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Cross-sectional analysis of cortical thickness across the lifespan

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CROSS-SECTIONAL ANALYSIS OF CORTICAL THICKNESS ACROSS THE LIFESPAN (22-92) – HUMAN CONNECTOME PROJECT AND THE MAYO CLINIC STUDY OF AGING

BY

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ABSTRACT

An understanding of the normal aging process across the lifespan is important for gaining an understanding the pathophysiological changes that occur in accelerated aging diseases, such as Alzheimer's Disease Dementia (ADD) and Vascular Dementia (VaD). The present study cross-sectionally analyzed cortical thickness values derived from T1-weighted magnetic resonance images from two large cohorts: The Human Connectome Project and the Mayo Clinic Study of Aging. The 897 participants aged between 22-36 from the Human Connectome Project and the 801 participants aged between 52-92 from the Mayo Clinic Study of Aging created a robust cohort of non-demented individuals across the lifespan. We found age effects in four out of five composite regions of interest (Sensorimotor Cortex, Parietal Lobe, Frontal Lobe, and Cingulate Gyrus) in both cohorts. As expected, the age effects were more significant in older individuals from the Mayo Clinic Study of Aging. There were additionally sex effects within the Mayo Clinic Study of Aging cohort, but not in the Human Connectome Project. By showing significant sex effects within older individuals but not in younger individuals, there is likely a point beyond age 36 in which there exists a transitional period that sparks future sex-specific decline.

INTRODUCTION

In order to understand the pathophysiological changes underlying dementia, it is first necessary to understand the normal aging process. By understanding the brains of those who aging normally and do not have dementia, perhaps we can better understand the risk factors of dementia. The purpose of this study is to elucidate the cortical thickness changes that occur in non-demented individuals throughout the life span.

Throughout the field of MRI data analysis and epidemiological research as a whole, a major driver for statistical power is the creation of cohorts containing many participants. As it is often difficult to obtain large cohorts of non-demented individuals from a single institution, and, with an understanding of the importance of generating a large cohort from which generalizations can be made, the present study seeks to combine sample populations from the Human Connectome Project Phase 1a/1b and Mayo Clinic Study of Aging. The resulting cohort identifies 1,698 individuals aged between 22 and 92 years of age. The generation of a robust cohort of non-demented individuals cross the life span allows for an understanding of the cortical thinning patterns that occur throughout life. An understanding of the morphological changes in the brains on non-demented individuals provides insight into normal aging and could provide an understanding of who some transition to accelerated aging pathologies. Identifying cortical thinning changes across a clinically normal cohort throughout the lifespan could allow for future studies to elucidate the contribution from other risk factors of dementia, such as cardiovascular and metabolic disease.

Human Connectome Project and the Mayo Clinic Study of Aging

The first cohort of interest is from The Human Connectome Project (HCP), which is a consortium, led by Washington University in St. Louis, University of Minnesota, and Oxford

University. Its goal is to elucidate macroscopic human brain connectivity maps using advanced non-invasive imaging techniques. Participants of the HCP underwent a total of 4 imaging session of 1 hour intervals so that researchers could acquire data for four imaging modalities: structural MR images (T1 weighted and T2 weighted), resting-state fMRI, task-evoked fRMI, and diffusion imaging (dMRI) images (Van Essen et al., 2013). The pilot project (also known as Phase 1a/1b) for the HCP, which began in 2010, sought to enroll 1200 healthy adults with ages ranging from 22-36. Subjects were scanned at Washington University in St. Louis with a 3 Tesla (3T) scanner that was specially designed to have higher temporal resolution than standard scanners of the time. One of the primary goals of the HCP is to amass a wealth of unprocessed and minimally processed MRI data and to make these data freely available to investigators. The objective of releasing public data is rooted in the promotion of scientific discovery for individuals who would not normally have access to such advanced data.

The second cohort of interest is the Mayo Clinic Study of Aging (MCSA). The MCSA is an epidemiological study of the prevalence, incidence, and risk factors of Mild Cognitive Impairment (MCI) and dementia among Olmsted Country, MN residents. This study was enumerated by the Rochester Epidemiological Project (REP), which sought to establish a population-based cohort of individuals aged 70+ (Roberts et al., 2008). Olmsted County is unusually suitable for this project, as most residents seek care from two providers, either the Mayo Clinic or Olmsted Medical Center. Because Olmsted Country residents were heavily concentrated between these two providers, medical records systems could be easily linked. The REP established this linkage of medical records systems and allowed researchers to generate a comprehensive list of all residents within the county (Melton, 1996). From this comprehensive list of Olmsted County residents, Mayo Clinic researchers are able to accurately evaluate risk factors of MCI and dementia

for a community-dwelling population. The MCSA is one of the largest and oldest running studies of aging. It has enrolled around 3,000 individuals to date and much research is dedicated towards the elucidation of biomarkers of Alzheimer's disease and other dementias, in the hope of the creation of interventions to ameliorate potential symptoms before they arise. While focusing on Olmsted County, the Mayo Clinic Study of Aging minimizes sample biases, which increases the generalizability of results. Though, Olmsted County is predominantly Caucasian, meaning there is the possibility for confounding factors, arising as a result of differences in ethnic background, socioeconomic status, and education levels, to name a few, which can have profound effects in epidemiological studies (Machulda et al., 2013).

By combining cohorts from different institutions, not only does statistical power increase as a result of the increased number of participants, but researchers are able to better capture the subtleties of communities that could be lost in homogenous populations.

Background

In the period between 2012 and 2050, the Unites States is expected to undergo rapid growth within the older population (65 and above). By 2050, the number of older individuals is expected to reach 83.7 million (Ortman, Velkoff & Hogan, 2014). This dramatic increase in the older population will likely result in higher incidence and prevalence of neurodegenerative disorders. Because age is the greatest risk factor for neurodegenerative disease, it is important to not only understand the process of normal aging but also factors that could contribute to the exacerbation of aging pathology (Fjell et al., 2014).

As the proportion of older individuals increases within the United States, it is additionally expected that drivers of mortality will also change (Ortman, Velkoff & Hogan, 2014). Whereas drivers of mortality among older individuals was typically seen as most commonly due to

complications from either smoking or obesity, it is possible that this dynamic could change over time. Ongoing campaigns aimed at reducing the likelihood of younger individuals exposed to cigarettes is likely to reduce smoking as a contributor of mortality over time. Conversely, rates of obesity have steadily increased. In fact, between 1980 and 2008, incidence of obesity has doubled in adults and has tripled in children (Centers for Disease Control and Prevention, 2011). Obesity can directly increase the risk of other health conditions, including hypertension, lipid imbalances, and type II diabetes (Ogden et al., 2012). The discussion of obesity and its related health risks is relevant to neurodegenerative disease due to literature noting the linkage between cardiovascular disease and the onset of dementia in older adults (Snyder et al., 2015; Geda et al., 2010; Marchant, Reed, & Sanossian et al., 2013; Krell-Roesch et al., 2017). Troublingly, the U.S. Census Bureau has yet to address to the effect of age-related cognitive decline and its contribution to changes in mortality. The issue becomes more complicated given that some with Alzheimer's disease dementia go undiagnosed, deaths due to Alzheimer's disease dementia are under reported, and it is possible that ADD can complicate other diseases or causes of death.

Given the expected increase in the older population and increases in obesity and related cardiovascular and metabolic disease, it necessary that researchers seek an understanding of the pathological progression of cardiovascular and metabolic disease with respect to the incidence and prevalence of neurodegenerative disease. In order to do so, one must understand the progression of normal aging to provide a baseline level against which additional pathologies (such as those arising from cardiovascular or metabolic disease) could arise. However, it is first necessary to understand (i) why aging is a risk-factor for dementia in later life and (ii) what morphological brain changes that occur within non-demented individuals.

In an attempt to address these issues, the present study seeks to investigate morphological changes that occur as non-demented individuals age. It does so by examining cortical thickness values in individuals aged between 22 and 92 years of age. Because measures of brain atrophy – for which cortical thickness is a measure – are strongly correlated to the severity of cognitive impairment, and because the rate of brain atrophy is correlated with rates of cognitive decline, the rate of brain atrophy is correlated with the rate of cognitive decline (Jack et al., 1992; Fox, Scahill, Crum, and Rossor, 1999; Jack et al., 2010). By cross-sectionally investigating cortical thickness across the lifespan in a clinically normal, non-demented population, the present study provides an understanding of cognitive decline that is attributable to the normal aging process.

Normal Aging

Aging is associated with significant morphological- and functional-related brain changes, which can result in dementia. These changes are reflected in observations of age-related decline in cognitively demanding tasks, such as declines in mental speed (Salthouse, 1996), executive functioning (Rabbitt et al., 2001), and episodic memory (Buckner, 2004). Normal aging is defined as cognitive decline that is attributable to one's age and level of formal education, as cognitive decline is expected in all individuals (Peterson et al., 1992).

Dementia

Dementia is a progressive neurodegenerative disease in which an individual is experiencing a level of cognitive decline that is worse than expected. As such, a diagnosis of dementia arises when individuals age more quickly than others of their same age and level of formal education (Jack et al., 1992).

Alzheimer's disease dementia (ADD) is the most common cause of dementia and the sixth most common cause of death among older individuals (Alzheimer's Disease Fact Sheet, 2017).

The pathology of ADD has been classically characterized with the appearance of (i) extracellular depositions of amyloid-ß (plaques), (ii) the intracellular accumulation of the microtubule associated protein, tau (tangles), and (iii) global atrophy of brain tissue (Jack et al., 2011). Ongoing research has identified a number of other pathological changes that occur within individuals with ADD, such as the appearance of alpha-synuclein, abnormalities of TDP-43, increased free radical production due to dysfunctional mitochondria, and increases in pro-inflammatory cytokines (Majbour et al., 2017; Niblock et al., 2016; Angelova & Abramov. 2017; Prasad, 2016; Regen, Hellmann-Regen, Costantini, & Reale. 2017). Taken together, these pathological changes emphasize the role of the neuroinflammatory response, glucose metabolism, as well as energy processing more generally (Kanvah and Schuster, 2005).

It is currently believed that around 5 million Americans have ADD (Alzheimer's Disease Fact Sheet, 2017). This number is expected to rise dramatically given the increases population of older individuals coupled with increased levels of obesity and related cardiovascular disease. Estimates predict that by 2050, prevalence of AD will increase to 1 in 85 individuals (Rocca *et al.,* 2011). Additionally, there is a higher frequency of ADD dementia among females compared to males (Mielke, Vemuri, & Rocca 2014).

Vascular dementia (VaD) is the second most common cause of dementia among older individuals. Symptoms between AD and VaD are similar, and it is often difficult to differentiate between the two without MRI analysis. VaD is the result of vascular disease within the brain. As individuals age, cholesterol and other substances accumulate in blood vessel walls, which results in the thickening and hardening of these walls. In turn, blood flow is either reduced or stopped entirely. The complete stop of blood flow throughout certain parts of the brain (ischemia) results in an infarction, or necrosis of tissue due to hypoxia (Thal., Grinberg, & Attems, 2012). These

infarctions can vary in seriousness depending on the amount of time areas of the brain are without the necessary oxygen. Current understanding of VaD posits that the cumulative necrosis as a result of many silent cerebral infarctions (silent strokes) accounts for the cognitive deficits seen in older individuals suspected of having VaD (Mayo Clinic, 2014).

Importance of imaging data in dementia research

As it is often difficult to determine whether an individual has dementia through neurological exams, measures of cognitive performance, and medical history alone, it is necessary to investigate neural tissue in order to determine if there exist clues of accelerated aging pathologies. Diagnostic radiologists and researchers studying dementia rely on magnetic resonance imaging (MRI) to non-invasively visualize brain areas related to dementia.

