THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DEPARTMENT OF KINESIOLOGY

AGE-RELATED WHITE MATTER CHANGES MEDIATE THE RELATIONSHIP BETWEEN AGE AND SPEED OF PROCESSING

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SPRING 2017

A thesis
submitted in partial fulfillment
of the requirements
for a baccalaureate degree
in Kinesiology
with honors in Kinesiology

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ABSTRACT

Aging is associated with changes in cognitive processing and changes in white matter. Decreasing white matter integrity disrupts networks in the brain which can be a potential mediator of the age-related cognitive decline. Diffusion Tensor Imaging (DTI) is a neuroimaging technique that is capable of extracting and investigating specific white matter tracts and their respective integrity by measuring the diffusion of water molecules in the brain by a value called FA. In this current DTI study, white matter tracts were investigated for their relationship with age and speed of processing cognitive domain in a data driven analysis in a study that included 45 older adults screened to be representative of healthy aging. Our results showed that correlations between age and cognitive function, age and tract integrity, as well as cognitive function and tracts of interest existed. As age increased, decreases in FA values and cognitive performance were observed for posterior corona radiata, anterior corona radiata, posterior thalamic radiation, external capsule, cingulum, and superior longitudinal fasciculus. Additionally, follow-up mediation analysis suggested that white matter tracts of interests were found to be significant mediators in the relationship between aging and the speed of processing cognitive domain. Our results suggest that the age-related changes in the white matter tracts play a significant role in the age-related decline in performance for speed of processing.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to say thank you thank you thank you to all of the individuals that made this project possible. First, thank you Dr. Dennis for this opportunity. I have learned so much from being a part of your lab and am so happy that I found your office two years ago when I was looking into research. Thank you for understanding me and my interests from the very first day, pushing me to reach outside my comfort zone to write this thesis, and working with me through the whole journey. And of course, thank you for placing me with Indira.

Indira – I can't say thank you enough. You have been more than a mentor to me. Thank you for putting up with me, my tears, my stories, my bad and my good days. I am not sure how you did it, but thank you for teaching me everything. Thank you for the knowledge, for the laughs, for the lightbulb moments. Thank you for being the most patient and the most kind, for listening to me and for taking the time to explain even when I already asked a thousand times. If you ever want to have a conversation about why white matter matters, give me a call. Thank you for being more than a mentor, for being a friend and a shoulder to lean on. I appreciate it and look up to you more than words can do justice.

And thank you to Dr. Hakun because I am not sure this paper would have been possible without you at all. Thank you for taking so much time to teach me and impart your knowledge. I consider myself lucky to have been able to work with someone as intelligent as you. It has been a growing, learning, and wonderful experience getting to write with you.

I would also like to thank John and Christina for supporting me through this past year. John, thank you for knowing exactly how to motivate me and make me laugh when I needed it most. Thank you for listening to me ramble and for all the wonderful conversation. It made the journey all the brighter. Christina, thank you for understanding, listening and guiding. I appreciated your knowledge, calmness, experience, and guidance more than you know!

Finally, thank you to family and friends for mostly listening to me ramble about white matter, age, and speed of processing. Thank you for heeding my calls, Mom. Dad, thanks for reading my abstract. Jill, thanks for being you. Shawn, thanks for the intellectual coffees. I appreciate you all so very dearly.

Thank you, thank you, thank you. This would not have been possible without all of you.

Casey Ryan

Chapter 1

Introduction

As the human brain ages, structural and cognitive changes take place. Degeneration of white matter tracts is one of the many structural changes that transpires in the brain during the natural aging process. Cognitive decline is also associated with increasing age (Salami, Eriksson, Nilsson, Nyberg., 2012). The disconnection hypothesis tries to explain how these two changes that are associated with aging might be related (Burgmans et al., 2011). Myelin degradation impairs the conduction of signals from one area of the brain to another area since white matter carries signals between two areas of cortex (Davis et al., 2009). These connections, when intact, are important for the integration of various and large amounts of information. Each tract's function depends on the two regions of the brain it connects. It is hypothesized that the degeneration of white matter, or loss of structural integrity, leads to a decrease in integration which has an impact on how well the major networks of the brain communicate and, thus, function effectively (Vernooij., 2009). Until recently, testing these types of hypotheses had been limited by technology. However, the past few years have seen great developments in neuroimaging and statistical analyses enabling the study of age-related white matter changes and see if these changes are influencing age-related cognitive changes (Salami et al., 2012).

Diffusion Tensor Imaging (DTI) is one of the major advancements in the field that enables the study of microscopic age-related structural changes (Davis et al., 2009). DTI is a type of MRI technique that measures the diffusion of water molecules in the brain and can extract

information about microstructural changes along the length of individual tracts (Salami et al., 2012). Normal white matter constrains the diffusion of water molecules more than degraded or aging white matter (Davis et al., 2009). Fractional anisotropy, or FA, is one DTI measures that can infer white matter integrity by measuring the directionality of water molecules along the length of a white matter tract (Bennett and Madden., 2014). Frequently used in DTI research, FA shows a negative correlation with age which has been replicated in numerous studies (Vernooij et al., 2009; Kochunov et al., 2012). Furthermore, pathologic evidence was discovered in a post-mortem study that shows that FA directly correlates with the amount of white matter (Schmierer et al., 2007) (Vernooj et al., 2009). Current studies are using diffusivity measures such as FA and mean diffusivity (MD) in conjunction to relate changes in integrity with age-related cognitive decline. This study focuses on FA as the main indicator of white matter integrity since FA is thought to have an advantage over other indices of integrity in predicting cognitive performance (Vernooij et al., 2009).

Speed of processing (SOP) is a cognitive domain of interest to many researchers because of its strong relationship with age (Salthouse, 2000). Evidence from numerous previous studies shows that as age increases, speed decreases (Vernooij et al., 2009; Kochunov et al., 2012). This strong relationship has increased interest in how speed might be involved in the relationship between aging and other cognitive variables (Turken et al., 2008). A previous study found that speed plays a role at least to some extent in the decline of other cognitive processes such as memory and higher-order cognitive functions as well (Turken et al., 2008). Although it is clear that aging is associated with slower speed and other cognitive functions, the underlying mechanism by which this occurs is unclear. Multiple mechanisms have attempted to explain the relationship between age and speed including mechanisms that disrupt or weaken links in the

neural network and loss of myelin (Miller, 1994). Even though mechanisms of mediation have been proposed, it is still unclear as to whether age-related slowing is task-specific or reflective of a broader, global influence of the entire aging brain (Salthouse., 2000).

Despite recent research successfully establishing age-related changes in performance on speed tests, there is still debate concerned the details of the relationship between age and SOP and the joint association with white matter microstructure (Salami et al., 2012). Previous studies have employed the causal steps approach by Barron and Kenny, the hierarchical regression approach, and the more modern statistical equation modeling approach to explain this complex relationship (Salami et al., 2012; Burgmans et al., 2011). Haye's mediation model is a more modern approach that is up to date with statistical and neuropsychological methods that, with its simplest statistical model, attempts to explain the relationship between two variables through an intervening or mediating variable (Hayes., 2009). This model uses a bootstrapping statistical model that addresses the shortcomings of the previous causal steps approach and simplifies the newer M-test model (SEM) which requires the use of complicated tables and additional assumptions that this current model does not employ. Haye's mediation model can thus be used to explain the relationship between age and SOP through white matter microstructure which is quantified with FA. It provides useful insight into understanding one of the mechanisms underlying age-related slowing because it examines the degree to which age-related white matter changes affect age-related declines in processing speed.

