The Longitudinal Effect of Structural Brain Measurements on Cognitive Abilities

Fatemeh Hosseininasabnajar

A Thesis

In

The Department

of

Mathematics and Statistics

Presented in Partial Fulfilment of the Requirements

for the degree of Master of Science (Mathematics) at

Concordia University

Montreal, Quebec, Canada

December, 2017

CONCORDIA UNIVERSITY

School of Graduate Studies

This is to certify that the thesis prepared

By: **Fatemeh Hosseininasabnajar**

Entitled: **The Longitudinal Effect of Structural Brain Measurements on Cognitive Abilities**

and submitted in partial fulfillment of the requirements for the degree of

Master of Science (Mathematics)

complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

Signed by the final examining committee:

_____ Chair
Dr. Arusharka Sen

_____ Examiner

_____ Examiner
Dr. Arusharka Sen

_____ Thesis Supervisor
Dr. Lisa Kakinami

_____ Thesis Co-supervisor
Dr. Yogen Chaubey

Approved by _____

Chair of Department or Graduate Program Director

_____

Dean,

Date _____

ABSTRACT

The Longitudinal Effect of Structural Brain Measurements on Cognitive Abilities

Fatemeh Hosseininasabnajar

Loss of brain tissues and cognitive abilities are natural processes of aging, and they are related to each other. These changes in cognition and brain structure are different among the cognitively normal elderly and those with Alzheimer's disease (AD). Despite the great development in the longitudinal study of decline in brain volume and cognitive abilities, previous studies are limited by their small number of data collection waves and inadequate adjustments for important factors (such as a genetic factor). These limitations diminish the power to detect changes in brain tissues and cognitive abilities over a longer period of time. In this study, firstly, we aimed to explore the longitudinal association between cognitive abilities and global and regional structural brain variables among individuals with normal cognitive status, mild cognitive impairment (MCI), and AD using mixed effects models. Secondly, we investigated the effect of education on the relationship between cognition and brain structure. Lastly, we utilized latent class growth analysis in order to study the change in cognition between different MCI sub-classes based on their functional abilities. The data in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) which contained 6 time points over three years ($n = 686$). The results showed that cognitive abilities decreased over time across different groups, and the rate of decline in cognition depended on the whole brain volume. Importantly, the effect of brain volume on the rate of decline in cognitive abilities was greater among MCI subjects who progressed to AD (pMCI) and participants with AD. Ventricle enlargement in the pMCI group also showed a significant influence on the rate of cognitive decline. Lastly, based on an assessment of functional abilities at baseline, this study demonstrated an efficient methodology to identify MCI subjects who are most at-risk for cognitive impairment progression.

Acknowledgements

First and foremost, I would like to express my sincere gratitude to my supervisor Dr. Lisa Kakinami for her patience, motivation, guidance, and the continuous support of my master's studies. Her valuable feedback and suggestions helped me conduct this research.

Besides my supervisor, I would like to appreciate the rest of my thesis committee: Dr. Yogendra P. Chaubey and Dr. Arusharka Sen for their insightful comments and encouragement which motivated me to improve my research.

I would also like to thank the faculty members and graduate students who helped me through my study at Concordia University.

Last but not the least, I would like to thank my family and friends for supporting me spiritually throughout the writing of this thesis and my life in general.

Contents

List of Figures

List of Tables

1 Introduction

1.1 Background

A low population growth rate and an increase in the aged population lead to unequal proportions of young and old people. It is predicted that the world population aged 60 and above will be the same as the number of individuals aged under 15 by 2050 (United Nations, (2017)). Although both aged people and societies may benefit from a longer life course, any opportunities provided by an aged population (such as direct contributions to economic growth) depends on the aged population's health (Franklin et al., 2014). Aging naturally results in some biological changes which affects people's abilities in different domains. For instance, cognitive skills (the person's abilities to carry out cognitively demanding tasks such a telephone use or preparing a meal (Kimbler, 2013)) are affected by aging (Harada et al., 2013). Physical abilities (such as housekeeping, commuting, and work-related activities) are also affected as people age (Milanovic et al., 2013).

Naturally, brain volume changes during a lifetime. In fact, it increases until early adolescence then starts to decline beginning in early adulthood (Courchesne et al., 2000). Scahill et al. (2003) reported that while the whole brain volume decreased by aging during adulthood, the rate of atrophy accelerated after 70 years of age. Aging also affects distinct domains of cognition differently. For instance, while episodic memory (remembering of events and experiences) declines over the life course, semantic memory (remembering of facts and information) declines in old age (after 65 years of age) (Ronnlund et al., 2005).

