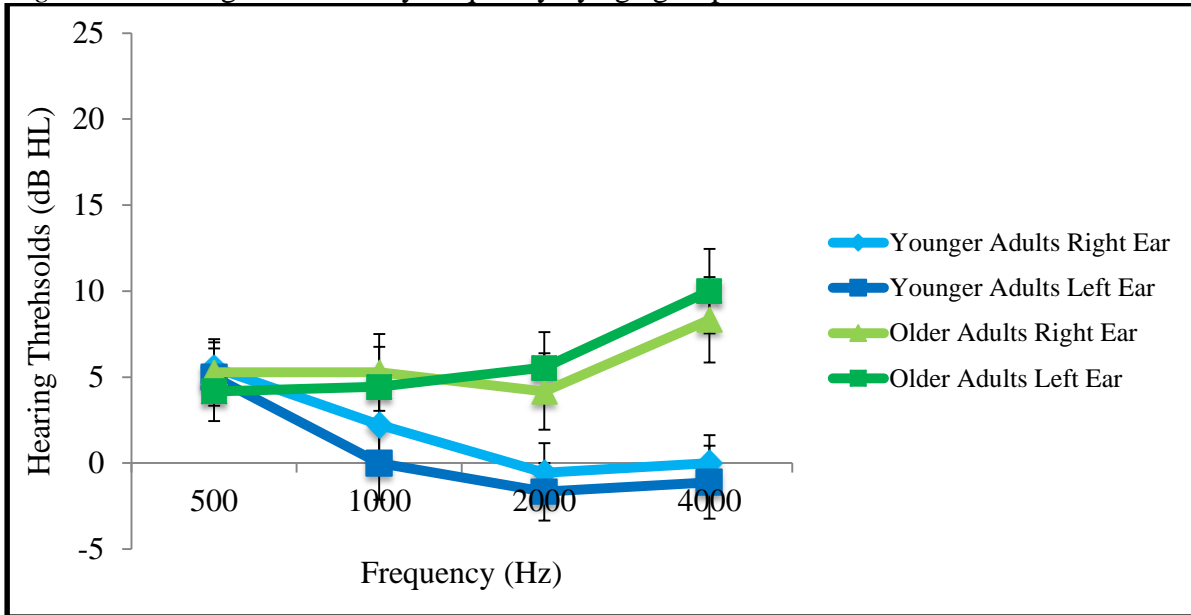*Figure 1*. Cross-modal Selective Attention (A/B/X) Task diagram.
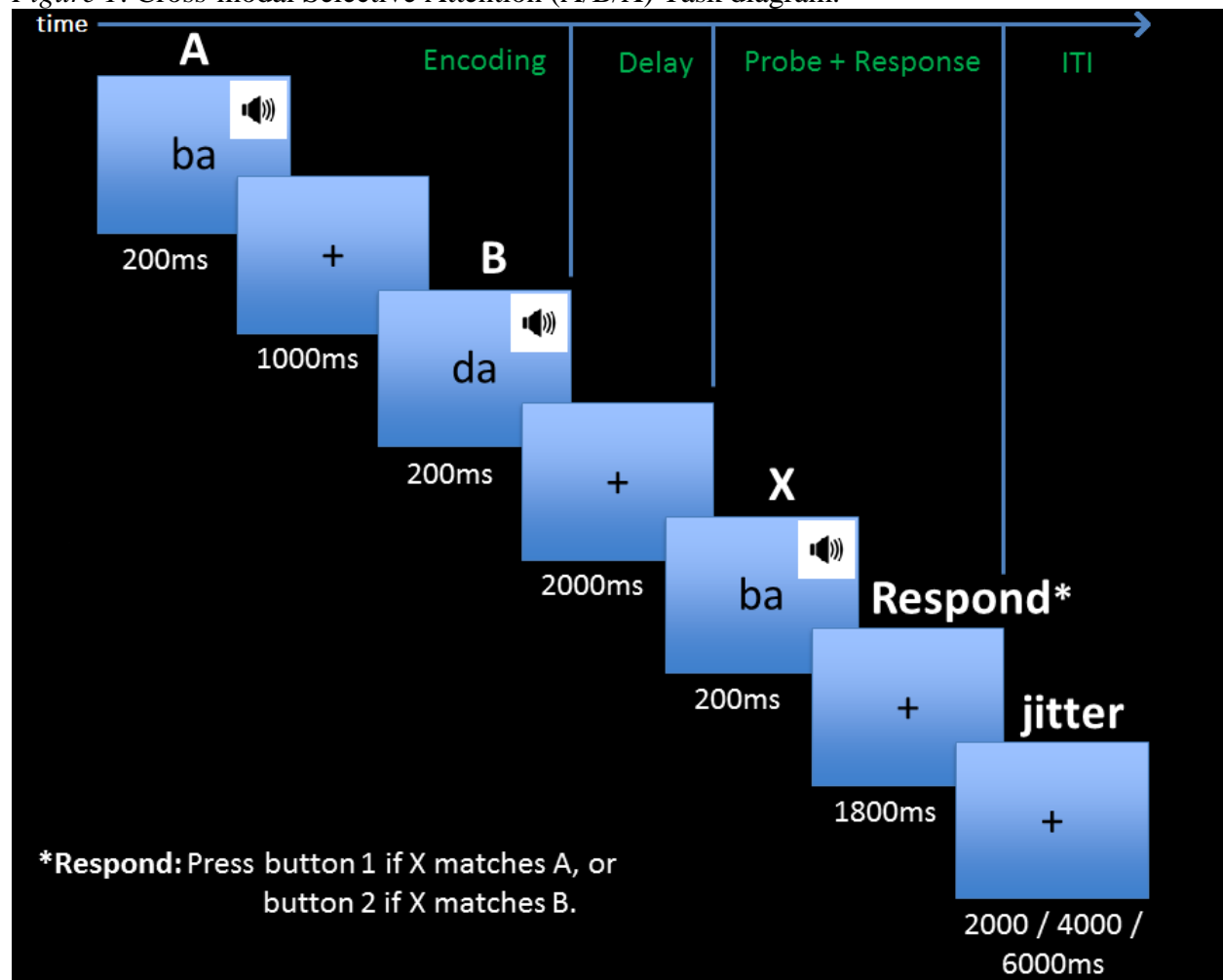
Note. Participants are instructed to discriminate syllables in either visual or auditory modalities with random or fixed distraction presented simultaneously in the opposite modality.