The objective of this present study was to identify white matter tracts that are significant mediators of the relationship between age and the SOP cognitive domain. In order to assess SOP, 45 older adults completed 3 speed of processing tests, Symbol Search, Digit Symbol Coding, and Symbol Copy from the WAIS-III that had been used in past research studies to quantify

processing speed (Royall, Miller, Wechsler). The scores of the three tests were z-scored and correlated and subjected to reliability statistics to justify the creation of a composite score. DTI data was collected for each participant. FA values were used as the DTI index of white matter integrity since prior research shows that diffusivity measures have slight advantages in predicting cognitive performance. First, the composite scores for SOP correlated with age. Then, FA values of white matter tracts selected via apriori hypotheses correlated with age. Finally, the last analysis checked if any significant correlations existed between tracts of interest and SOP. Tracts of interest (TOI) that were correlated with speed of processing were subjected to a mediation analysis. The goal of the mediation analysis was to identify tracts that were significant mediators in the relationship between age and SOP. In addition to better understanding white matter microstructure as an underlying mechanism of age-related decline, mediation analysis can potentially give insight into how much each tract played a role in the relationship which would help to identify whether or not the slowing down process is a result of tract-specific decline or reflective of global white matter changes in the brain.

I hypothesized that increasing age would be correlated with decreasing cognitive performance, specifically a reduction in processing speed. I expected increasing age to correlate negatively with FA values of relevant tracts. I hypothesized that the third correlation would be a positive relationship between cognitive assessment and TOI showing that as scores increased on cognitive tests, FA values would be higher representing more intact white matter. Statistically, I did not expect all of the significant tracts from the correlation analyses to be significant mediators of the relationship between age and cognition. TOI that were suspected to be significant mediators of the relationship between age and SOP included tracts that connected the frontal lobe of the brain to the parietal and temporal lobes because of the tendency of SOP

processing tests to reflect integration of multiple brain regions. Furthermore, I assumed tracts involved in the dorsal attention network and incorporating the occipital lobe had the potential to be involved in SOP because of the visual and attention aspects that are inherent in speed tests of the neuropsychological battery.

Chapter 2

Methods

2.1 Subjects

Forty-five older adults from the State College Area participated in this study. Their ages ranged from 62 to 85 with a mean age of 73.6 (SD= 6.17). Participants were selected from two existing datasets collected at the Pennsylvania State University that utilized the same neuropsychological assessment battery and underwent the same imaging protocol. Inclusion criteria required that participants had normal or corrected-to-normal vision and no history of neurological or psychiatric disease. All participants scored above a 24 on the Mini-Mental State Exam (MMSE), suggesting that all participants were cognitively normal. Subjects scored within an age-normative range, averaging 29.62 on the exam. All participants gave informed consent and received financial compensation for their participation in the study. The Pennsylvania State University's Institutional Review Board approved all experimental procedures and ethical treatment of all human subjects.

2.2 Behavioral testing

Subjects completed a neuropsychological assessment that consisted of standardized tests of cognitive functioning. The symbol search, digit symbol coding, and symbol copy subtests of the WAIS-III were selected to assess the SOP cognitive domain (Wechsler, 1997). They were scored manually according to the WAIS-III scoring manual.

2.2a Symbol Search

Symbol search is a measure that assesses processing speed and visual perception (Kreutzer, 2011). Subjects are given two symbols on the left and a group of five symbols on the left. Subjects are instructed to check the "yes" box if one of the symbols presented on the left is also present in the set of five symbols on the right. If neither of the two symbols are present, the subject should check the "no" box. The goal is to get through as many rows correctly in the allotted time. Raw scores are based on the total number of correct answers.

2.2b Digit Symbol Coding

In the digit symbol coding task, participants associate a geometric symbol with a numerical digit (Kreutzer, 2011). They are initially presented with a key that includes the numbers 1-9 and their associated symbols. Below the key, there is a series of boxes with numbers with empty boxes below them. The task is to fill in the empty box with the proper symbol from the key that corresponds with the given number. The raw score is equal to the number of correct answers in the allotted time limit.

2.2c Symbol Copy

During the symbol copy subtest, subjects are asked to copy rows of symbols into a row of empty boxes below it (Kreutzer, 2011). Raw scores are equal to the amount of symbols the participant can accurately copy in the allotted time.

2.3 Imaging Data Acquisition

Imaging data was collected using a Siemens 3T scanner with a 12-channel head coil. Diffusion tensor images used a single-shot echo- planar sequence (TR= 6500 ms, slices= 48, thickness= 3.0 mm, FOV = 240 mm, matrix size= 128×128, voxel size=1.9mm×1.9mm×3.0mm, b value= 1000 s/mm2, diffusion-sensitizing directions= 20, total images= 21). There were two acquisitions of this DTI sequence. Total scan time was approximately 5 minutes per subject. The

same scanner was used for all tested subjects and there were no hardware or software updates during the collection period.

2.4 DTI Analysis

Data was processed with University of Oxford's Functional Magnetic Resonance Imaging of the brain (FMRIB) Software Library (FSL). Analysis of the DTI data was conducted following a series of procedures known as Tract-Based Spatial Statistics [TBSS v1.2; http://www.fmrib.ox.ac.uk/fsl/tbss/)]. The raw data was manually inspected for artifacts including electromagnetic interference-like artifacts, severe signal loss artifacts, venetian blind artifacts, and checkerboard artifacts. No images were removed after inspection. Raw images were corrected for the effects of head movement and eddy currents using the tools in the FDT FSL toolbox. The b=0 images were separated and averaged from the diffusion-weighted images and then used to make the brain mask. These b=0 images were skull-stripped with the Brain Extraction Tool (BET) and retained to compute the normalization parameters necessary to normalize DTI to standard space. DTI data was fit with a single tensor model and these parameters were used to create Fractional Anisotropy (FA) images with FMRIB's Diffusion toolbox. Participants' FA images were aligned to a common target (FMRIB's 1×1×1 mm3group average DTI template) using a nonlinear registration method. FA images were averaged into a mean FA image which was used to create a white matter skeleton of all the subjects. The aligned FA images were then projected onto a white matter tract skeleton and thresholded at 0.2 in order to correct for partial voluming.

TOI were isolated using the JHU ICBM-DTI-81 white matter labels developed at Johns Hopkins University and packaged with FSL. The JHU white matter labels atlas contains 48

white matter tracts. White matter TOI were selected from the atlas based on two criteria based on previous evidence suggesting that they are related to SOP and to age-related decline. Based on these two criterion, twenty TOI were selected from the original JHU atlas (Table 1).

White matter TOI were defined using the JHU white matter labels as discussed above. All voxels falling within each TOI were used to extract FA values per tract per subject. Mean FA from within all homologous tracts were averaged across hemispheres to create a single representative FA value per tract.

2.5 Statistical Analyses

Participant's cognitive assessments were scored according to the WAIS-III scoring manual (Wechsler, 1997). All correlation, reliability and mediation analyses were computed in SPSS v. 22 (IBM Corp, released 2013, Armonk, NY, USA). The final analysis used mediation models to test the hypothesis that white matter microstructure accounts for age-related processing speed changes. Mediation analysis based on multiple linear regression was performed using macros (PROCESS; Hayes, 2013) that estimates all the paths between variables as well as indirect effects simultaneously. PROCESS uses bootstrapping and generates confidence intervals which enable statistical inference. The 95% confidence interval of the indirect effect was obtained with 5,000 bootstrap resamples. Indirect effects that have 95% confidence intervals that do not cross zero are accepted as significant mediators.

Chapter 3

Results

Results of a correlation analysis on the three speed of processing tests revealed significant correlations between each test. Symbol Search was significantly positively correlated with both Digit Symbol Coding (r=0.295, p=0.049) and Symbol Copy (r=0.363, p=0.014). Digit Symbol Coding also correlated with Symbol Copy (r=0.589, p=<0.001). Reliability analysis suggested that the subtests were reliable markers of speed of processing (α= 0.681). The cognitive assessment scores for each test were z-scored in order to standardize the scores across the participants and subtests. Resulting z-scores were averaged to create a composite SOP score.