Moreover, changes in cognitive abilities are related to changes in brain structure. For instance, as shown by Ritchie et al. (2015), people with lower initial levels of cognitive abilities experienced greater brain volume changes over their late lifetime. Sluimer et al. (2008) also reported that the brain atrophy rate was significantly associated with a decline in cognitive abilities. Similarly, a study by Royle et al. (2013) indicated that brain tissue deterioration contributed significantly to lower cognitive ability in later life.

In addition, biological changes accompany or coincide with a variety of chronic diseases

such as depression and dementia but depend on an individual's personal characteristics and lifetime circumstances (WHO, 2015). For instance, when brain atrophy or loss of cognitive functions is severe enough to impact a person's social and occupational life (Chertkow et al., 2013), the person can be diagnosed with dementia. Dementia has a prevalence of 47 million people worldwide in 2017, with 9.9 million new cases diagnosed every year (WHO, 2017). Alzheimer's Disease (AD) is a progressive brain disease that brings about memory, thinking, and behavior problems (Fischer, 2002) and is the main cause of dementia among aged people (accounting for 60-70% of dementia cases) according to the World Health Organization (2017). AD develops gradually over time and affects daily activities, such that at the last stage patients may not be able to talk and respond to their environment (Alzheimer's Association). AD has numerous physical, psychological, and economic impacts not only on the patients but also on caregivers and societies (WHO, 2017).

People with AD live for 3 to 10 years after diagnosis (Zanetti et al., 2009), however, research indicates that the brain started changing, years before the onset of neurodegenerative biomarkers and cognitive symptoms (Jack Jr et al., 2010). Due to this latency period (Sperling et al., 2011), researchers are interested in persons with mild cognitive impairment (MCI – the transitional stage between normal aging and AD (Petersen et al., 2001)). Researchers have targeted patients with MCI to investigate the relationship between structural brain changes and onset of disease symptoms over this preclinical phase of AD. In fact, studying this phase can help to have a better understanding of the early stages of AD and to develop intervention treatments to decrease the risk of disease progression. Generally, people with MCI experience more memory loss than is expected due to normal aging, but the memory loss is insufficient for AD diagnosis. Moreover, the rate of conversion to dementia among MCI patients is higher than among cognitively normal individuals (Roberts & Knopman, 2013). Driscoll et al. (2009) conducted a ten-year longitudinal study to explore the age-related regional volume loss in cognitively normal controls and people with MCI. The authors found that while natural changes in the whole brain volume and specific regions of the brain (such as the hippocampus and entorhinal cor-

tex) were due to aging among cognitively normal controls, the rate of global and regional changes were accelerated by aging in the MCI group.

Nevertheless, not everyone with MCI will progress to dementia. Indeed, some will revert back to normal cognitive health, and others will remain MCI (Roberts & Knopman, 2013). Important demographic and health differences between those who remain MCI and who revert to normal have been reported. For instance, MCI patients who reverted to normal did not carry any alleles of Apolipoprotein E-ε4 (APOE-ε4) and showed less impairments in cognitive and functional abilities than MCI patient who did not revert back to normal (Koepsell & Monsell, 2012). In contrast, Risacher et al. (2010) revealed that MCI patients who converted to AD had greater whole brain atropy and ventricle enlargment rates compared to people who remained MCI throughout study follow-up. In addition, deficits in functional abilities at baseline was also reported as a predictor of conversion from MCI to dementia (Farias et al., 2009). This great heterogeneity in people with MCI (Petersen et al., 2001) underline the need for investigating this group of individuals in order to learn about the characteristics which differentiate between those who remain stable with MCI, progress to AD, or revert back to normal. By being able to accurately identify those at highest risk for progression, results will have clinical implications on the development of interventions to prevent or slow down the progression of MCI.

People with MCI are classified into four sub-types: (1) single-domain or (2) multiple domain amnestic MCI (aMCI) and (3) single or (4) multiple domain non-amnestic MCI (naMCI). While aMCI groups contain individuals with memory deficits, naMCI refers to people with deficits in domains other than memory (Roberts & Knopman, 2013). A 6-year population-based study conducted by Busse et al. (2006) revealed that while prevalence of single-domain MCI was greater than the prevalence of multiple-domain, aMCI type was as common as naMCI. However, the authors declared that persons with aMCI were significantly more likely to progress to dementia than individuals with naMCI.