Figure 2. Sample trials of Cross-modal Selective Attention (A/B/X) Task.
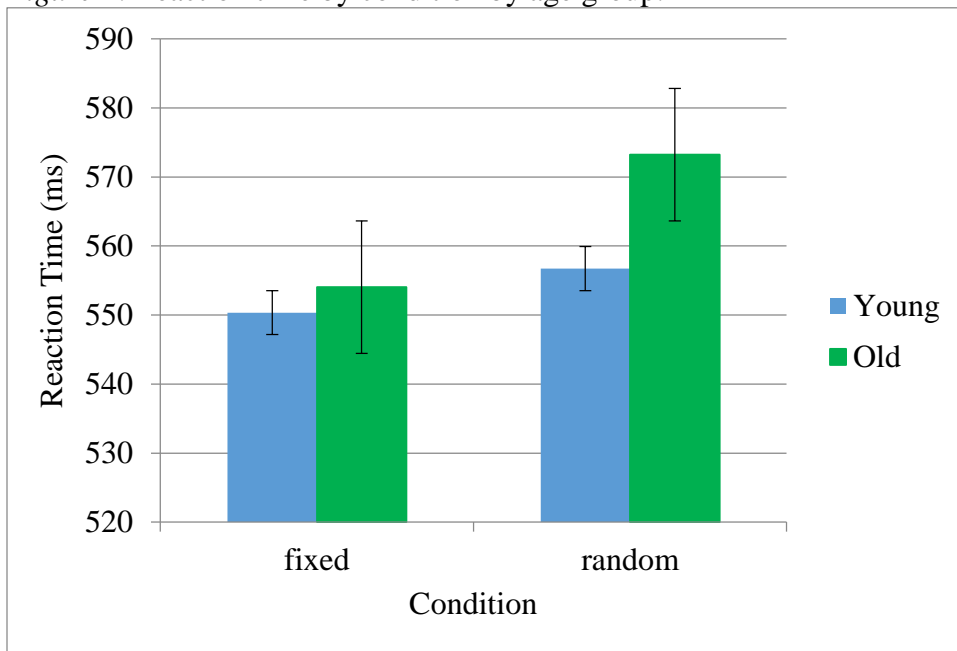

Note. | indicates inter-trial interval.