Structural MRI provides both qualitative and quantitative representation of gray and white matter structures. Gray matter can be thought of as areas of the brain in which there is an abundance of neuronal cell bodies or glial cells. In contrast, white matter areas are primarily composed of sections of myelinated axons. Depending on the type of neural tissue researchers are interested in, it is possible to adjust sequences of the scanner to maximize the visualization capabilities. Changing the sequence parameters of repetition time (TR) and echo time (TE) can be used to emphasize differences between gray and white matter within images. The two types of images derived from structural MRI scans are known as T1-weighted and T2-weighted images.

T1-weighted images are used because of their high degree of contrast between gray matter (appearing dark gray), white matter (appearing as a lighter gray), and cerebral spinal fluid, which is void of signal and appears black. T1-weighted images are produced by establishing a short retention time and a short echo time. The resulting image allows for maximal contrast between

neocortical gray matter and white matter; though, contrast between subcortical gray and white matter is reduced.

T2-weighed images are typically used when one is interested in the white matter integrity of an individual. They are the result of a long retention time and a long echo time. Resulting images show CSF as bright and brain tissue shown in gray. Gray matter is seen in a lighter gray, whereas white matter is shown in a darker gray color. Because polar solutions, such as water and CSF appear dark, they can be easily differentiated from fatty structures, such as the myelin sheath of axons.

Together, both T1- and T2-weighted images allow noninvasive measures of architectural properties such as myelin content within the cerebral cortex and cortical thickness that recapitulate with corresponding invasive measures (Glasser et al., 2016; Fischl, 2000; Glasser et al., 2014; Glasser & Van Essen, 2011).

Within the context of research, the type of scan analyzed is determined by the cohort of individuals one is seeking to study. Typically, cortical thickness data, derived by T1-weighted

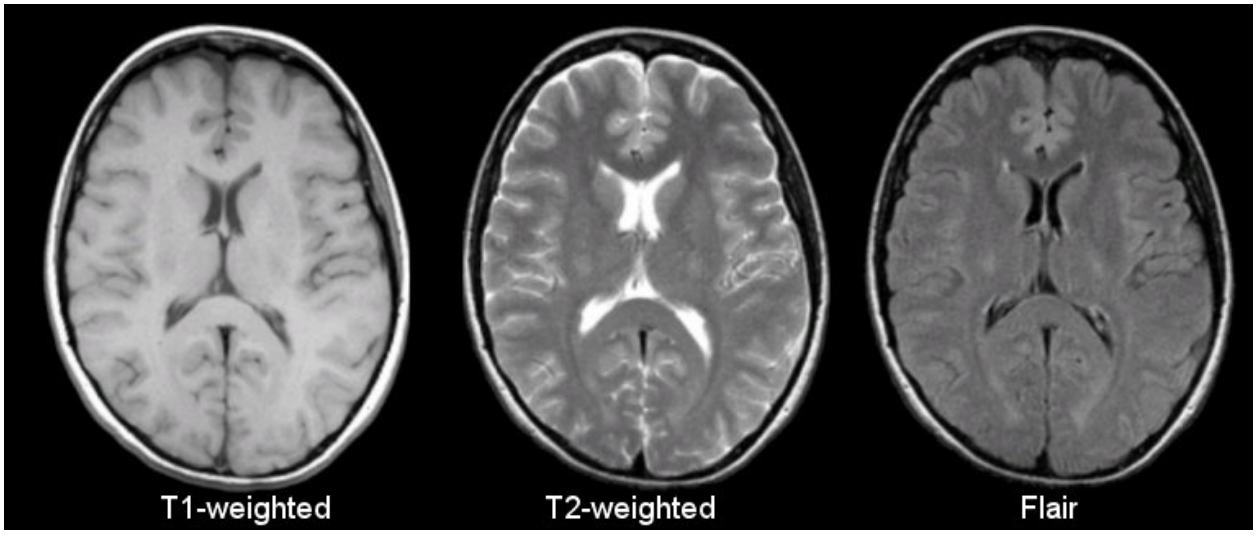

Figure 1 Comparison of diffusion weighted images: T1-weighted, T2-weighted, and Flair images (Preston, 2006)

images, are used when researchers are interested in individuals who are non-demented and are aging normally. T1-weighed images would not be suitable for accelerated pathological aging or for diseases of white matter because of the low contrast that exists in T1-weighted images between subcortical gray and white matter. If one were interested in severe dementia or white matter diseases, volume data, derived from T2-weighted images, would be preferred. These T2-weighted images would provide adequate contrast between white and gray matter structures and allow for the elucidated of the integrity of white matter tracts.

In epidemiological research, cortical thickness measurements are preferred for studies using non-demented individuals because it is the best measurement for separating individuals based on diagnoses. This means that differences in T1-weighted scans between non-demented and demented individuals is most obvious. Additionally, T1-weighted images are less likely to be confounded by total intracranial volume (TIV), unlike volumetric measurements (Schwartz, 2016). Taken together, it is clear that for investigations regarding the structural integrity of gray matter within non-demented individuals, T1-weighted images should be used. Further, the usage of cortical thickness data is best-suited for research, as it has less potential to be confounded.

Sex differences in cortical thickness and cardiovascular/metabolic diseases

There exists growing interest in understanding the morphological changes that occur in the normal aging process. Researchers are further interested in determining whether there exist sex differences in non-demented individuals. While there is established literature supporting sex differences in cognitive performance – i.e. a male advantage in spatial abilities (Kimura, 2000) and a female advantage in verbal memory tasks and speed of articulation (Sommer, Aleman, Bouma, & Kahn, 2004) – the identification of the morphological underpinnings of these advantages and their relationship to the normal aging processes remains unknown. Indeed, the

current literature is conflicting. Some studies have noted differences between the sexes (Chung et al., 2006; Cowell et al., 1994; Good et al., 2001; R. C. Gur, Gunning-Dixon, Bilker, & Gur, 2002; Murphy, DeCarli, Mclntosh, & al, 1996; Pruessner, Collins, Pruessner, & Evans, 2001; Raz, Rodrigue, Head, Kennedy, & Acker, 2004; Riello et al., 2005; Scahill et al., 2003; Sowell et al., 2007); (Arani et al., 2015; Gong et al., 2009; Hazlett et al., 2010; Jiang et al., 2014; Liu et al., 2011; Nunnemann et al., 2009; Sundermann et al., 2016); while others have not (Fjell et al., 2012; Greenberg et al., 2008; Lemaitre et al., 2005; Salat et al., 2004).

Additionally, there are also established differences in cardiovascular and metabolic disease profiles between the sexes. Notably, it has been hypothesized that women experience a lower cardiovascular risk than men (Mosca et al., 2004). This lower cardiovascular risk culminates the effect of common disorders, such as obesity, type II diabetes, and hypertension. Though, it is unknown how these differences effect the potential for cortical thinning.

Sample Sizes & Cohort Consolidation

Because the goal of epidemiological studies is to provide generalizable results that correspond to larger patient populations, it is paramount that cohort sizes are maximized. A common technique to maximize cohort sizes is to combine datasets between research groups and institutions. There are, however, a number of factors that could confound results to produce an unreliable data set, from which it would be inappropriate to extrapolate. In order to facilitate the combination of cohorts, it is preferred that the cohorts mirror one another in multiple categories. Of major importance are the usage of similar: statistical analyses, demarcation for ROI, image quality, segmentation procedures, and sample characteristics (Fjell et al., 2009). These factors will be discussed in greater detail later.

Objective

The purpose of this study is to investigate cortical thickness changes that occur in non-demented individuals throughout the life span. To do so, we will combine sample populations from the Human Connectome Project Phase 1a/1b and Mayo Clinic Study of Aging to create a robust cohort of 1,698 non-demented individuals aged between 26 and 92 years of age.

METHODS

Sample Populations

The Human Connectome Project Phase 1a/1b 1200 subjects project identified 970 participants. Of these participants, 897 participants, aged between 22 and 36, completed the MRI battery, which included Diffusion Imaging (T1 and T2 weighted imaged), Resting-state fMRI and Task-fRMI. Participants of the Human Connectome Project were subject to a wide array of behavioral measures. These measures were conducted on both on the computer and with self-reported pen-and-paper tests. The computer tests, as part of the NIH toolbox included testing the "domains of cognition (verbal IQ, working memory, executive function, attention, language, and processing speed), emotion (negative affect, positive affect, stress and coping, and social relationships), motor function (locomotion, dexterity, strength, and endurance), and sensation (hearing, taste, touch, and smell)" (Van Essen et al., 2012). The broad behavioral tests employed

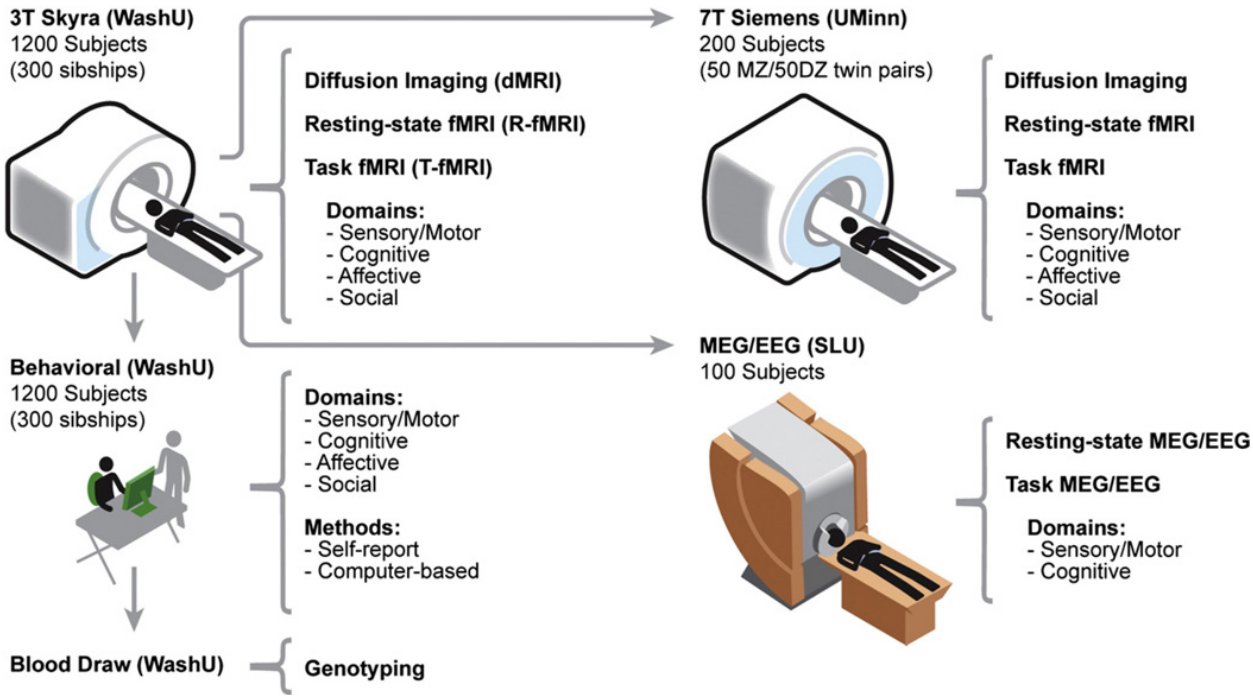

Figure 2 Schematic summary of behavioral testing procedure, and MR, MEG, and EEG scanning procedure for the Human Connectome Project (Van Essen et al., 2012).

by the Human Connectome Project was done intentionally in order to produce large amounts of data to facilitate many comparative studies in the future.