Different cognitive abilities including memory and non-memory domains have been examined separately to differentiate their impairments due to normal aging from impairments due to different stages of AD. Backman et al. (2004) declared that AD is best

characterized by impairments in multiple cognitive domains. The authors explained that accounting for other indicators (such as brain volumetric measures) could increase the accuracy of AD prediction. In fact, brain deterioration in the elderly with normal health and different stages of AD is diverse, and the changes in brain tissues vary in distinct regions. The study conducted by Evans et al. (2010) indicated that people with AD had a greater rate of whole brain atrophy and ventricles enlargement compared to control groups. Moreover, some brain regions were influenced at earlier stages of AD than others (Driscoll et al., 2009; Scahill et al., 2003). However, the literature assessing for brain tissues changes across distinctive regions while accounting for brain volumetric measures is limited.

Instead studies have tried to identify demographic characteristics and other predictors which may affect brain degeneration and impairment in cognition among healthy individuals or people with AD. For instance, similar to the finding that MCI carriers of APOE-ε4 alleles are more likely to progress to AD, carrying at least 1 allele APOE-ε4 may accelerate the rate of cognitive decline in early stages of AD (Cosentino et al., 2008) and may impact the decline in brain volume in late life (Manning et al., 2014). Other factors such as demographic characteristics which might influence AD progression have also been explored. Lipnicki et al. and his colleagues in 2013 found that older age and being male increased the risk of cognitive decline. Lipnicki et al. (2013) also found that having more education increased cognitive decline risk. In contrast, Lindsay et al. (2002) reported the opposite finding: that fewer years of education increased the risk of AD. Lindsay et al. (2002) did not find any difference between men and women at-risk for dementia. However, the mixed findings regarding education's role on cognitive decline may be an artifact due to differences in samples and should be further explored.

Importantly, cognitive decline is accompanied with decreased autonomy. Thus the association between cognitive decline and a person's ability to independently conduct instrumental activities of daily living (IADL, such as cleaning, doing the laundry, shopping, driving, and managing finances (Marshall et al., 2011)) has been of interest. Pérès et al. (2008) suggested that deficits in IADLs years before diagnosis of dementia could be an

early sign of the disease. A 1-year study of aMCI individuals by Rozzini et al. (2007) showed that baseline IADL, and executive functions independently predicted conversion to AD over 1 year. Burton et al. (2009) also declared that MCI participants showed more deficits in IADL functioning than those with normal cognitive status.

1.2 Limitations of the existing literature

Despite the great development in the longitudinal study of age-related declines in brain volume and cognitive abilities, notable limitations of the literature exist. For instance, most longitudinal studies have a small number of follow-up visits (only 2 time points over 1 or 2 years) (Sluimer et al., 2008; Rozzini et al., 2007), which not only decreases the power and precision of the results (Ritchie et al., 2015) but also limits the ability to detect changes in the factors over a longer period of time (Lipnicki et al., 2013). Moreover, some of the previous studies used the Mini-Mental State Examination (MMSE) test to assess the global change in cognitive skills (Sluimer et al., 2008). However, the MMSE is a screening test developed to detect AD and to distinguish between the different levels of AD, but is poor in identifying changes over time (Fischer, 2002), particularly among well-educated individuals (Jacqmin-Gadda et al., 1997). More importantly, as some participants revert or convert to other cognitive statuses throughout the study, not accounting for these variations may bias the associations toward the null (Plassman et al., 2010). Lastly, some studies applied simple analyses such as partial correlation or linear change scores (Lipnicki et al., 2013; Sluimer et al., 2008). Mixed models or latent class growth curve models are more statistically powerful and are better equipped to handle missing values and mistimed data (Curran et al., 2010).

Many previous studies did not properly adjust for known covariates between cognitive status and cognitive abilities. Inadequate covariate adjustment for important factors (Wilson et al., 2009) will result in residual confounding, which may mask important associations. For instance, whole brain, hippocampus, and ventricles volume plus entorhinal cortex thickness are reportedly significantly different between MCI and cognitively healthy controls (Evans et al., 2010; Driscoll et al., 2009) but are oftentimes not controlled for

in the analysis. Similarly, while health and genetic factors such as the APOE-$\varepsilon 4$ allele (Cosentino et al., 2008; Manning et al., 2014) and the ability to perform IADL have been linked with cognitive skills (Pérès et al., 2008; Jekel et al., 2015), the literature linking all of these factors together alongside longitudinal brain changes is sparse. Indeed, these covariates have been inadequately controlled for in previous studies. Lastly, potential moderators for the association between cognitive status and cognitive decline have been suggested but with inconsistant results. For instance, Karp et al. (2004) reported that a low level of education and a low socioeconomic status (based on occupation) were independently associated with increased risk of AD and dementia. In contrast, a study by Wilson et al. (2009) reported that education was associated with level of cognitive function but not with the rate of cognitive decline. However, drawing conclusions from these studies is difficult due to their variability in study quality and covariate adjustment (Plassman et al., 2010).