3.1 Age and Speed of Processing Composite Score

Results of a correlation analysis of the neuropsychological SOP tasks revealed significant positive correlations between age of participants and performance on the speed composite (r= -0.42, p=0.004). As the age of the participants increased, their processing speed decreased or slowed.

3.2 Age and White Matter Microstructure

Results of the correlation analysis between white matter microstructure and age revealed significant negative correlations between FA and age for the fornix column and body(r= -0.51, p<0.001), anterior corona radiata (r=-0.37, p= 0.013), posterior corona radiata (r=-0.30, p=0.045), posterior thalamic radiation (r=-0.38, p=0.009), external capsule (r=-0.29, p=0.05), cingulum (r=-0.43, p=0.003), fornix stria terminalis (r=-0.56, p<0.001), and superior longitudinal fasiculus (r=-0.38, p=0.01) (Table 1). No significant correlation was observed between the corticospinal tract included as a control to represent tracts that are not as sensitive to

the effects of aging showed no significant changes with respect to increased age (r=0.10, p=0.514).

3.3 Speed of Processing and White Matter Microstructure

Results of correlation analyses between SOP and FA showed positive correlations in the anterior corona radiata (r=0.48, p=0.001), posterior corona radiata (r=0.48, p=0.001), posterior thalamic radiation (r=0.51, p=0.0), external capsule (r=0.30, p=0.043), cingulum (r=0.35, p=0.018), and superior longitudinal fasciculus (r= 0.40, p=0.007) (Table 1).

Table 1 Correlations of FA with Age and Speed of Processing Composite Score

Tract Name	Mean FA	Age	Speed Composite
Genu of CC	0.72±0.04	-0.21	0.22
Body of CC	0.64±0.05	-0.22	0.28
Splenium of CC	0.80±0.02	-0.19	0.46*
Fornix (column and body)	0.40±0.10	**-0.51**	0.17
Corticospinal Tract	0.60±0.03	0.10	0.15
Medial lemniscus	0.62±0.02	-0.05	0.28
Anterior limb of IC	0.60±0.02	-0.28	0.24
Posterior limb of IC	0.68±0.02	0.10	0.003
Retrolenticular part of IC	0.60±0.03	-0.05	0.16
Anterior corona radiata	0.49±0.04	**-0.37**	**0.48**
Superior corona radiata	0.50±0.03	-0.22	0.27
Posterior corona radiata	0.50±0.03	**-0.30**	**0.48**
Posterior thalamic rad	0.62±0.05	**-0.38**	**0.51**
External capsule	0.44±0.03	**-0.29**	**0.30**
Cingulum - cingulate gyrus	0.55±0.04	**-0.43**	**0.35**
Cingulum - hippocampus	0.53±0.05	-0.08	0.26
Fornix/ Stria terminalis	0.55±0.04	**-0.56**	0.26
SLF	0.51±0.03	**-0.38**	**0.40**
SFOF	0.54±0.04	0.04	0.02
Uncinate fasciculus	0.52±0.04	-0.10	0.10

Note. All r-values are significant at p<0.05. CC= Corpus Callosum, IC= Internal Capsule, SLF= Superior Longitudinal fasiculus, SFOF= Superior Fronto-Occipital Fasciculus. *=significant for composite, but not for age.

3.4 Mediation

Six TOI were both negatively associated with age and positively associated with Sop. In order to examine our central hypothesis that age-related changes in white matter microstructure may contribute to speed of processing declines in aging, we constructed mediation models to estimate the effect of white matter decline on SOP for these six TOI.

Results of a single mediator model estimating the indirect effect of the anterior corona radiata on the relationship between age and speed of processing (total effect =-0.0535) revealed a significant indirect effect of the anterior corona radiata (indirect effect = -0.0174, 95% CI [-0.0417, -0.0048] on the relationship between speed and age (direct effect = -0.0361, 95% CI [-0.0717, -0.0006].

Results of a single mediator model estimating the indirect effect of the posterior corona radiata on the relationship between age and speed of processing (total effect=-0.0535) revealed a significant indirect effect of the posterior corona radiata (indirect effect= -0.0149), 95% CI [-0.0384, -0.0018] on the relationship between speed and age (direct effect= -0.0387), 95% CI [-0.0728, -0.0045].

Results of a single mediator model estimating the indirect effect of the posterior thalamic radiation on the relationship between age and speed of processing (total effect=-0.0535) revealed a nonsignificant indirect effect of the posterior thalamic radiation (indirect effect= -0.0444), 95% CI [-0.0444, -0.0061] on the relationship between speed and age (direct effect= -0.0338), 95% CI [-0.0690, 0.0015].

Results of a single mediator model estimating the indirect effect of the external capsule on the relationship between age and speed of processing (total effect=-0.0535) revealed a significant indirect effect of the external capsule (indirect effect= -0.0073), 95% CI [-0.0301, 0.0008] on the relationship between speed and age (direct effect= -0.0462), 95% CI [-0.0828], [-0.0096].

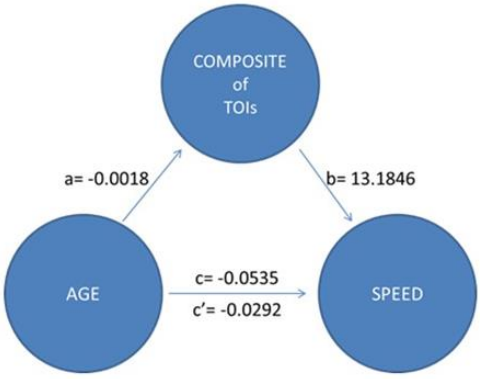
Results of a single mediator model estimating the indirect effect of the superior longitudinal fasciculus on the relationship between age and speed of processing (total effect=-0.0535) revealed a significant indirect effect of the superior longitudinal fasciculus (indirect effect= -0.0133), 95% CI [-

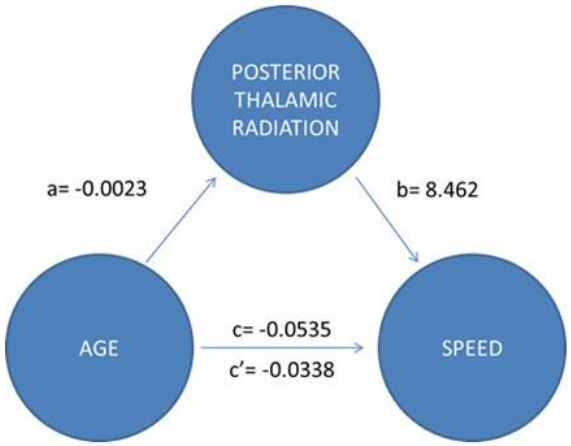
0.0350, -0.0020] on the relationship between speed and age (direct effect= -0.0402), 95% CI [-0.0773, -0.0032].

Results of a single mediator model estimating the indirect effect of the cingulate gyrus on the relationship between age and speed of processing (total effect=-0.0535) revealed a nonsignificant indirect effect of the cingulate gyrus (indirect effect = -0.0114), 95% CI [-0.0333, 0.0010] on the relationship between speed and age (direct effect= -0.0421), 95% CI [-0.0808, -0.0034].

The results for mediation analyses show a greater total indirect effect of the white matter tracts then the total direct effect of age on speed (total indirect effects accounted for 123% of the relationship between age and speed of processing). This suggests that there is a significant amount of shared variance between each of the white matter tracts. As a result, a white matter composite was generated by z-scoring FA within each tract and averaging FA across the four significant TOIs. Composite FA was then entered into a mediation analysis on the relationship between age and speed of processing. Results of a single mediator model estimating the indirect effect of the composite TOI on the relationship between age and speed of processing (direct effect=-0.0535) revealed a significant indirect effect of the composite TOI (indirect effect= -0.0133), 95% CI [-0.0350, 0.0020] on the relationship between speed and age (direct effect= -0.0402), 95% CI [-0.0773, -0.0032].