The Mayo Clinic Study of Aging identified 801 older participants, aged between 51-92 years old, for analysis. Participants in the Mayo Clinic Study of Aging underwent a neuropsychological battery of nine tests, described in previous work (Roberts, 2008), which was used to assess four cognitive domains. The domains evaluated were (i) executive functioning (Trail Making Test Part B, Wechsler Adult Intelligence Scale-R Digit Symbol), (ii) language (Boston Naming Test, category fluency), (iii) memory (Wechsler Memory Scale-R Logical Memory-II, Wechsler Memory Scale -R Visual Reproduction II, Rey Auditory Verbal Learning Test, delayed recall), and (iv) visuospatial performance (Wechsler Adult Intelligence Scale-R Picture Completion, Wechsler Adult Intelligence Scale-R Block Design).

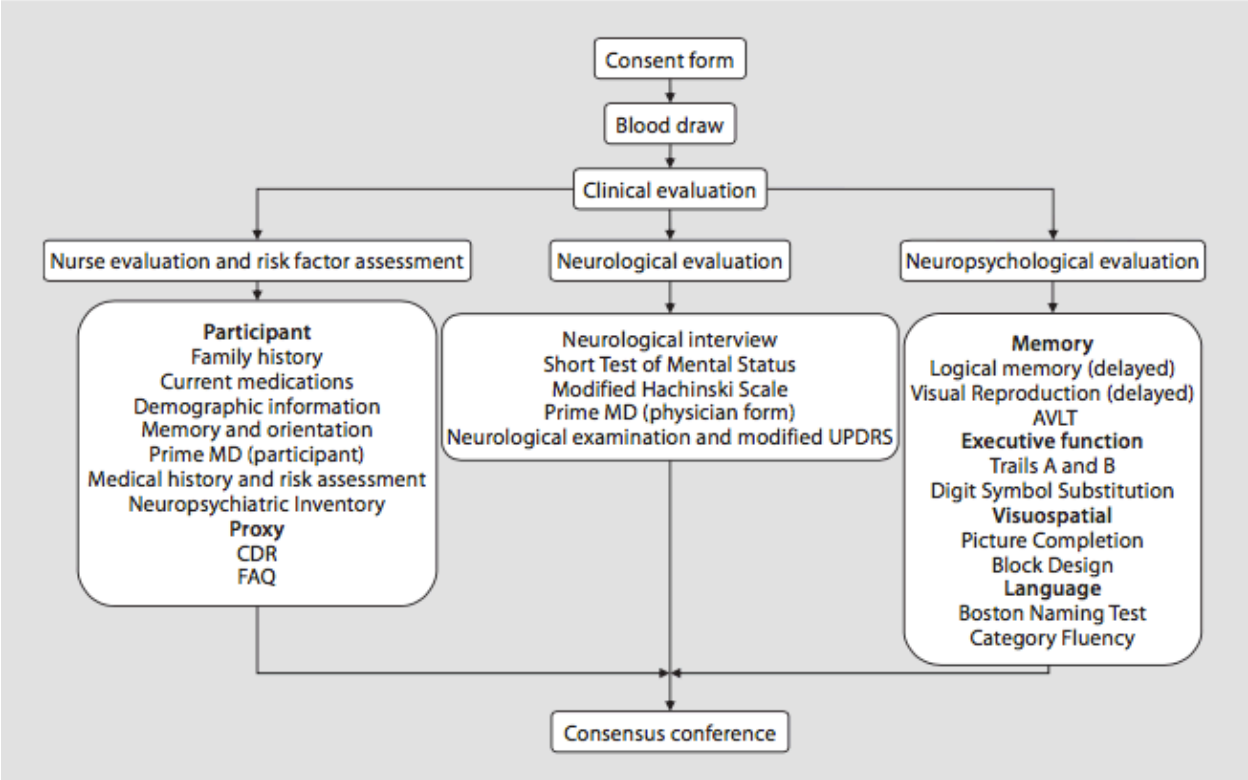

Figure 3 Flow chart of the protocol of the Mayo Clinic Study of Aging, from initial blood draws and clinical evaluations to neuropsychological battery (Roberts et al., 2008)

Sample Characteristics

Table 1 Demographic characteristics of Human Connectome Project and Mayo Clinic Study of Aging cohorts, as well as cognitive evaluations

	Female N=885			Male N=813		
	Age	N	MMSE	Age	N	MMSE
Human Connectome Project N=897	22-25	73	28.88 ± 1.09	22-25	111	28.81 ± 1.18
	26-30	222	29.10 ± 0.93	26-30	169	29.00 ± 1.08
	31-35	205	29.00 ± 1.00	31-35	111	29.06 ± 0.99
	36+	3	29.00 ± 1.00	36+	3	28.50 ± 1.66
Mayo Clinic Study of Aging N=801	50-59	34	28.82 ± 0.90	50-59	24	28.71 ± 0.91
	60-69	72	28.47 ± 1.09	60-69	105	28.54 ± 0.85
	70-79	200	28.54 ± 1.02	70-79	194	28.33 ± 1.33
	80+	76	28.40 ± 1.13	80+	96	27.97 ± 1.40

Table 1 Legend. Mini-Mental State Examination (MMSE) scores are displayed as mean ± standard deviation. MMSE scored between 0-30 with higher scores denoting a lower degree of impairment (Folstein. Folstein, & McHugh, 1975).

The characteristics of all participants are shown in Table 1. The 897 participants from the Human Connectome Project and the 801 participants of the Mayo Clinic Study of Aging were combined to create a cohort of 1,698 individuals aged between 22-92 years old. Of the 1,698 individuals, 813 (48%) were male. As such, the proportions of men and women were well balanced within the combined cohort. Because the Human Connectome Project did not account for education level within pre-screening, it is unknown whether the two cohorts vary in level of education. MMSE scores, reported as mean score plus or minus the standard deviation of each age range, indicate no significant differences in level of impairment between any age range or between the sexes. Despite similar levels of cognitive performance, it is clear that there exist discrepancies in the proportion of individuals within each age range. Potential ramifications of these cohort effects will be discussed in a later section.

MR Acquisition & Cortical Thickness Measurement

For the Human Connectome Project, T1-weighted MRI (MP-RAGE) scans were performed on Skyra 3T scanners manufactured by Siemens with the following specifications: repetition time = 2400 ms, echo time (TE) = 2.14 ms, and inversion time (TI) = 1000 ms; voxel dimensions were 0.7 mm isotropic. The HCP calculated cortical thickness using the minimal preprocessing pipeline from FreeSurfer, which encapsulates *PreFreeSurfer, FreeSurfer,* and *PostFreeSurfer*.

For the Mayo Clinic Study of Aging cohort, T1-weighted MRI (MP-RAGE) scans were performed on 3T scanners (models Discovery MR750, Signa Excite, Signa HDx, Signa HDxt) manufactured by General Electric (GE) with the following specifications: repetition time was ≈2300 ms, echo time (TE) ≈ 3 ms, and inversion time (TI) = 900 ms; voxel dimensions were ≈ 1.20 × 1.015 × 1.015 mm. Cortical thickness values were computed using the DiReCT algorithm (Das & Sandhitsu, 2009) in combination with tissue segmentations by SPM12 (Ashburner, 2005).

Regions of Interest (ROI)

For both cohorts, seven composite anatomically defined regions of interests were generated by computing average thicknesses derived from the greater dataset. The medial temporal lobe was excluded from subsequent analyses, as this region was highly correlated with intracranial volume due to the sulcal folding of subcortical structures such as the hippocampus. To minimize the number of comparisons, averages of the remaining six ROI (temporal lobe, cingulate gyrus, parietal lobe, frontal lobe, occipital lobe, and sensorimotor cortex) were calculated and subsequently analyzed.

Statistical Analyses

All analyses were performed using MATLAB (MathWorks Inc., Natick, MA). Scatter plots

of cortical thickness data for six anatomically defined regions of interest were created versus age, dichotomized by sex. Generalized linear regression models were run to test the relationship between age and cortical thickness dichotomized by sex and by region of interest. Analysis of Covariance (ANCOVA) and Analysis of Variance (ANOVA) were subsequently performed to compare the cortical thinning patterns between men and women for the combined HCP + MCSA cohort.

RESULTS

Sample Characteristics

The participant characteristics are shown in Table 1. The proportion of men and women were well balanced in the combined cohort. There were no significant differences in cognitive performance, according to MMSE scores between age ranges and between the sexes. Due to differences in neuropsychological testing, there existed few characteristics that were present within both studies. As such, comparison of cognitive performance was limited to the MMSE. Despite the presence of a well-balanced cohort between the sexes, dichotomization by age group showed clear discrepancies in number, the potential ramifications of which will be described elsewhere.

Linear regression results

Figures 3-12 show the cortical thinning patterns in all ROI with linear regression lines. Analysis of Covariance (ANCOVA) and Analysis of Variance (ANOVA) were performed to examine age, sex, and age x sex effects.

In the temporal lobe, there existed significant sex effects ($F=4.24$, $p<0.05$) within the Human Connectome Project cohort, with no significant age ($F=3.77$, $p=0.53$) or age x sex effects ($F=0.74$, $p=0.39$). Within the Mayo Clinic Study of Aging, analyses showed significant sex ($F=20.62$) and age ($F=138.21$) effects ($p<0.0001$) but no significant age x sex interactions ($F=0.07$, $p=0.7933$).

Within the sensorimotor cortex, the younger cohort exhibited no significant sex effects ($F=0.43$, $p=0.51$) or age x sex effects ($F=0.06$, $p=0.80$); though, there did exist significant age effects ($F=17.58$, $p<0.0001$). Within the older cohort, there existed significant sex ($F=17.97$) and age ($F=353.89$) effects ($p<0.0001$) but no significant age x sex interactions ($F=1.83$, $p=0.18$)

Younger participants in the Human Connectome Project cohort showed no significant sex effects within the parietal lobe ($F=1.55$, $p=0.21$) or age x sex effects ($F=0.87$, $p=0.35$); while showing significant age effects ($F=6.78$, $p=0.0094$). Older participants in the Mayo Clinic Study of Aging cohort showed significant sex ($F=15.79$, $p=0.001$) and age effects ($F=60.49$, $p<0.0001$) but no significant age x sex interactions ($F=0.06$, $p=0.80$)

Within the frontal lobe, the Human Connectome Project cohort exhibited no significant sex ($F=1.89$, $p=0.17$) or age x sex effects ($F=2.04$, $p=0.15$). However, younger individuals did show significant age effects ($F=33.51$, $p<0.0001$). In the Mayo Clinic Study of Aging, older participants showed significant sex ($F=15.79$, $p=0.001$) and age effects ($F=60.49$, $p<0.0001$); while showing no significant age x sex interactions ($F=0.06$, $p=0.80$).

Finally, in the cingulate gyrus, younger individuals showed no significant sex effects ($F=0.68$, $p=0.41$) or age x sex effects ($F=0.85$, $p=0.35$); though analyses did show significant age effects ($F=5.91$, $p<0.05$). Older participants showed significant sex ($F=7.91$, $p=0.005$), and age effects ($F=87.02$, $p<0.0001$). Conversely, there did not exist significant age x sex effects ($F=0.67$, $p=0.41$).

Table 2 provides a summary of results obtained from the linear regression analyses performed within the present study. As shown, there existed significant age effects in four out of the five composite regions of interest analyzed. There existed no sex x age effects in any of the regions between the two cohorts. Age effects were present within both the younger cohort (22-36+) as well as in the older cohort (52-92). Unsurprisingly, age effects were more significant within older individuals. It is interesting to note that only the temporal lobe showed sex effects without age effects within the Human Connectome Project cohort.