To address some of these previous limitations, we propose to analyze the longitudinal association between brain atrophy and cognitive decline in a large sample of older adults with 6 time points over 3 years. In particular, in recognition of the better exploration of the relationship as compared to a basic linear change score (Cardenas et al., 2011), we propose to investigate the relationship through a mixed effects model and to explore potential moderators for this association among subjects classified in two sub-groups: those who remain stable in the same cognitive status throughout the study ("stable") and those who convert to a different status over time ("converters"). In addition, there is not a single test to assess cognitive abilities that is universally recommended. Thus, to meet the objective of the current study, the Alzheimer's Disease Assessment Scale-cognition sub-scale (ADAS-Cog) is used to study changes in general cognitive abilities over time (Rosen, Mohs, & Davis, 1984). ADAS-Cog is commonly used in clinical trials of AD (Connor & Sabbagh, 2008). In addition, due to the heterogeneity of MCI and the high risk of conversion to dementia among aMCI, we are interested in (1) exploring sub-classes of aMCI individuals, (2) better characterizing these sub-classes, and (3) studying their patterns of cognitive ability changes over time. Therefore, we propose to apply a

latent class growth curve model based on functional assessments in order to identify MCI subgroups, and then studying the change in cognition across MCI sub-groups based on a mixed effects model.

More specifically, our first objective is to study the association between global and regional brain atrophy and change (decline) in cognitive abilities and to compare their rates of decline across the five groups (stable control normal, progressed control normal, stable MCI, progressed MCI, and AD). Our second objective is to examine whether education can play a moderating role for the changes in brain volume and cognitive abilities. The last objective is to explore MCI sub-classes and study the change in cognitive abilities among them.

2 Methods

The Alzheimer's Disease Neuroimaging Initiative (ADNI), which began in 2004, is a longitudinal study with open and ongoing recruitment designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection of different stages of AD in over 50 sites in US and Canada. ADNI has four phases in which participants are followed over time: Original ADNI (ADNI1, 2004-2010), ADNI Grand Opportunities (ADNIGO, 2009-2011), ADNI2 (2011-2016), and ADNI3 (2016-2021). While Magnetic Resonance Imaging (MRI) scans, cognitive assessments, and biomarker tests were conducted at each clinical visit, the phases differed in their target populations and their MRI scan technologies. For instance, ADNI1 conducted MRI by scanners with two magnetic field strengths: 1.5 Tesla (T) and 3 T (More information on MRI procedures and protocols is available at $http://adni.loni.usc.edu/about/centers-cores/mri-core/$). While ADNI1 mainly implemented 1.5 T MRI scans, participants in ADNIGO and ADNI2 had only 3 T image scans. Compared with 1.5 T, 3 T is preferable due to the larger signal to noise ratio and flexibility for advanced technical scans (Jack Jr et al., 2010, 2015). Although 3 T MRI was exclusively used in ADNIGO, ADNI2, and only among 25 percent of participants in ADNI1, Ho et al. (2010) found that 1.5 T and 3 T scans were comparable to one another and did not differ significantly. Thus, in order to avoid adding any probable extra variation and bias, this study included only participants with 1.5 T scans collected throughout ADNI1 waves ($n = 819$). Data from the "ADNImerge" dataset specific to ADNI1 waves were used for this analysis. More information about ADNI is available at $http://adni.loni.usc.edu$.

2.1 ADNI participants

ADNI1 enrolled people with different cognitive status who were between 55 and 90 years of age, and in a "good general health condition with no disease expected to interfere with the study"(Petersen et al., 2010). Other eligibility criteria included speaking in English or Spanish and with a reliable study partner able to independently evaluate the participant's functioning. Participants were classified into a cognitive group based on their

memory complaints, score on the Logical Memory II sub-scale from the Wechsler Memory Scale (LM II, which is adjusted for education), Mini-Mental State Examination (MMSE) score, and Clinical Dementia Rating (CDR) (see Table 1) (Petersen et al., 2010). A site physician also assessed their cognitive status based on the significant impairment in cognitive functions or activities of daily living, and stability of permitted medications for 4 weeks.