Figure 1
Mediation Triangles with FA of TOIs as the mediating variable on the Relationship between Age and Speed

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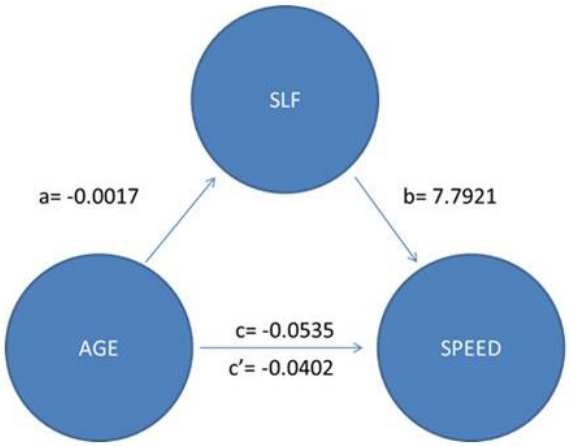
SPEED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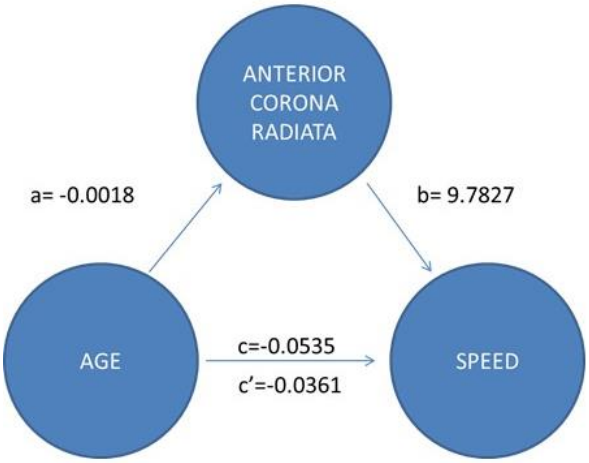
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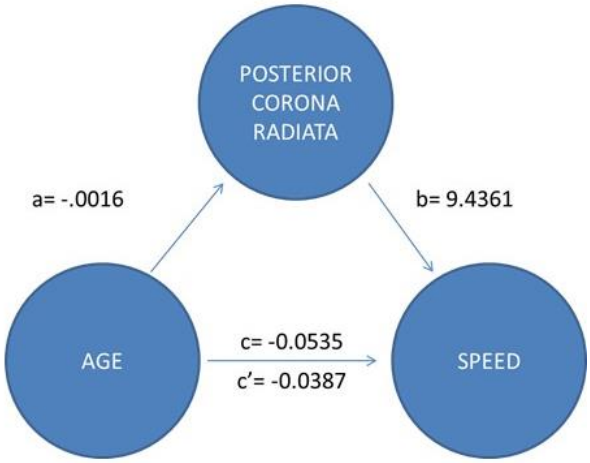
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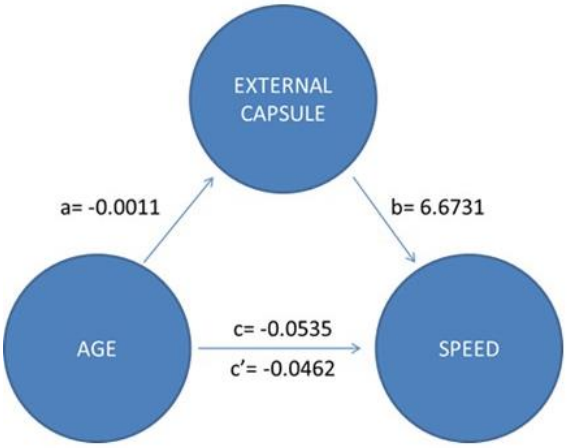
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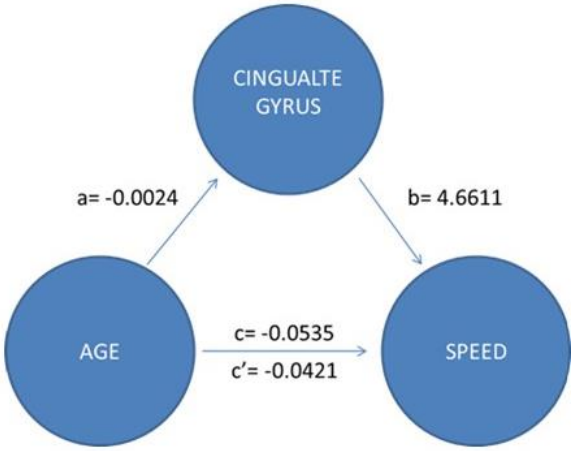
SPEED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AGE
c= -0.0535
c'= -0.0421
SPEED

Chapter 4

Discussion

The relationship between age and speed of processing was examined with a measure of white matter integrity, FA, as a potential mediator. Three subtests from WAIS-III were used to create a composite score that was representative of the SOP cognitive domain based on simple correlations and reliability analysis. Age was negatively correlated with the composite which is consistent with age-related slowing findings of previous studies (Salthouse., 1996, Turken., 2008). Age-related decreases in white matter microstructure were observed across numerous tracts. Tracts that showed decreases in FA with aging, including the fornix, anterior/ posterior corona radiata, posterior thalamic radiation, cingulum bundles, superior longitudinal fasciculus, and external capsule, were consistent with prior research findings that suggested these white matter tracts were sensitive to the effects of aging (Salami et al., 2012; Bennett, I., & Madden, D., 2014; Jang, S., Hong, J., 2012; & Ly et al., 2016). Of these TOI, the anterior/ posterior corona radiata, posterior thalamic radiation, cingulum – cingulate gyrus, superior longitudinal fasciculus, and external capsule were also significantly postively correlated with the SOP composite. Mediation analyses showed that the anterior/ posterior corona radiata, posterior thalamic radiation, external capsule and the superior longitudinal fasciculus were significant mediators of the relationship between age and speed of processing. Previous research has identified these tracts and their associations to age-related decline and SOP (Salami et al., 2012; Bennett, I., & Madden, D., 2014; Jang, S., Hong, J., 2012; & Turken et al., 2008).

4.1 Speed and Age

Findings from this study suggest that there is general slowing as people age. Several cognitive domains have been shown to decline with increased age; furthermore, previous research has identified specifically that SOP is especially susceptible to the effects of aging and may be part of the underlying mechanism of decline in other cognitive functions as well (Horn., 1986; Burgmans et al., 2011; & Turken

et al., 2008). Although the exact mechanism of this observed decline is unclear, current research has proposes the "disconnection hypothesis" which aims to suggest one reason for age-related slowing (Burgmans et al., 2011). This hypothesis suggests that the deterioration of white matter disrupts neural networks, which in turn causes cognitive decline. Intact white matter transmits information across these neural networks and then ensures the temporality and integration of functions carried out in specific regions of cortex. This facilitation of communication between the networks of the brain is required for efficient SOP because of its reliance on integration of numerous, widespread cortical areas. Prior research has also observed that SOP is an integrative process incorporating visual scanning, mental flexibility, and sustained attention (Salami et al., 2012). With its diverse requirement for multiple functional regions of the brain, the disruption in neural networks across the brain affects the speed at which elders can process information and perform. For this reason, previous studies have hypothesized that SOP as a cognitive domain might be reliant on global brain function (Salami et al., 2012). The current findings of this study are consistent with prior research that age is associated with decreasing performance on speed of processing tasks.