Table 2 Summary of Linear Regression Analyses from both the Human Connectome Project cohort and the Mayo Clinic Study of Aging

Human Connectome Project			
ROI	Sex Effects	Age Effects	Age x Sex Effects
Temporal Lobe	yes	no	no
Sensorimotor Cortex	no	yes	no
Parietal Lobe	no	yes	no
Frontal Lobe	no	yes	no
Cingulate Gyrus	no	yes	no
Mayo Clinic Study of Aging			
ROI	Sex Effects	Age Effects	Age x Sex Effects
Temporal Lobe	yes	yes	no
Sensorimotor Cortex	yes	yes	no
Parietal Lobe	yes	yes	no
Frontal Lobe	yes	yes	no
Cingulate Gyrus	yes	yes	no

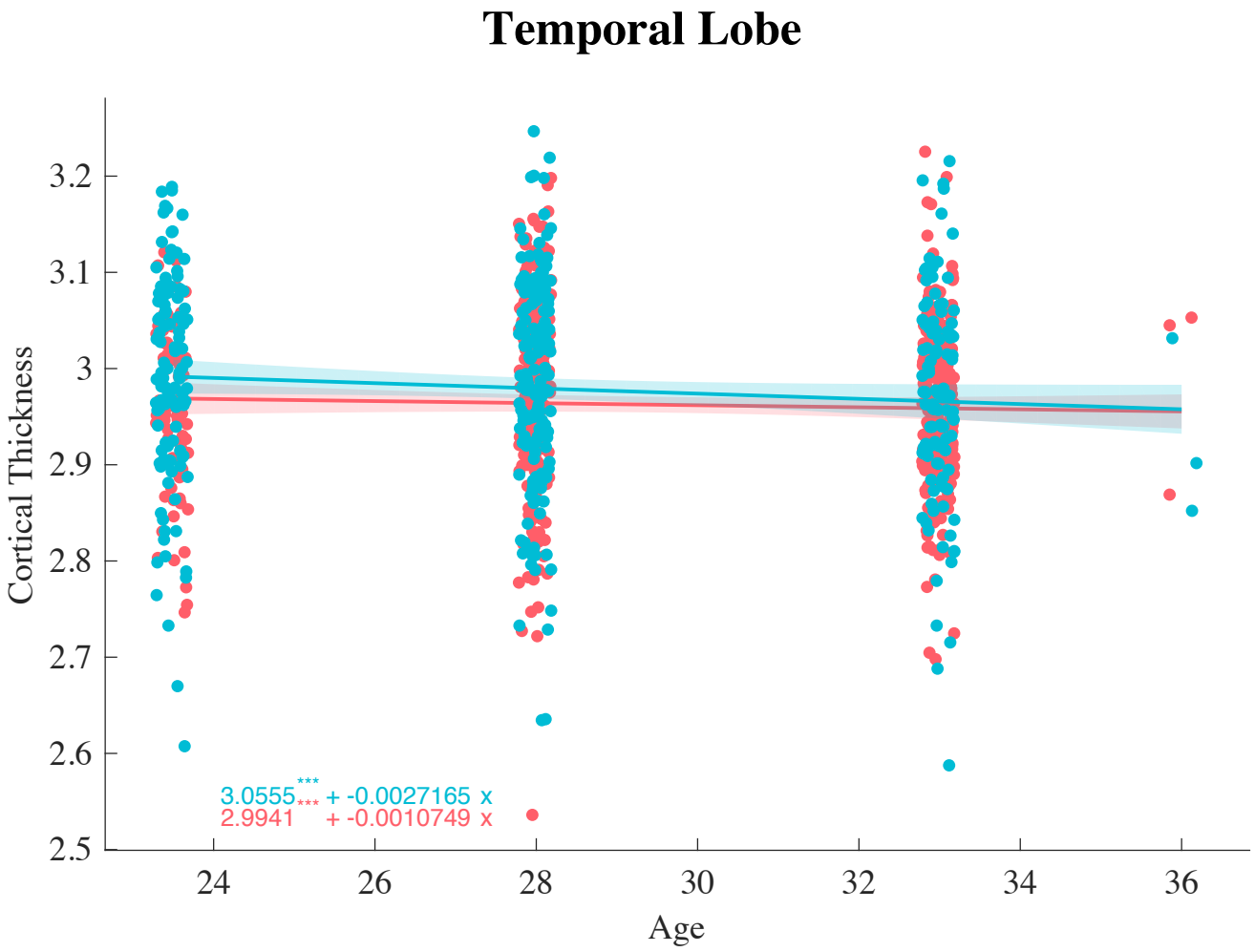

Figure 4 Temporal Lobe cortical thinning patterns for individuals aged 22-36+ from the Human Connectome Project cohort of 897 healthy young participants. Thickness values derived from 3T T1-weighted structural MR images with processing by FreeSurfer. Analysis of Covariance (ANCOVA) showed no significant delineations between male and female cortical thinning patterns. Analysis of Variance (ANOVA) showed significant sex effects ($F=4.24$, $p<0.05$); while there existed no significant age ($F=3.77$, $p=0.53$) or age x sex effects ($F=0.74$, $p=0.39$).

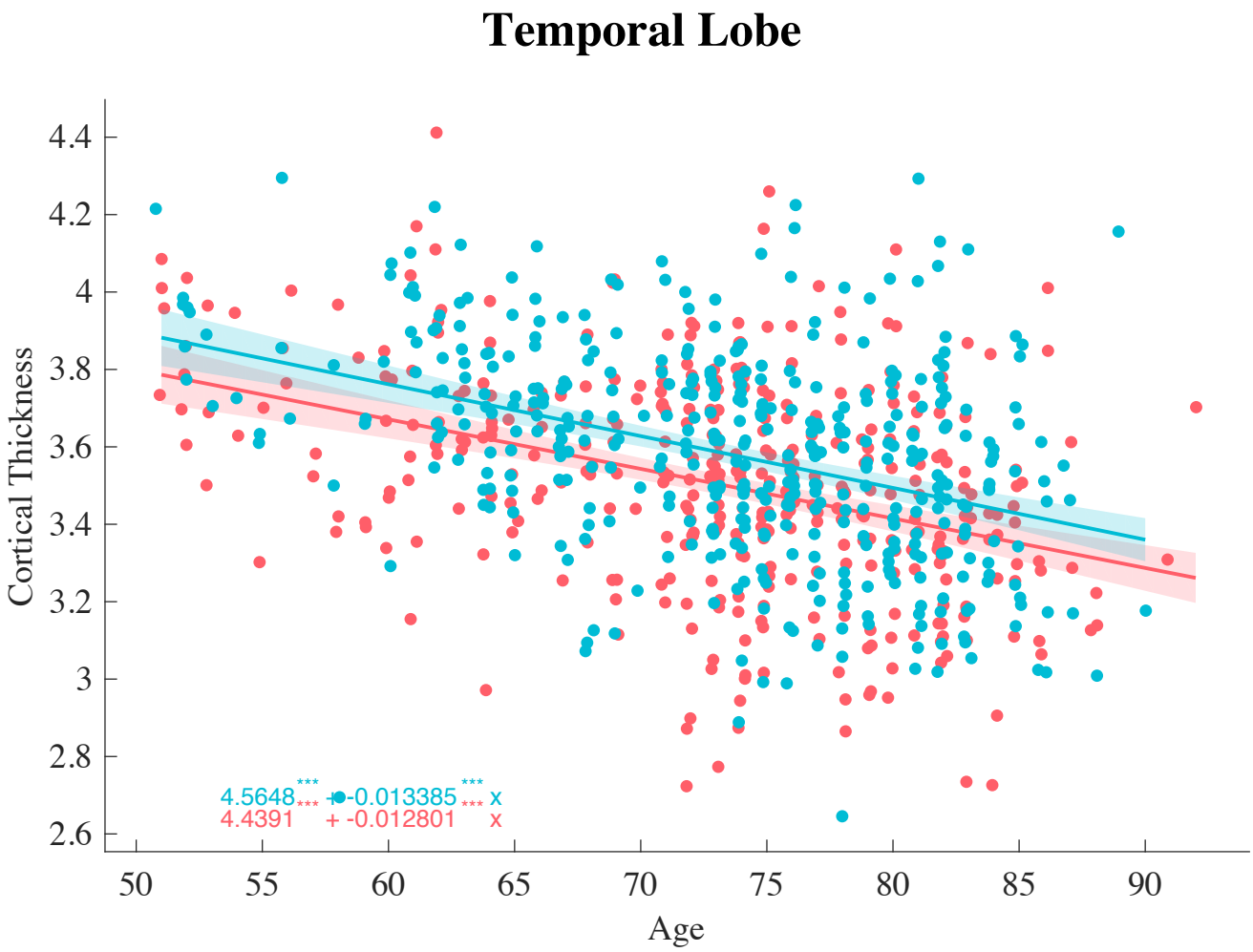

Figure 5 Temporal Lobe cortical thinning patterns for individuals aged 50-92 from the Mayo Clinic Study of Aging cohort of 801 individuals. Thickness values derived from 3T T1-weighted structural MR images with processing by SPM12+DiRect. Analysis of Covariance (ANCOVA) showed no significant delineations between male and female cortical thinning patterns. Analysis of Variance (ANOVA) showed significant sex ($F=20.62$) and age ($F=138.21$) effects ($p<0.0001$); while no significant age x sex effects were present ($F=0.07$, $p=0.7933$).

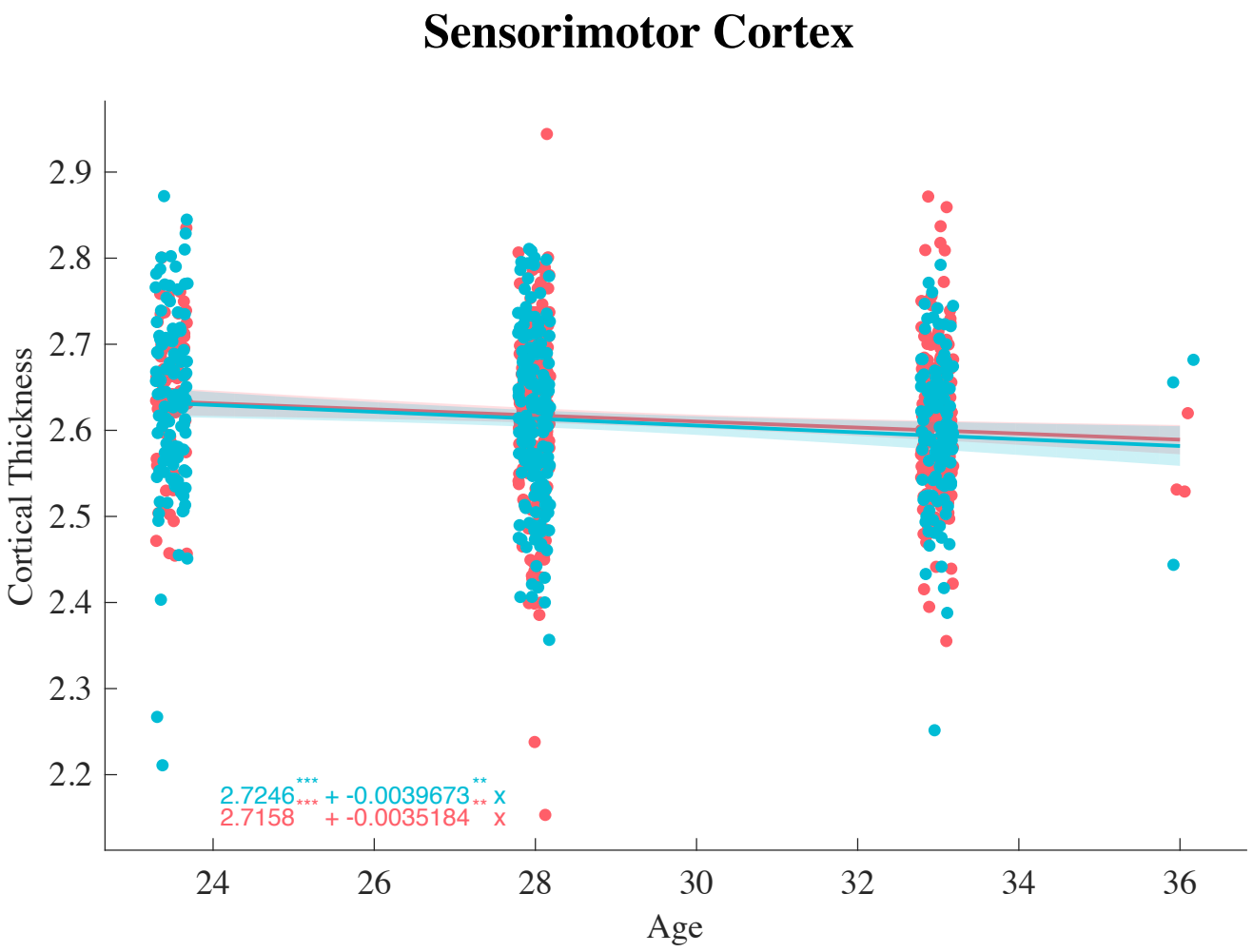

Figure 6 Sensorimotor Cortex cortical thinning patterns for individuals aged 22-36+ from the Human Connectome Project cohort of 897 healthy young participants. Thickness values derived from 3T T1-weighted structural MR images with processing by FreeSurfer. Analysis of Covariance (ANCOVA) showed no significant differences in cortical thinning patterns between the sexes. Analysis of Variance (ANOVA) showed no significant sex ($F=0.43$, $p=0.51$) or age x sex effects ($F=0.06$, $p=0.80$); though there did exist significant age effects ($F=17.58$, $p<0.0001$).