Table 1: Scores on psychological tests for inclusion in ADNI

Cognitive status	MMSE	CDR	LM II		
			Education, year		
			0-7	8-15	>=16
CN	24-30	0	>=3	>=5	>=9
MCI	24-30	0.5	<=2	<=4	<=8
AD	20-26	0.5 0r 1	<=2	<=4	<=8

CN: control normal, MCI: mild cognitive impairment, AD: Alzheimer's disease,
MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating,
LM II: Logical Memory II sub-scale of the Wechsler Memory scale-revised

Based on these tests and the physician's assessment, subjects with normal cognition, (control normal, CN) were defined as those who did not have any symptoms of depression, cognitive impairment or dementia. However, people who did not have subjective memory concerns (but without any effect on their daily activities reported by themselves, their partners or a site physician), and without any signs of dementia, were classified as subjects with MCI. Participants who met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable AD were classified into the AD group (Petersen et al., 2010). Clinical assessment and imaging data were collected at baseline, 6 months after baseline, and subsequently on an annual basis. Subjects in the MCI group also had an in-clinic visit 18 months after baseline for a cognition assessment and MRI scan. Moreover, subjects were followed up via telephone interviews after 18 and/or 30 months from baseline (depending on cognitive group) to assess change in cognition. CN and MCI in-

dividuals were followed at least for three years while people with AD were followed for at least 2 years. Further information about the ADNI study and inclusion criteria can be found at $http://www.adni-info.org/Scientists/ADNIStudyProcedures.html$. Of the total ADNI1 participants, 229 had normal cognitive status at baseline, and 398 and 192 of them were classified in aMCI and AD groups, respectively. Normal subjects were age-matched with aMCI and AD participants.

2.2 Cognitive measure

In 1984, Rosen et al. designed the classic ADAS-Cog (Rosen et al., 1984) in order to (1) assess the severity of cognitive and non-cognitive dysfunctions in people with AD, (2) measure change in general cognitive abilities over time, and (3) monitor the treatment effects in clinical trials of dementia (Connor & Sabbagh, 2008). It was further developed by Mohs et al. (1997) to increase the range of cognitive domains and to increase its sensitivity to detect change in early stages of AD and is known as Modified ADAS-Cog (often referred to as ADAS-Cog 13). In addition to 11 items from the classic ADAS-Cog covering memory, language, praxis, and orientation domains, ADAS-Cog 13 includes delayed verbal recall and digit cancellation measuring visual attention and concentration. It ranges from 0 to 85 points with higher scores indicating greater degree of cognitive dysfunctions and greater progression of the disease, and is commonly used in clinical trials of AD (Connor & Sabbagh, 2008). As ADAS-Cog 13 measures general cognitive abilities and covers more cognitive domains compared with ADAS-Cog, the ADAS-Cog 13 is the outcome of interest in this study. For our third objective aiming to identify MCI subgroups, our primary predictor of cognitive status was replaced with a measure representing degree of autonomy. IADL assessing functional abilities were used to identify any sub-population in MCI group with distinctive baseline values and trajectories over time to characterize potential sub-classes. Functional Activities Questionnaire (FAQ) (Pfeffer et al., 1982) filled by the subjects' study partners was used to assess IADL, with scores ranging between 0 and 30 where higher scores indicate higher impairment.

2.3 Covariates

Covariates were considered for inclusion into this study based on their reported associations in the literature. For instance, whole brain, hippocampus, and ventricles volume plus entorhinal cortex thickness are reportedly significantly different between MCI and cognitively healthy controls (Evans et al., 2010; Driscoll et al., 2009). These volumetric and brain-related covariates were acquired from MRI scans over each clinical visit. In addition, as several studies have found that carrying at least 1 allele of the APOE-$\varepsilon 4$ may accelerate the rate of cognitive decline in brain volume (Cosentino et al., 2008; Manning et al., 2014), whether the person was a carrier of APOE-$\varepsilon 4$ alleles was considered as a covariate. This was collected based on conducting genotyping on blood samples collecting at the screening visit (for more information see $http://adni.loni.usc.edu/data-samples/genetic-data$). In addition to time (in months from baseline), demographic characteristics such as gender, baseline age, and years of education were also included.