4.2 Tracts and Age

Another finding from this study is that the FA values, a measure of the integrity of white matter microstructure, are negatively correlated with age. Certain white matter tracts have previously been shown to be more sensitive to effects of aging. A few hypotheses have been proposed to explain which tracts are more susceptible to the effects of aging including the anterior-posterior gradient, the superior-inferior gradient, and the last-in-first-out retro-genesis hypothesis (Bennet, I., & Madden, D., 2014). Another study separated tracts into functional categories and found that association fibers are more likely to have significant decreases in FA as opposed to projection and callosal fibers (Salat et al., 2005; Salat., 2011). Consistent with these findings, the superior longitudinal fasciculus and the cingulum are association fibers that had age-related decreases in FA in the current study (Wakana et al., 2007; Bennet,

I., & Madden, D., 2014). Other fibers that are not categorized as association fibers also showed age-related decline including the fornix, anterior/ posterior corona radiata, posterior thalamic radiation, and the external capsule. However, all of these tracts have been previously identified in research and are known to experience age-related decline (Ly et al., 2016, Salami et al., 2008). The corticospinal tract, included as a control because it is known to have limited if any changes with age, showed no significant negative FA correlation with age as expected and consistent with the current research of age-related changes in white matter microstructure (Bennet, I., & Madden, D., 2014, Salat., 2011).

4.3 Tracts of Interest and Speed

Our findings suggest that numerous white matter tracts correlate with speed of processing tasks. Previous DTI research has also identified tracts that may be involved in SOP tasks. Speed of processing is an integrative function that utilizes more than one brain network (Turken et al., 2008). It relies on the effective communication between networks. Pre-frontal cortex is important for higher order association and temporal and parietal areas are important for various tasks including, attention, working memory and response selection which are all a fundamental aspect of efficient SOP (Turken et al., 2008). For this reason, researchers predict that association tracts that incorporate and integrate these areas of the brain ought to play a significant role in speed of processing tasks. Tracts that connect the frontal lobe with the temporal and parietal, like the superior longitudinal fasciculus and corona radiate, are commonly hypothesized as being involved with speed tasks (Turken et al., 2008; Salami et al., 2012). This current study's findings show significant negative correlations between superior longitudinal fasciculus and corona radiata with speed suggesting that they might play a role in the processing. Past research has identified these two tracts and the implications that a decrease in FA might have on them which support the disconnection hypothesis. Decreases in FA of the superior longitudinal fasciculus may represent a disruption in the intra-hemispheric pathway connecting the frontal lobe to posterior brain regions.

Decreases in FA of the anterior corona radiata may represent a disruption in the thalamo-cortical pathway in the frontal lobe. The disruption of these tracts could potentially explain why processing speed is correlated since they are both important for the communication and integration of brain regions involved in processing (Salami et al., 2012).

Findings also show that the cingulate gyrus and external capsule correlate negatively with age. A previous study found that white matter tracts that had trajectories along the anterior posterior axis of the brain may be more likely to play a role in SOP tasks which is applicable to both the these tracts anatomically (Turken et al., 2008; Salami et al., 2012). Another study also found significant correlations between the FA in the external capsule and speed of processing and Mean Diffusivity (MD – another measure of white matter integrity) in the cingulum and SOP (Salami et al., 2008). Similarly, this study suggests significant correlations between both these tracts' FA values and performance on tests of processing speed. Finally, this study finds that posterior thalamic radiation correlates negatively with speed of processing. Previous research identifies the role of the dorsal attention network and the occipital lobe's role in SOP in combined fMRI-DTI studies of subcortical to cortical projections (Ystad et al., 2011). Occipital lobe involvement may be a result of the visual scanning and visual attention that some of the speed tests, like symbol search, require (Bennet, I., & Madden, D., 2014; Ystad et al., 2011). Although, to my knowledge, posterior thalamic radiation is not associated with SOP it is sensible that it might play a role in the more visual-dependent aspects of the test since it structurally connects thalamus to occipital lobe.

Prior research has also suggested that since SOP involves multiple aspects of cognition such as visual scanning, planning, and attention, it might reflect global brain function (Salami et al., 2012, Salthouse, 2000). Findings from this study are consistent with this hypothesis since the tracts are reflective structurally and functionally of whole brain integration. This also supports other hypotheses that speed of processing might be an underlying mechanism of performance in other cognitive domains because SOP might be a core cognitive process (Turken et al., 2008, Salami et al., 2012 Salthouse, 2000).

Thus, age-related slowing might be able to explain some aspects of decline in other cognitive domains that are known to experience age-related changes.

4.4 Mediation

Results from this mediation analysis show that certain white matter tracts are significant mediators of the relationship between age and cognition. However, a composite of white matter tracts that are associated with both age-related decline and SOP is even more representative of the how age affects age-related slowing through white matter. It is a more reliable indicator of white matter than any single tract suggested above since the mediation composite had a greater indirect effect than any other indirect effect a single tract. The significant mediation analysis shows that these white matter tracts as a whole are sharing variance in that they collectively mediate the relationship with 45% attenuation. This suggests that age-related decline in SOP may be related to a global effect of white matter microstructure rather than tract-specific effects. This possibility is both supported and argued against in the current literature (Bennet, I., & Madden, D., 2014; Penke et al., 2010; & Lovden et al., 2013). Findings from this study support the idea that there is potentially a global effect of white matter microstructure that can explain some of the variance that is observed with age-related slowing.

4.5 Limitations, Conclusion, and Future Directions

The findings stated should be viewed in light of some limitations pertaining to the study. First, the sample size was small with only 45 healthy older adults. A similar, but larger and more representative study should be repeated to see if the results are replicated in a larger population. Furthermore, the study did not include any younger or middle-aged adults to compare performance on speed tests and FA values between the different age groups. Secondly, the cross-sectional study design excludes the aspect of causality that longitudinal studies are capable of assessing. Furthermore, longitudinal studies do not always confirm the findings and results from cross-sectional studies (Royall et al., 2005; Kochunov et al.,

2012). Finally, the DTI analysis involved in this study included some simplifying assumptions that current research on the tract-based analysis methods has already exceeded. These were made in an effort to conserve time.

In conclusion, I investigated the relationship between age and speed of processing with white matter integrity as a potential mediator of the relationship. I assessed older adults' performance on SOP tests using a composite score created from three speed subtests from WAIS-III that have been documented repeatedly as measuring processing speed, were highly correlated, and reliable according to statistics. FA values quantified white matter microstructure. Mediation analysis computed the role of white matter microstructure in the relationship between age and speed of processing. The study had 4 main findings. First and consistent with prior research, SOP and age are negatively correlated entities. Secondly, the FA values of some white matter tracts are negatively correlated with age potentially suggesting that some white matter tracts are more susceptible to the effects of aging than others. Next, some TOI are also positively correlated with SOP suggesting that they are involved in performing speed tasks and are also subject to age-related decline. Finally, mediation analysis shows that a composite of white matter tracts that are related to age and speed is a more representative measure of mediation between age and speed than any single tract on its own. White matter tracts of interest as a whole share variance that helps explain one mechanism of age-related cognitive slowing.