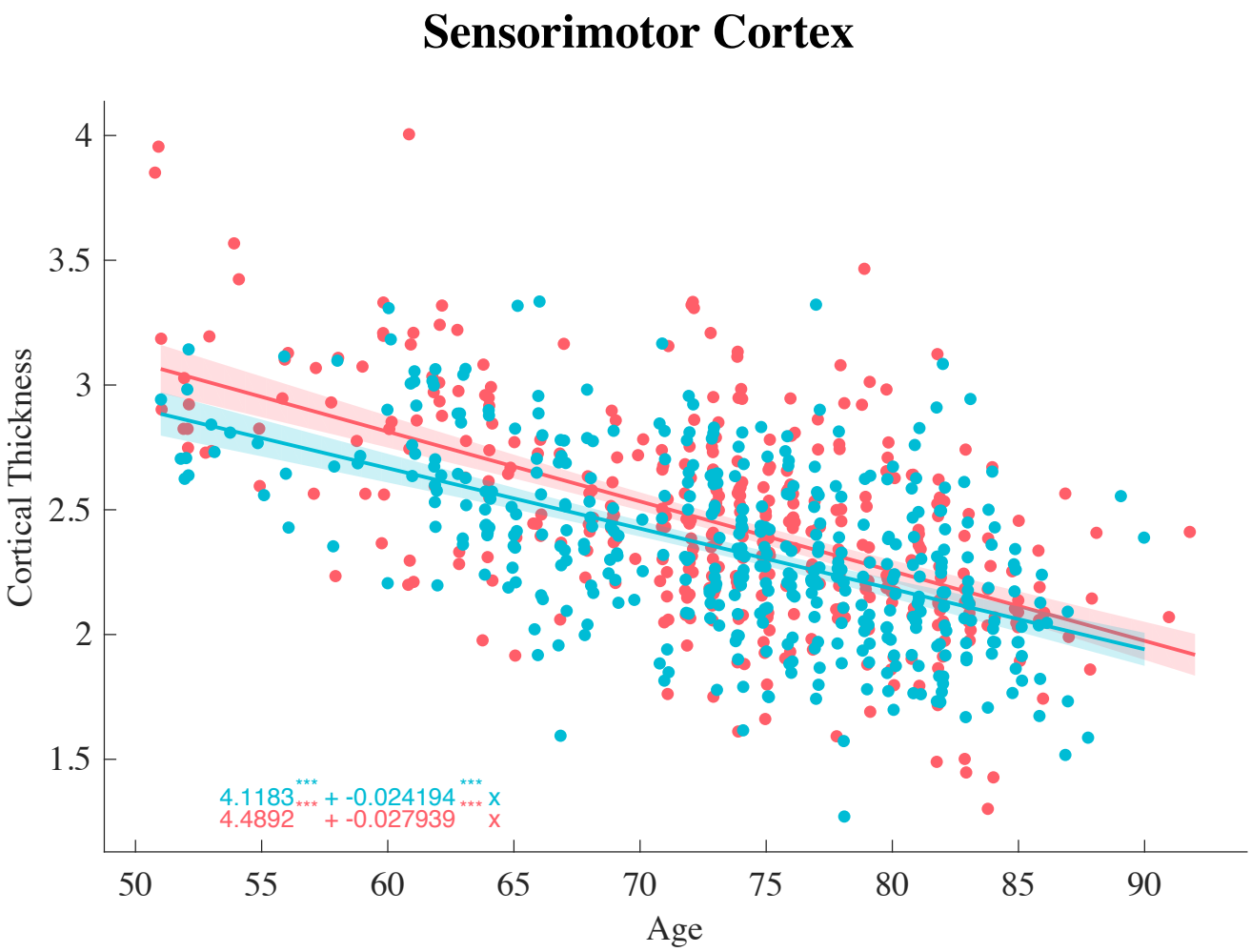

Figure 7 Sensorimotor Cortex cortical thinning patterns for individuals aged 50-92 from the Mayo Clinic Study of Aging cohort of 802 individuals. Thickness values derived from 3T T1-weighted structural MR images with processing by SPM12+DiRect. ANCOVA showed no significant differences in cortical thinning patterns between the sexes. ANOVA showed significant sex ($F=17.97$) and age ($F=353.89$) effects ($p<0.0001$) but no significant age x sex effects ($F=1.83$, $p=0.18$).

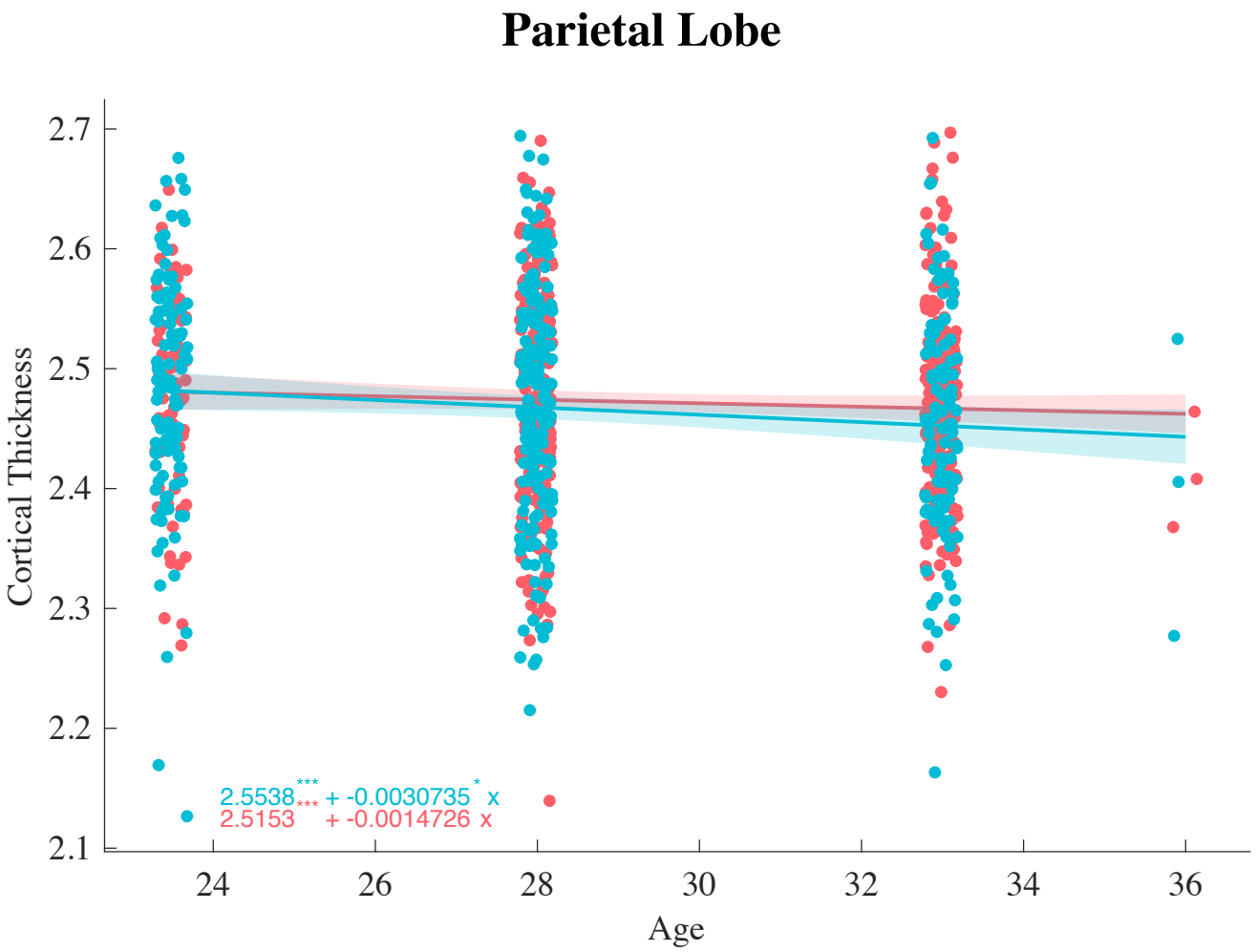

Figure 3 Parietal Lobe cortical thinning patterns for individuals aged 22-36+ from the Human Connectome Project cohort of 897 healthy young participants. Thickness values derived from 3T T1-weighted structural MR images with processing by FreeSurfer. ANCOVA showed no significant differences in cortical thinning patterns between the sexes. Analysis of Variance (ANOVA) showed no significant sex effects (F=1.55, p=0.21) or age x sex effects (F=0.87, p=0.35); though, there did exist significant age effects (F=6.78, p=0.0094)