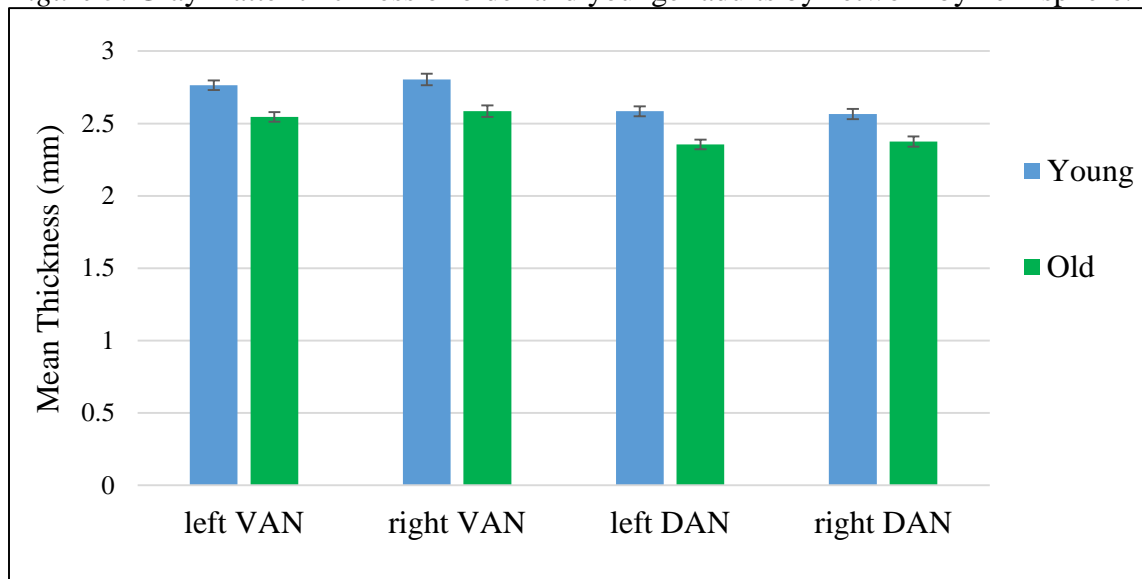*Figure 3*. Hearing thresholds by frequency by age group.

Note. Mean hearing thresholds in dB HL for left and right ears across 500-4000 Hz. Error bars indicate standard error.

*Figure 4*. Reaction time by condition by age group.

Note. Error bars indicate standard error.

Figure 5. Gray matter thickness of older and younger adults by network by hemisphere.

Note. Represents main effect of age group, main effect of network, and interaction of network by hemisphere, all $p < .05$; VAN = Ventral Attention Network; DAN = Dorsal Attention Network; Error bars indicate standard error.

Figure 6. White matter integrity of older and younger adults by network by hemisphere.
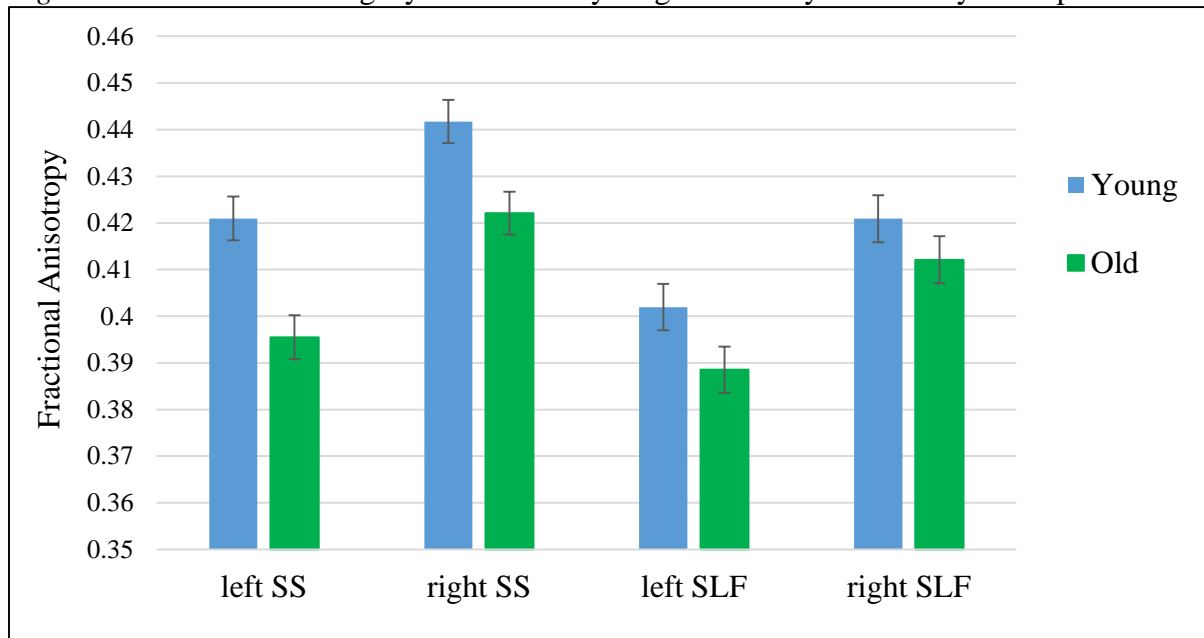
Note. Represents main effect of age group, main effect of network, and main effect of hemisphere, all $p < .05$; SS = Sagittal stratum; SLF = Superior longitudinal fasciculus; Error bars indicate standard error.

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