Future research on this topic is necessary and can follow multiple avenues to add to the current literature. There is a need for longitudinal studies that can assess causality of white matter microstructure and age-related variance on cognitive tests. Future studies should also consider gaining a better understand of whether the effect of white matter microstructure is tract-specific or a more global phenomenon by employing more mediational analyses assessing the attenuation of individual tracts versus global white matter. Furthermore, multiple indices of white matter integrity including mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) should be combined in one study to potentially explain different aspects of white matter microstructure, which can work to better explain the

underlying mechanisms of white matter decline. This will provide more insight into what is actually occurring structurally in the brain that can explain age-related changes in structure and performance. Finally, structure and function can be assessed in future studies by combining DTI and fMRI techniques to gain a better understanding of how white matter relates to activation in the brain. This can provide better insight into the activity of the brain while participants perform speed of processing tasks, which can lead to a better understand of how potential interventions can be utilized to decrease or combat age-related slowing. Finally, future studies can assess how much speed of processing mediates performance on how other domains of cognitive functioning such as working memory and attention

Chapter 5

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Appendix A

WAIS-III and DTI Analysis Pipeline

WAIS-III

WECHSLER ADULT INTELLIGENCE SCALE – THIRD EDITION

Name _____

Date _____

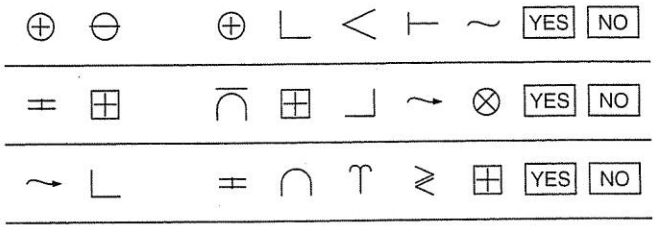
Examiner _____

Handedness (circle one): Left Right

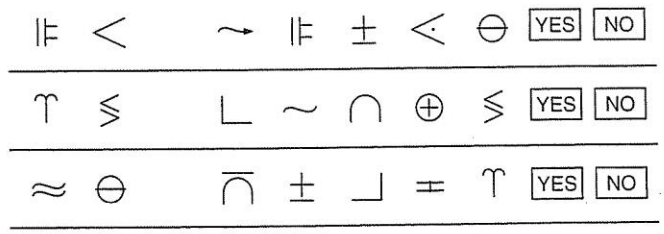
Response Booklet

Symbol Search

Sample Items



Practice Items



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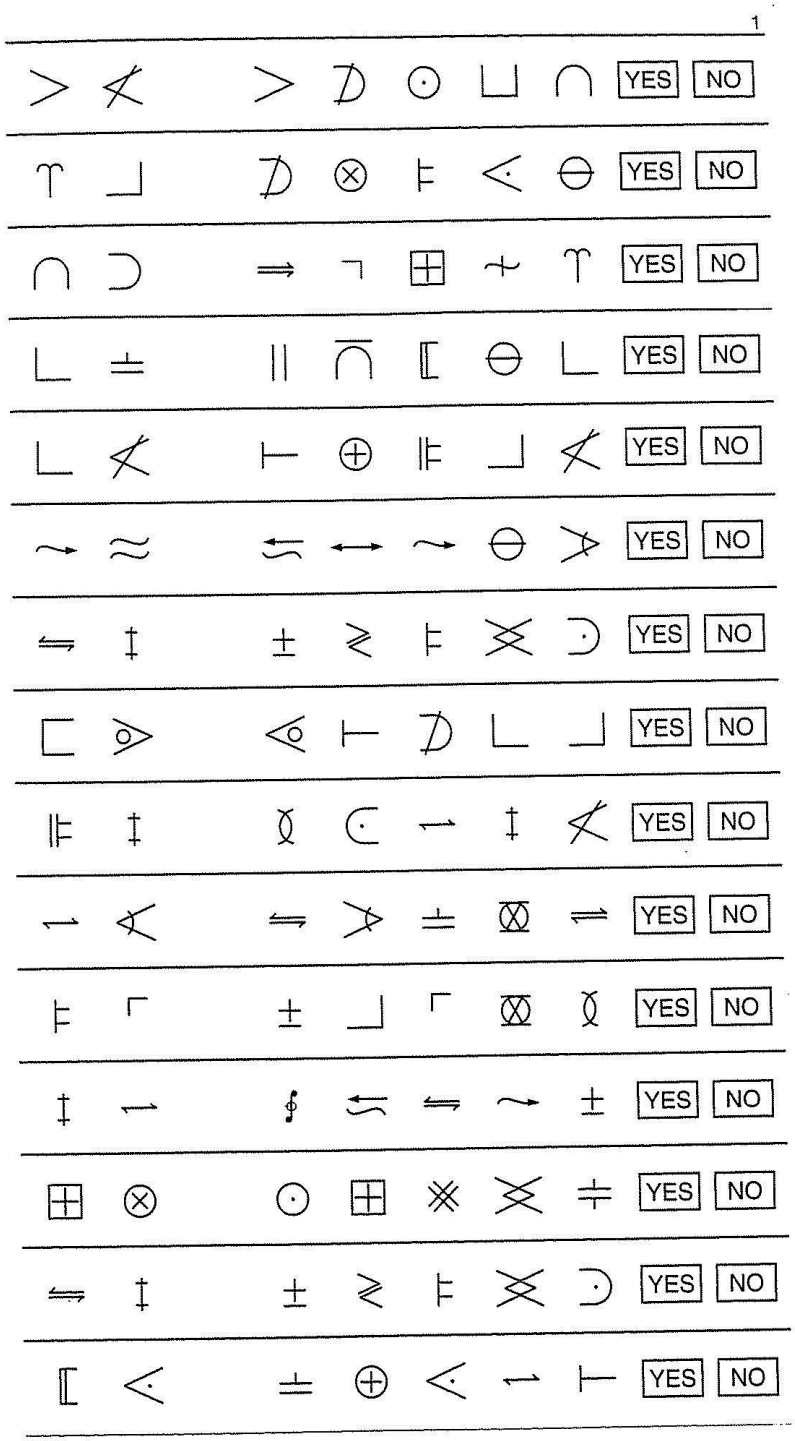
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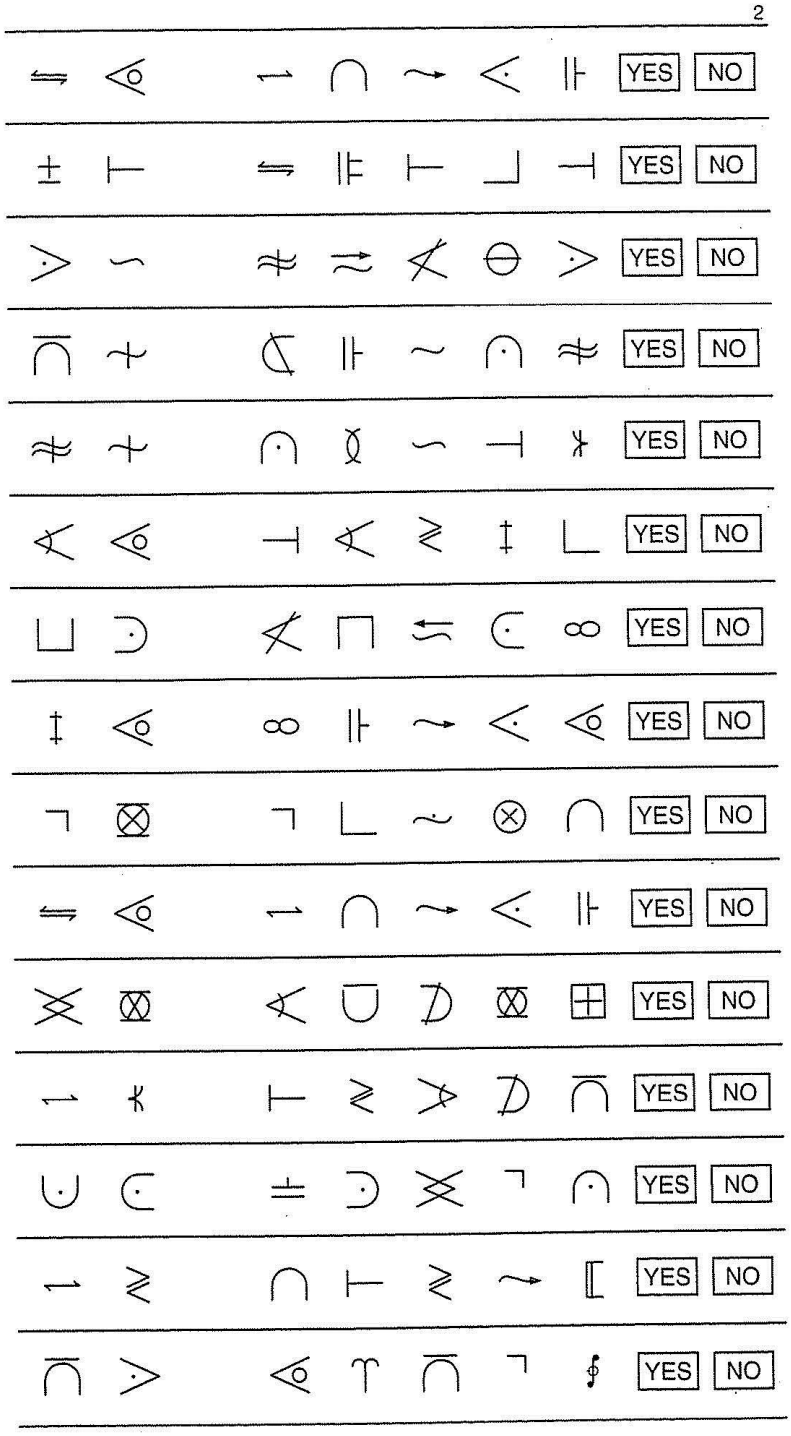
YES NO
YES NO
YES NO
YES NO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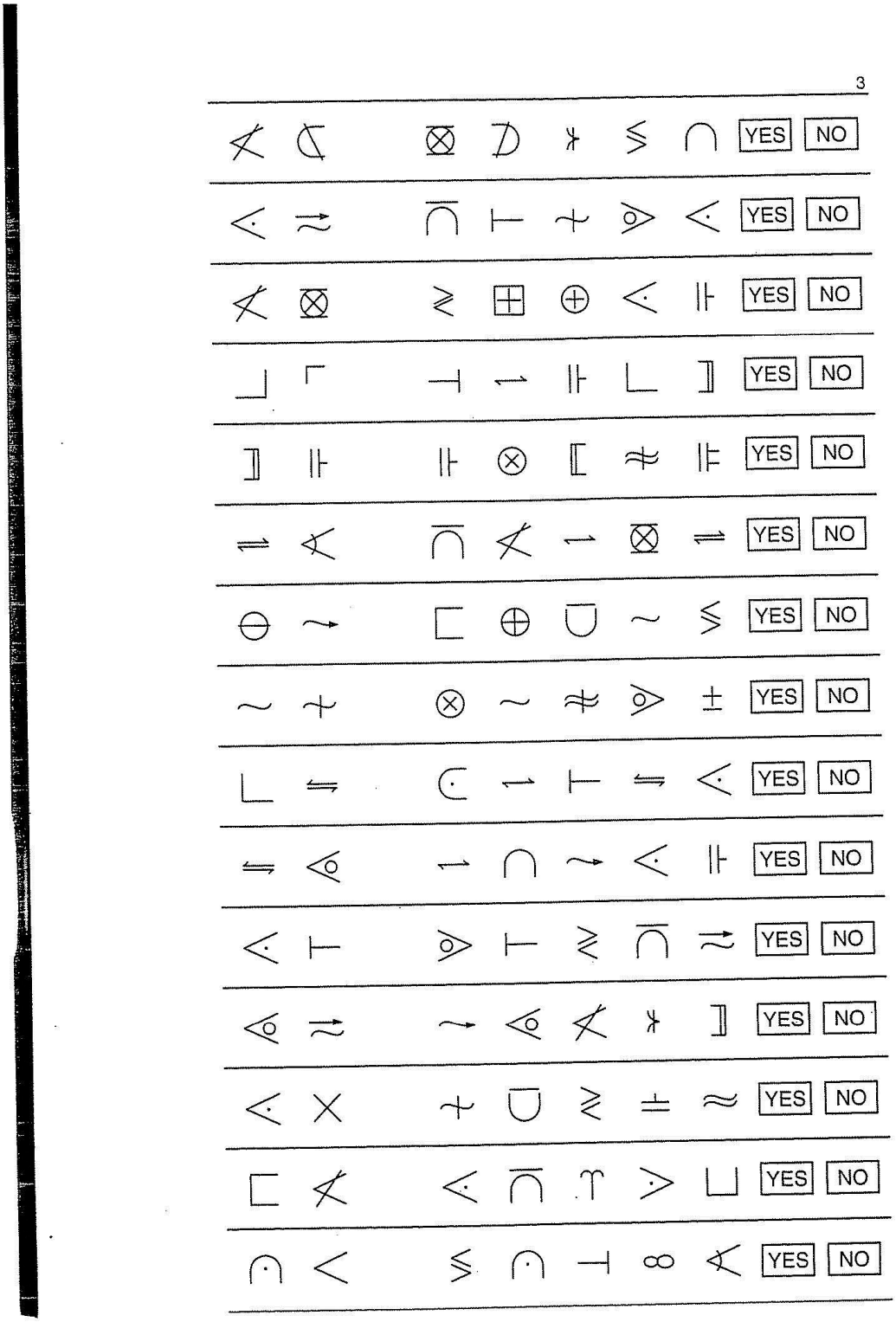
YES NO
YES NO
YES NO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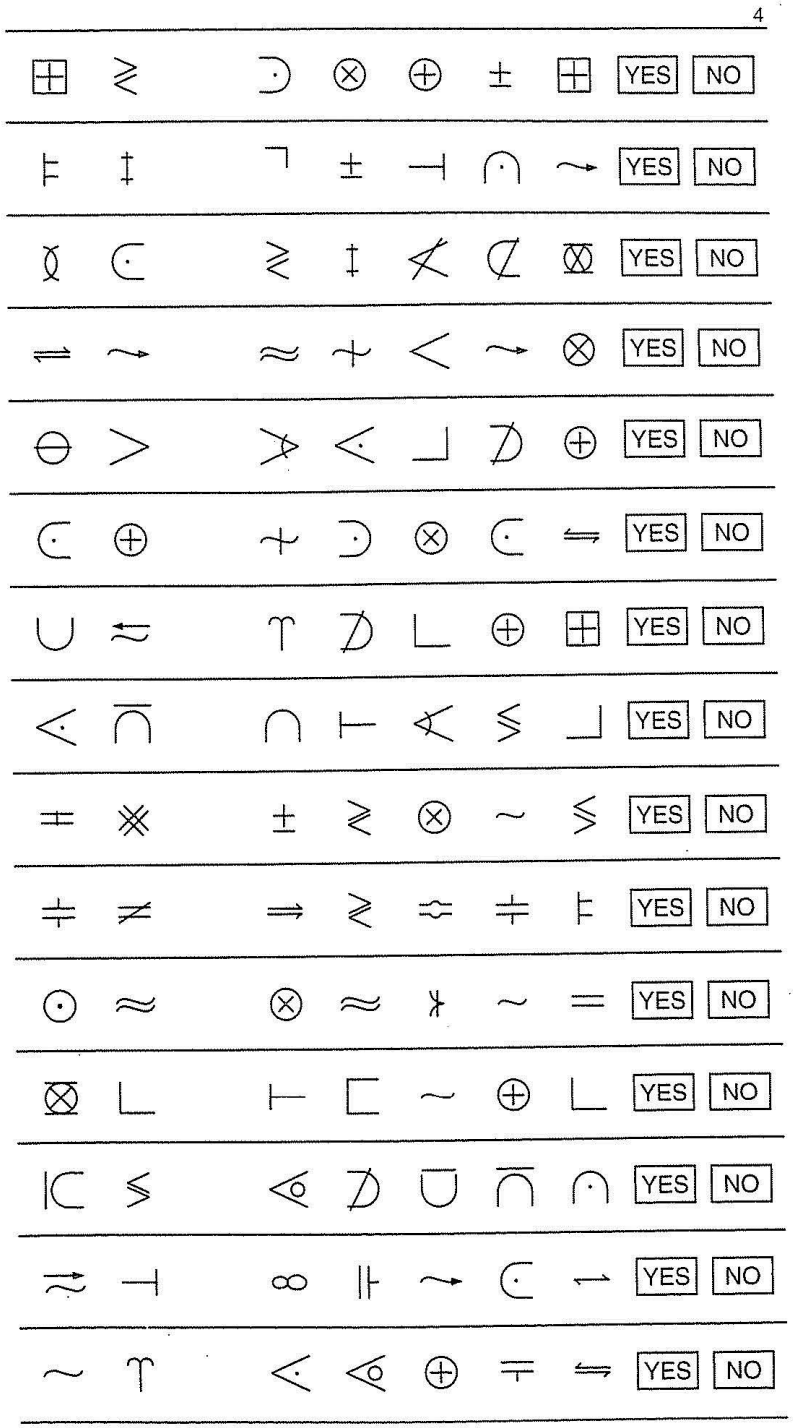
YES NO
YES NO
YES NO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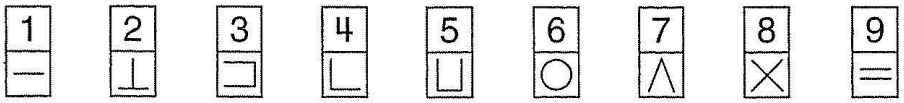
YES NO