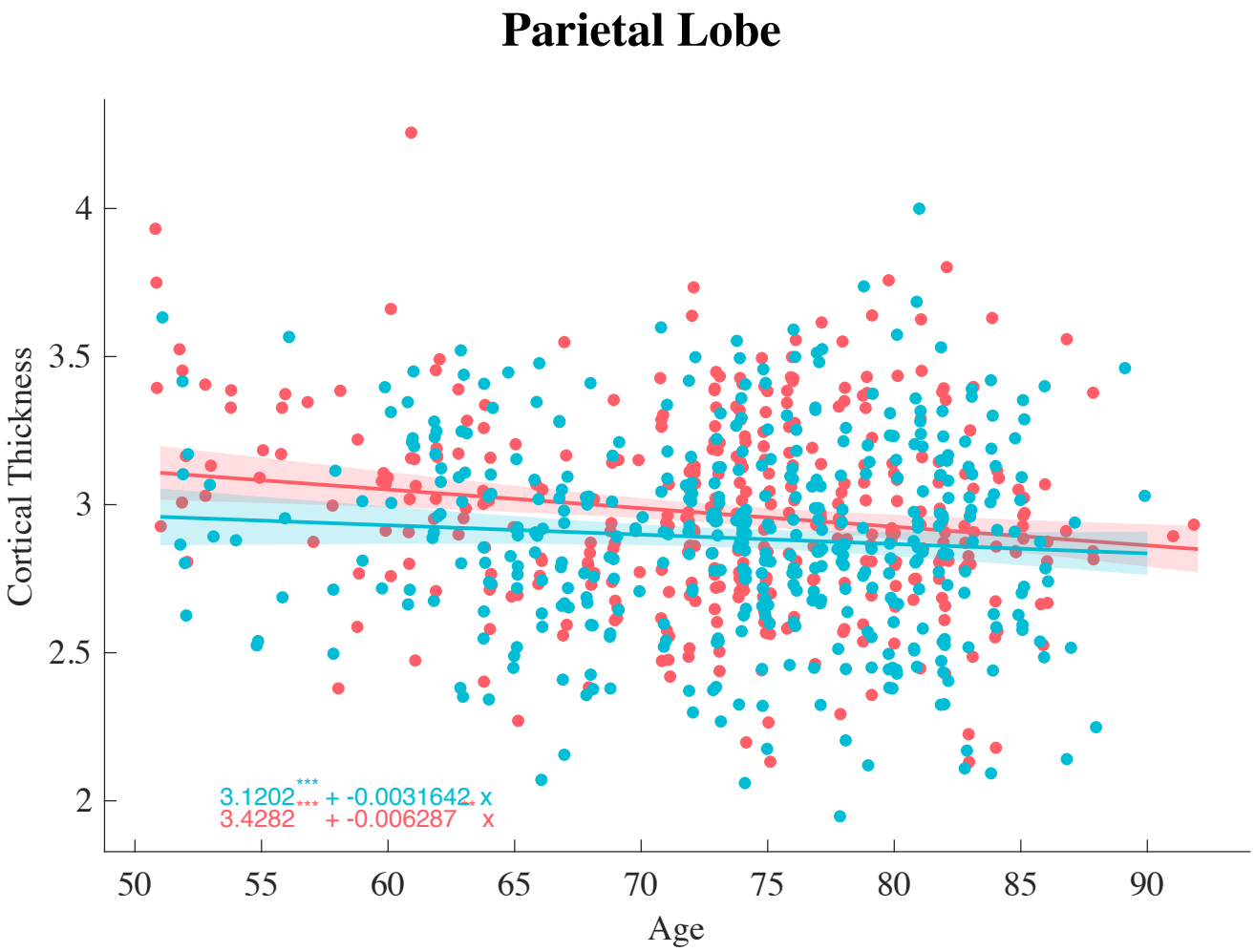

Figure 4 Parietal Lobe cortical thinning patterns for individuals aged 50-92 from the Mayo Clinic Study of Aging cohort of 802 individuals. Thickness values derived from 3T T1-weighted structural MR images with processing by SPM12+DiRect. ANCOVA showed no significant differences in cortical thinning patterns between the sexes. Analysis of Variance (ANOVA) showed significant sex ($F=15.79$, $p=0.001$) and age effects ($F=60.49$, $p<0.0001$); while there existed no significant age x sex effects ($F=0.06$, $p=0.80$).

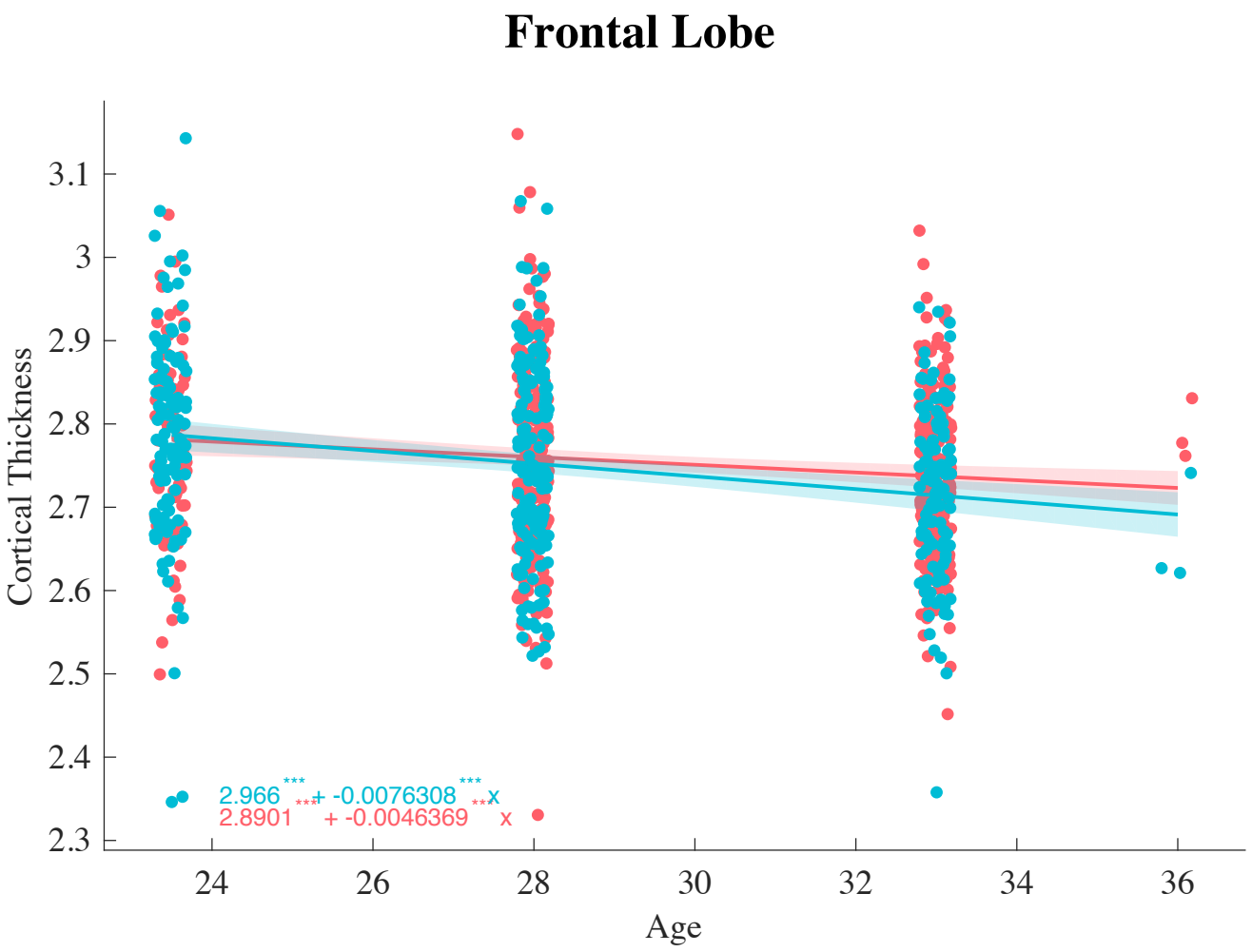

Figure 10 Frontal Lobe cortical thinning patterns for individuals aged 22-36+ from the Human Connectome Project cohort of 897 healthy young participants. Thickness values derived from 3T T1-weighted structural MR images with processing by FreeSurfer. ANCOVA showed no significant differences in cortical thinning patterns between the sexes. ANOVA showed no significant sex ($F=1.89$, $p=0.17$) or age x sex effects ($F=2.04$, $p=0.15$), but there did exist significant age effects ($F=33.51$, $p<0.0001$).

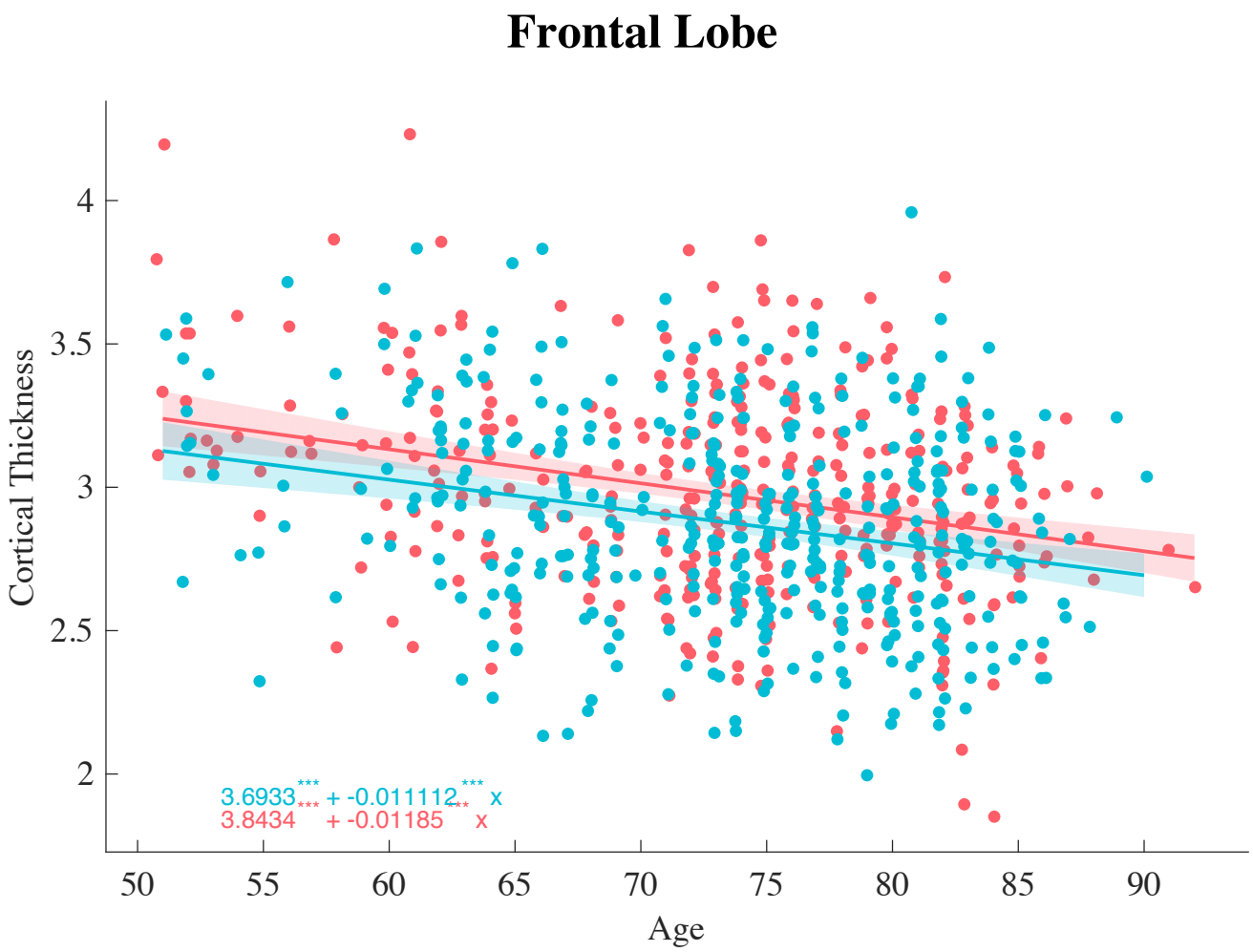

Figure 5 Frontal Lobe cortical thinning patterns for individuals aged 50-92 from the Mayo Clinic Study of Aging cohort of 802 individuals. Thickness values derived from 3T T1-weighted structural MR images with processing by SPM12+DiRect. ANCOVA showed no significant differences in cortical thinning patterns between the sexes. ANOVA showed significant sex ($F=15.79$, $p=0.001$) and age effects ($F=60.49$, $p<0.0001$); while showing no significant age x sex effects ($F=0.06$, $p=0.80$).

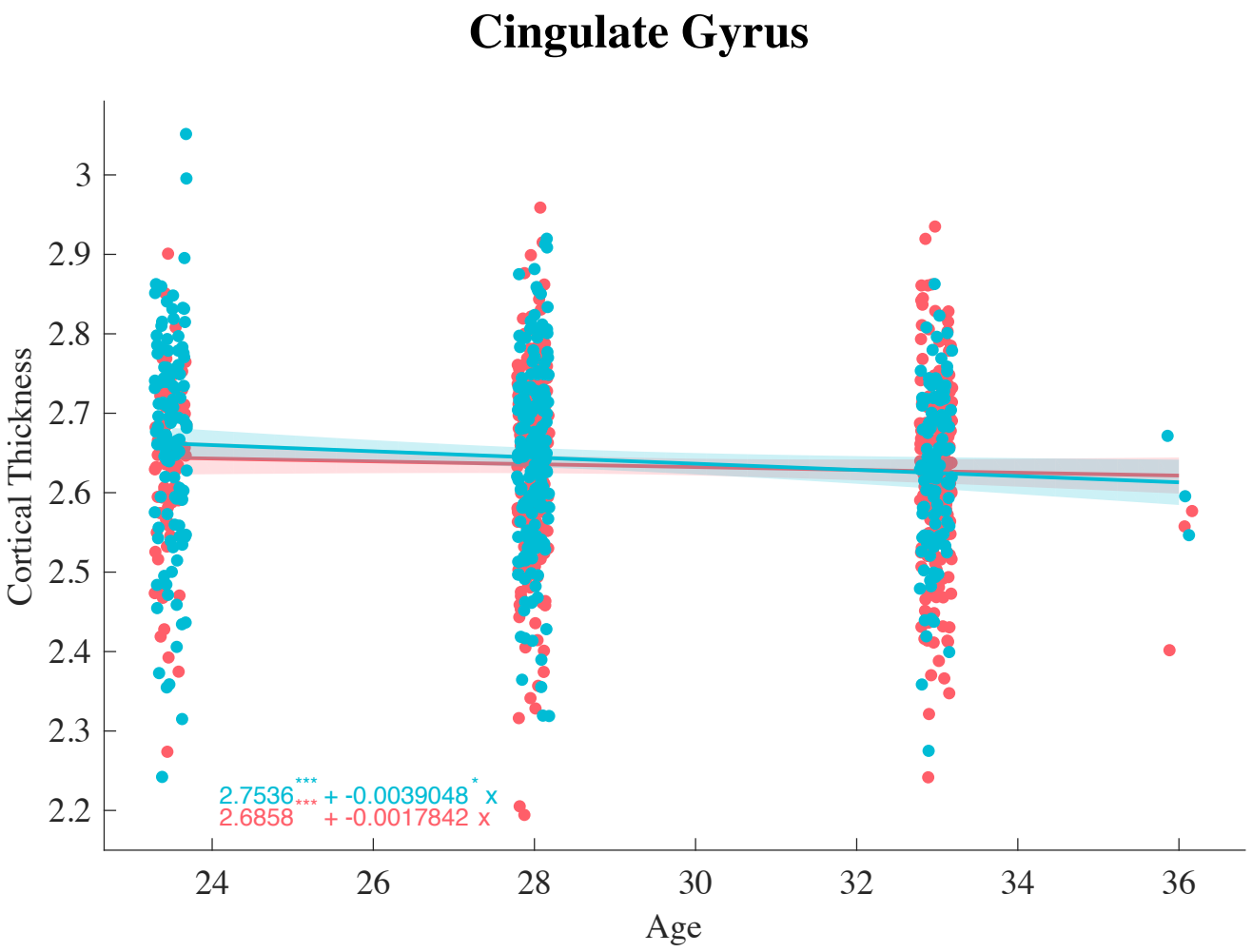

Figure 12 Frontal Lobe cortical thinning patterns for individuals aged 22-36+ from the Human Connectome Project cohort of 897 healthy young participants. Thickness values derived from 3T T1-weighted structural MR images with processing by FreeSurfer. ANCOVA showed no significant differences in cortical thinning between the sexes. ANOVA showed no significant sex effects ($F=0.68$, $p=0.41$) or age x sex effects ($F=0.85$, $p=0.35$); while there did exist significant age effects ($F=5.91$, $p<0.05$).

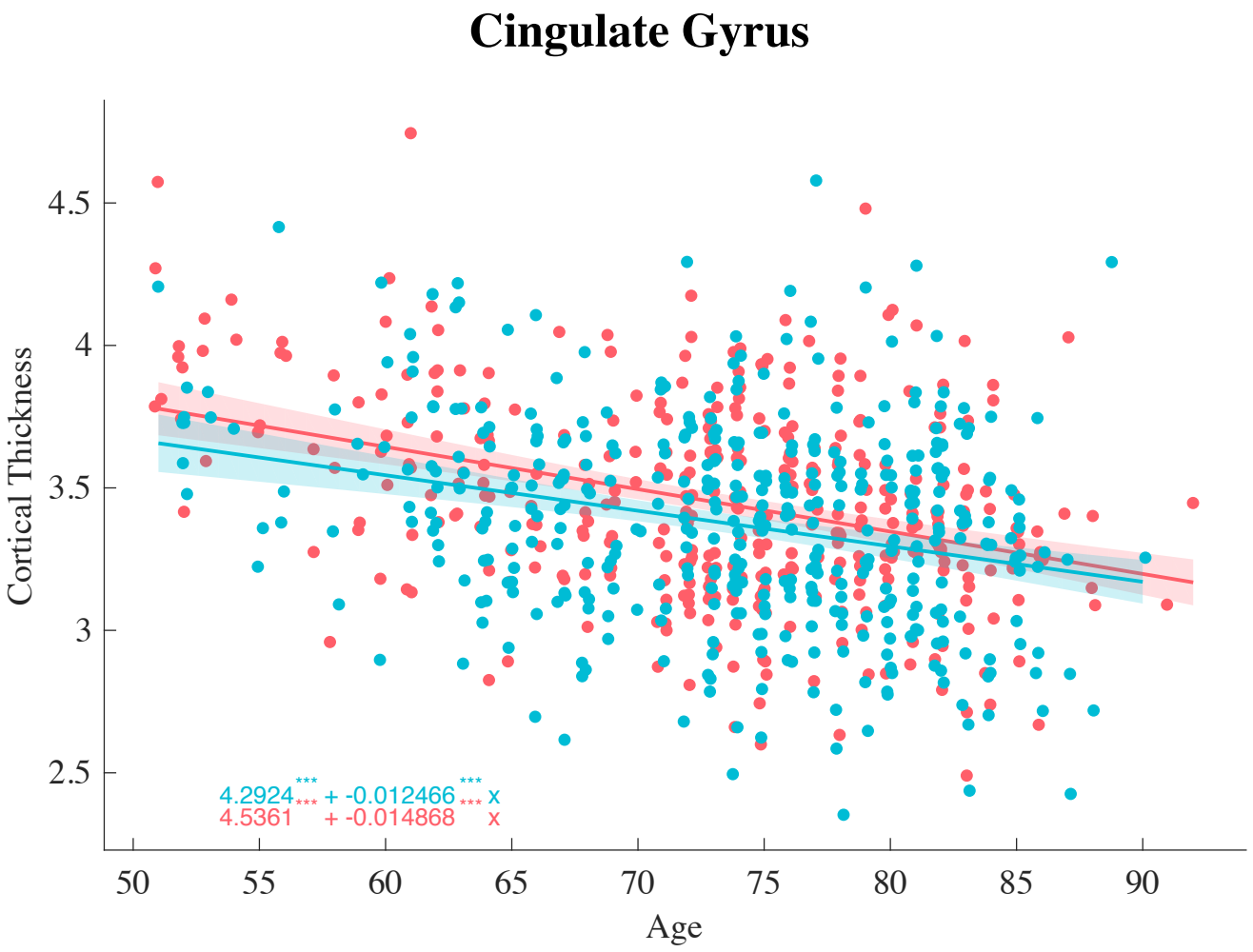

Figure 6 Cingulate Gyrus cortical thinning patterns for individuals aged 50-92 from the Mayo Clinic Study of Aging cohort of 802 individuals. Thickness values derived from 3T T1-weighted structural MR images with processing by SPM12+DiRect. ANCOVA showed no significant differences in cortical thinning patterns between the sexes. ANOVA showed significant sex ($F=7.91$, $p=0.005$) and age effects ($F=87.02$, $p<0.0001$); though there did not exist significant age x sex effects ($F=0.67$, $p=0.41$).

DISCUSSION

Underlying the need to understand the accelerated aging pathologies, such as Alzheimer's disease dementia and Vascular dementia, researchers must first understand the morphological and functional changes that occur within a normally aging brain across the lifespan. The present study sought to elucidate morphological differences between men and women across the lifespan by cross-sectionally analyzing cortical thinning patterns in a combined Human Connectome Project-Mayo Clinic Study of Aging cohort. The ultimate goal of this project was to investigate the effects of cardiovascular and metabolic disease between the sexes across the lifespan.

While the present study was unable to investigate the effect of cardiovascular disease on cortical thinning across the lifespan as a result of imperfect compatibility between the data sets, it was able to investigate sex and age effects across the lifespan. The major findings of this study were: (i) there existed significant age effects across the lifespan in four out of five composite ROIs analyzed, (ii) sex effects were only present within older individuals from the Mayo Clinic Study of Aging cohort (52-92), but not in the younger participants (except in the temporal lobe), and (iii) age effects were more significant in older individuals.

The two data sets were not perfectly compatible with one another, as the values of cortical thickness varied significantly between the two cohorts. Despite the inability to perform analyses across the lifespan about cardiovascular disease, a number of analyses were still able to be performed. While the analyses performed provided valuable insight into some of the processes underlying normal aging, it is also necessary to determine why discrepancies existed between the two cohorts, as the consolidation of cohorts will continue to be used to achieve large sample populations. Fjell and colleagues (2009) posited that the variability arising from the consolidation of multiple cohorts arose due to one of more of at least 5 factors. These factors included (i) different

statistical analyses performed, (ii) different demarcation criteria for ROI analyses, (iii) image quality, (iv) different segmentation procedures, and (v) sample characteristics. Following a comparison of the similarities and differences between the present study and the Fjell (2009) study, the five potential factors that could have contributed for some of the issues arising from the attempt to consolidate the Human Connectome Project and Mayo Clinic Study of Aging Cohorts will be explored.

Similarities and differences between present study and Fjell (2009)

There were a number of analogous elements between the Human Connectome Project and Mayo Clinic Study of Aging processing pipelines that could contribute to the combination of the two cohorts to produce a single larger cohort that spanned the lifespan. The rationale behind the combination of the two cohorts was rooted in previous success by other groups. Notably, Fjell and colleagues (2009) successfully combined six cohorts from three countries and four research centers while using scanners that varied in both manufacturer and model. The group attributed their success to the usage of a "uniform semiautomated method" of measuring values of cortical thickness using the FreeSurfer algorithm. Researchers summarized their preference for the usage of FreeSurfer as follows:

> "First, they require minimal intervention by highly trained personnel and allow processing of many brains in a reasonable time frame. Second, they are characterized by very high reliability and repeatability of measures. Third, they allow a hypothesis-free search for patterns of differences without the need to define anatomically plausible ROIs, enabling detection of differences in regions where precise anatomical definitions and placement of anatomical borders would not be feasible" (Fjell et al., 2009).

There were a number of factors which were analogous between the Fjell study and the present study. First, both studies utilized multi-center cortical thickness values derived from T1-weighted MR images from both GE and Siemens scanners. As such, scanners varied in a variety

of MR parameters, notably, voxel size, retention time, and echo time. The analysis performed by Fjell and colleagues did differ from what was done in this experiment, which could have contributed to the different results. For example, scans performed in the Fjell analysis were 1.5T scans, meaning there existed a lower contrast between white and gray matter structures with which FreeScanner could elucidate cortical thickness values. This could be compared to the 3T scanners used in both the Mayo Clinic Study of Aging and the Human Connectome Project. The usage of 3T scanners allows for both a higher signal to noise ratio, meaning 3T scans will produce a more accurate representation of underlying cortical networks than would a 1.5T scan.

Further in the Fjell study, the six cohorts analyzed had participants in each cohort which did not vary significantly. Each cohort had similar mean ages, education levels, and similar IQ/MMSE scores. Contrary to the Fjell study, the present study sought to investigate across the lifespan using two extreme age ranges: one in early adulthood and one in the "older" years.