Digit Symbol—Coding



Sample Items

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6	5	9	4	8	3	7	2	6	1	5	4	6	3	7	9	2	8	1	7

9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

2	7	3	6	5	1	9	8	4	5	7	3	1	4	8	7	9	1	4	5

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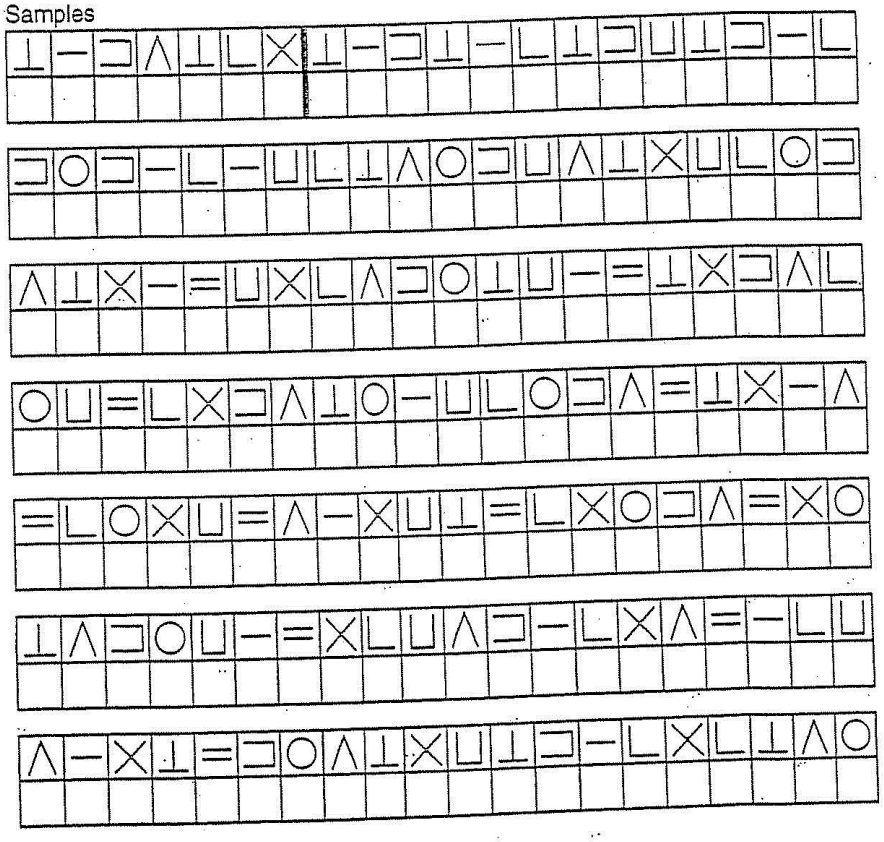
Symbol Copy

Samples



DTI preprocessing in FSL

To begin FSL:

--type in terminal: "module load fsl"

–cd to Ss folder

–Ensure correct bval and bvec files are in the Ss folder

fslsplit *.nii

–This gives you the vol000* files. Split files into all directions

fslmaths vol0000.nii.gz -add vol0021.nii.gz sumb0

–Sums up all of the B0 images (if more than one b0 image) and names it sumb0 image

fslmaths sumb0 -div 2 avgb0

–Gets the average B0 Image

rm vol0000.nii.gz

–Remove the 1st volume (B0 image)

fslmerge -a dwi_avgb0 avgb0.nii.gz vol00*

–Replaces 1st B0 image with the Avg B0 Image calculated above

/usr/global/fsl/071513/fsl/bin/eddy_correct dwi_avgb0.nii.gz data 0

–Runs eddy current correction

/usr/global/fsl/071513/fsl/bin/bet data data_brain -f 0.2 -g 0 -m

–Runs brain extraction – separate skull and other tissues from brain

- Input
- Output
- -f (fractional intensity threshold (0->1); default=0.5; smaller values give larger brain outline estimates) **– I used .2**
- -g (vertical gradient in fractional intensity threshold (-1->1); default=0; positive values give larger brain outline at bottom, smaller at top **– I used the default of 0**
- -m (generate binary brain mask)

/usr/global/fsl/071513/fsl/bin/dtifit --data=data.nii.gz --out=dti --mask=data_brain_mask.nii.gz --bvecs=DTI20dir3mm.bvec --bvals=DTI20dir3mm.bval

–Outputs AD, FA, MD, etc.

TBSS begins here!

Create FA images from your diffusion study data

-This is really done in the previous step during preprocessing
Go here for details of each step: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide
Go to DTI folder Type: “mkdir LAB_DTI_mytbss”
Create “mytbss” for older and for younger
Copy Ss’s FA data/file into this tbss folder/directory “cp 18y404_FA.nii.gz mytbss” on ANVIL
Go into this newly created directory “ cd my tbss”
“ls” to see all FA files.. once all ni “mytbss” run the commands below, one at a time.

tbss_1_preproc - prepare your FA data in your TBSS working directory in the right format
“tbss_1_preproc *.nii.gz”

tbss_2_reg - apply nonlinear registration of all FA images into standard space

The target image used in the registrations can either be a pre-defined target, or can be automatically chosen to be the most "typical" subject in the study. In general they recommend using the `FMRIB58_FA` standard-space image as the target in TBSS. The third option is to align every FA image to every other one, identify the "most representative" one, and use this as the target image

“tbss_2_reg -T”

tbss_3_postreg - create the mean FA image and skeletonize it

-applies the nonlinear transforms found in the previous stage to all subjects to bring them into standard space
-In general we they recommend using the -S option (derive the mean FA and skeleton from the actual subjects you have)

“tbss_3_postreg -S”

tbss_4_prestats - project all subjects' FA data onto the mean FA skeleton

- Use .2 for FA threshold

stats (e.g., randomise) - feed the 4D projected FA data into GLM modelling and thresholding in order to find voxels which correlate with your model

- Various options can be used with the randomize function
- We recommend using the TFCE (Threshold-Free Cluster Enhancement) option in randomise. This is somewhat similar to cluster-based thresholding, but generally more robust and avoids the need for the arbitrary initial cluster-forming threshold. To use this on TBSS-preprocessed data, add the `--T2` option to randomise.
- Create design files and run voxelwise statistics and inferences, including cluster-based thresholding

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Institution/Company: ScribeAmerica assigned at Mount Nittany Medical Center in State College, PA
Supervisor's Name: Rachel Bautsch

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Women's Leadership Initiative (2015-2016)
Teaching Assistant for Functional Human Anatomy and Cadaver Dissection (2015-2016)
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Lead Volunteer for The Alzheimer's Association (Fall 2016)

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