Five potential factors of inconsistency

(i) Statistical Analyses

The present study used generalized linear models of cortical thickness values across the life span for both the Human Connectome Project and the Mayo Clinic Study of Aging. In neither case were there corrections utilized or removal of data points for any reason. By nature of the exploratory nature of this study and the vast amounts of secondary data that was available in both data sets, the present study sought to primarily look for the potential of age and sex effects across the lifespan between men and women. As such, it was paramount that statistical analyses were kept constant. It is therefore unlikely that inconsistencies in the data arose as a result of the statistical analyses used.

(ii) Difference Demarcation criteria for ROI

By nature of the study, calculated cortical thickness values were taken from the databanks of the Human Connectome Project and the Mayo Clinic Study of Aging. The Human Connectome Project identified 34 regions of interest in both the left and right hemispheres; while the Mayo Clinic Study of Aging identified 43 regions of interest in each hemisphere. These regions of the brain are known as meta-ROIs. For both samples, it was necessary to average values of meta-ROIs for the left and right hemispheres to consolidate analyses. Because calculations of cortical thickness values were determined by respective institutions, meta-ROI differed, and the raw data were not available for one of the cohorts. Because of the differences in meta-ROI, it was necessary to consolidate them into larger "consolidated ROIs." To do so required the consultation of a brain atlas to determining which region of the brain (Temporal Lobe, Sensorimotor Cortex, Parietal Lobe, Frontal Lobe, Cingulate Gyrus, and Medial Temporal Lobe) each meta-ROI belonged to. Due to the complexity of the brain and the uncertainty about how these regions of the brain interact, not every meta-ROI had an obvious corresponding consolidated ROI. Following the identification of a consolidated ROI for each meta-ROI, cortical thickness values for each of the meta-ROI were averaged to produce a mean cortical thickness value for the consolidated ROI for each participant. These individual values were then plotted and subsequently analyzed. Undoubtedly, the prescribed practice would inherently produce some level of uncertainty. Though, due to the nature of the data, this was likely the most practical and time-sensitive matter to approach the situation. While it would have been possible to collect the raw data of the Human Connectome Project and recalibrate the semi-automated procedure of FreeSurfer to produce a data set more like the Mayo Clinic data set, to do so would have required vast computing power and time. It is therefore possible that some of the inconsistencies in the data arose not only from the differential determination of meta-ROI but also the consolidation of these ROI. If we were to only have compared meta-ROI that were

present in both cohorts, the following analyses would have had large gaps within certain regions of the brain, which would have produced less meaningful analyses.

(iii) Image Quality

Ongoing research is investigating the accuracy and reliability of cortical thickness values when inherent factors differ, such as field strength, manufacturer, and pulse sequence are changed. While there remain unanswered questions, the wide adoption of high magnetic field strength scanners (3T and some 7T scanners for humans and as high as 15T for mice) has produced more reliable results. The increase in reliability from the transition from 1.5T scanners to 3T scanners is derived from the increase in signal to noise ratio. While some of the technical downfalls of the increasing magnetic field strength scanners are beyond the scope of this paper, it is worth noting that increasing magnetic field strength yields sharper images with optimal contrast between white and gray matter structures. Because the determination of cortical thickness values from T1-weighted images relies upon the contrast between gray and white matter structures, it would follow that an image constructed with a high magnetic field strength scanner would yield more accurate cortical thickness values (Schmitt, 2004). In fact, one study found that the difference between 1.5T and 3T field strength changed cortical thickness values by 0.17 mm (Han et al., 2006). Contrary to the Fjell (2009) study that successfully consolidated six cohorts using 1.5T scanners, the present study likely benefitted from the usage of 3T scanners. This upgrade in magnetic field strength likely attenuated the potential for inconsistencies between cortical thickness values. However, the effect of the difference of spatial resolution is unclear. The Human Connectome Project utilized a Siemens Skyra that was advanced for its time, due to its unusually high spatial resolution as a result of a 0.7mm isotropic voxel, which can be compared to the Mayo Clinic Study of Aging's usage of GE scanners, which had a voxel size of 1.20 × 1.015 × 1.015 mm. It is likely that the

increased temporal resolution yielded more reliable measures of cortical thickness; though the effect has not been quantified. Also of note is the fact that the scanners in each did differ in terms of manufacturer. For reasons that are not fully understood, a common confounder of studies using MRI analysis content that the manufacturer of scanner has an effect on the corresponding values used. One study found that the difference in cortical thickness as a result of the usage of Siemens and GE scanners was about 0.15 mm on average (Han et al., 2006). Because Fjell and colleagues were able to consolidate multiple cohorts while using scanners of a different manufacturer and the fact that the cortical thickness values from this study differed by more than 0.15mm, it is likely that the inconsistencies between did not arise due to the usage of different manufactured scanners. Instead, it is likely that the inconsistency arises from one or a combination of other factors.

(iv) Different segmentation procedures

As previously described, the general process by which values of cortical thickness are calculated is done by computing the difference between the gray matter and white matter pial surfaces within T1-weighted MR images. The high degree of contrast between gray and white matter tissue facilitate this computation (Fjell et al., 2009). Segmentation procedures allow for the quantification and differentiation of gray and white matter tissue. The usage of different segmentation procedures can produce cortical thickness values that can upon "imaging modality, the set-up, and the parameters chosen for data recording" (Schick, 2016). Because imaging modality, set-ups, and data parameters were largely congruous between the two data sets, there exists the possibility that data inconsistencies could have arisen from a step performed prior to segmentation, known as spatial normalization. Spatial normalization is the process by which brain volumes are scaled versus a standardized template in order for data to be compared across individuals in like terms (Crivello et al., 2002).

FreeSurfer was the program of choice employed by the Human Connectome Project. It is a surface-based segmentation procedure that normalizes data based on a Talaraich alignment, which has been previously described in great detail (Fischl et al., 2002 & Fischl et al., 2004). On the other hand, the Mayo Clinic Study of Aging used a combination of SPM12 and the DiReCT algorithm to calculate measures of cortical thickness. SPM12 (Statistical Parametric Mapping) is a voxel-based morphometry method of tissue segmentation, which "requires the images to be spatially normalized, segmented into different tissue classes, and smoothed, prior to performing statistical tests (Ashburner & Friston, 2005). The result is a tissue-segmentation map of the cortex that can be directly inputted into the algorithm that calculates cortical thickness, DiReCT. In the Mayo Clinic Study of Aging, rather than using a standardized tissue normalization structure, such as the Talaraich or Montreal Neurological Institute (MNI) atlases, it uses a customized, in-house template derived from an elderly individual and adapted to the Tailarach atlas. This modified template was used to create a common atlas that was more similar to the population of interest, older individuals (Schwartz, 2016).

Fjell and colleagues (2009) claimed that different segmentation procedures could lead to inconsistencies across the combination of multiple cohorts. However, we posit that the discrepancies between cortical thickness values from the Human Connectome Project and the Mayo Clinic Study of Aging are derived from different spatial normalization procedures, rather than different segmentation procedures. Previous studies have reported that cortical thickness values derived from FreeSurfer are within a ¼ mm in accuracy to the true histological thickness of the brain (Rosas et al., 2002). Given this finding, it is likely that FreeSurfer cortical thickness values are accurate representations of true morphology. Additionally, a recent study has found no significant differences in reliability between FreeSurfer cortical thickness values and SPM12 +

DiReCT values (Schwartz, 2016). As such, it is clear that both methods can accurately determine cortical thickness values when a common template is utilized. As such, these cortical thicknesses are accurate relative to the index from which these values are derived. If these indices differ, discrepancies within the data can arise.

Typically, differences arising from the usage of different spatial normalization procedures can be easily corrected for. For example, it is known that there exist significant differences between data derived from Talaraich and MNI atlases. Accordingly, there exist highly effective conversion techniques to reduce differences between data (Laird et al., 2010). Because the usage of non-standardized atlases is rare, there does not exist a method to convert data between atlases. Therefore, the effect of using two different Talaraich atlases cannot be quantified. What is clear though is that there do exist significant discrepancies between the data that likely did not arise due to some of the common confounders suggested by Fjell. Therefore, it is possible that the increased cortical thickness values seen in the Mayo Clinic Study of Aging cohort relative to the Human Connectome Cohort, could have arisen due to the elderly template which was utilized by the Mayo Clinic Study of Aging.

(v) Sample characteristics

Fjell and colleagues (2009) noted the potential for differences between the six samples as a potential confounder for some of their results. In that study, authors raised the possibility of confounders arising due to differences in age range between the six samples. The present study represents an extreme of that issue. Because the present study sought to understand cortical thinning across the lifespan and the fact that no cohort has encapsulated the entire lifespan, it was necessary to use two cohorts of which there was no overlap in the age range. Fjell and colleagues posited that the difference in age range between the six samples could have contributed to some of

the differences in age effects from their analyses. It would then follow that the same issue could have arisen due to the two cohorts in this study having different age ranges. Though, one of the main objectives of this study was to determine whether different age ranges differed in cortical thinning patterns; whereas the Fjell study sought to determine whether the age effect differs between a single age range, using multiple samples. As such, the present study requires differences in age range as an independent variable; while Fjell sought to hold age range constant in an attempt to understand a different question.

Additionally, a secondary objective of this study, to investigate the potential effects of cardiovascular and metabolic disease profiles to determine its effect on cortical thinning patterns, was inappropriate. Such an analysis could have only been completed if the two cohorts differed with respect to their disease profiles. As such, it is likely that cortical thickness values differed between the two samples as a result of cardiovascular and metabolic diseases, which would contribute to differential characteristics between the samples. Similar to the age range, the differences in cardiovascular metabolic disease profiles was one essential to the analyses performed by this experiment. Besides age and cardiovascular disease, there is the potential that the two cohorts differ with respect to level of education. The Mayo Clinic Study of Aging accounts for education level within their analyses following literature suggesting the importance of education levels and its effect on the phenomenon of cognitive reserve (Vemuri et al., 2011; Sundermann et al., 2016). On the other hand, the Human Connectome Project does not account for level of education. There exist many discrepancies in the data collected between the Mayo Clinic Study of Aging and the Human Connectome Project due to each having different objectives. Without the ability to correct, or even be aware of, these differences it is possible that this could limit the utility of the present analyses.

Rationale for inconsistencies

Taken together, it is unlikely that the differences in the cortical thickness values from the Human Connectome Project differed as a result of factors one, three, or five: the statistical analyses performed were constant between the data sets, both scanners were highly advanced scanners with a large magnetic field strength, and there did not exist significant differences in sample characteristics, relevant to the study. On the other hand, it is likely that some discrepancies arose from the different segmentation procedures used between the studies which resulted in slightly varied meta-ROIs. Perhaps, most importantly, the discrepancies between the two data sets could have arisen as a result of the usage of different spatial normalization techniques. While spatial normalization is an accepted procedure to create datasets that are not confounded by total intracranial volume, the usage of two different atlases, both derived from the Talaraich atlas, likely produced the difference in scaling between the data sets.

CONCLUSION

The present study sought to investigate the normal aging process by cross-sectionally analyzing cortical thinning patterns across the lifespan using two large cohorts, from the Human Connectome Project and the Mayo Clinic Study of Aging. Despite the imperfections seen in the cortical thickness values between the two cohorts, generalized linear models were constructed to investigate age and sex effects. We found age effects in four out of five composite regions of interest (Sensorimotor Cortex, Parietal Lobe, Frontal Lobe, and Cingulate Gyrus) between both cohorts. There were additionally sex effects within the Mayo Clinic Study of Aging cohort, but not in the Human Connectome Project. Age effects were more significant in older individuals than in younger individuals. Taken together, the present study could suggest a critical point after the age of 36 wherein sex begins to affect global thinning of the cortex.

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