2.4 Statistical analysis

Both participants who had progressed in their disease or remained stable over follow-up were included in this study. Based on clinical tests, subjects were classified as 'stable cognition' if their follow-up measures were consistent with their baseline classification, and were classified as 'progression' if their cognition classification worsened over time. As we were interested in studying subjects who had stable or progressed cognitive status, subjects who reverted to healthier cognitive status were excluded from the study: MCI who reverted to normal: $n = 15$; AD who reverted to MCI or normal: $n = 2$. In addition, subjects with progression during the follow-ups who reverted to their baseline status were excluded from the study ($n = 7$). One subject was also eliminated from the study due to missing values at all time-points. As a result, data collected from 794 participants with stable or progressed status were used to conduct this study.

Descriptive statistics and bivariate tests between cognitive abilities and potential risk factors at baseline were assessed with analysis of variance and chi-square tests. Linear regression was used to investigate the (1) cross-sectional association between cognitive

status and ADAS-Cog 13 at baseline and the (2) longitudinal association between cognitive status changes and ADAS-Cog 13. All models included baseline age (centered at the grand mean age (75.3) to have a meaningful interpretation of the intercept), years of education, and a binary variable as an indicator of APOE-ε4 carrier (coded as 0 for non-carrier or 1 for those who carried 1 or 2 ε4 alleles), as well as volumetric variables (such as whole brain or hippocampus volume) which were divided by intracranial volume (ICV) prior to analyses in accordance with the literature (Whitwell et al., 2001) to control for head size and inter-images variation.

Linear regression models to investigate the cross-sectional associations between global and regional brain measurements and ADAS-Cog 13 at baseline adjusting for cognitive status and all the covariates previously described were conducted.

2.4.1 Linear mixed effects models

Linear mixed effects models were used to study changes in cognitive abilities over time. These models are applied to analyze changes in longitudinal data accounting for individuals effects. In fact, in mixed effects models, it is assumed that the mean response is a combination of the population effects that are shared by all individuals (fixed effects) and subject-specific effects that are unique to a particular subject (random effects) (Fitzmaurice et al., 2012). The response of each individual differs from the mean population by subject-specific effects and within-subject measurement errors, and the within-subject (measurement errors) and between-subject (random effects) variations in the response are modeled explicitly. In linear mixed effects models, including random intercepts and random slopes of time allows individuals to be different from one another not only in their baseline level of the response but also in changes in their response over time. It is also assumed that the error terms and the random effects are normally distributed with zero mean and an unknown variance-covariance matrix.

In this study, four linear mixed effects models with both random intercepts and random slopes of time were conducted to test the longitudinal associations between structural brain measurements and ADAS-Cog 13 over time across different cognitive groups. It was

assumed that random intercepts, slopes of time, and measurement errors were normally distributed with mean zero and unknown variance-covariance structure. Model 1 included cognitive status (stable- control normal (sCN), progressed control normal (pCN), stable-MCI (sMCI), progressed MCI (pMCI), and AD) and proportionate whole brain volume (WBV/ICV) as the primary predictors in addition to all the covariates previously described (demographic variables, APOE-$\varepsilon 4$ carrier the genetic factor, cognitive status, time). Model 1 also included an interaction between cognitive status*time and WBV/ICV*time. Interaction terms were included to test if the change in ADAS-Cog 13 was different across groups, and if this change depends on brain volume. Model 2 additionally had an interaction term between cognitive status and whole brain volume to test if baseline cognitive dysfunctions can differ between groups. Model 3 aimed to examine if effect of brain volume on longitudinal changes in cognitive abilities can be different across groups, thus additionally included the interaction between cognitive status, WBV/ICV, and time. Lastly to investigate the moderation effect of education on cognitive abilities and global brain measurements, Model 4 additionally included an interaction between education and WBV/ICV. In all models, sCN was considered as the reference group (see equations 2.1 to 2.4).

Model 1:

$$\begin{aligned} Y = {} & \beta_0 + b_0 + \beta_1 Time + b_1 Time + \beta_2 Age + \beta_3 Gender + \beta_4 (APOE - \varepsilon 4) \\ & + \beta_5 Cog.status + \beta_6 Education + \beta_7 WBV/ICV \\ & + \beta_8 WBV/ICV \times Time + \beta_9 Cog.status \times Time + \varepsilon \end{aligned} \tag{2.1}$$

Note that β_is for $i = 1, 2, ..., 9$ represent fixed effects, while b_0 and b_1 represent the random effects (random intercept and random slope of time respectively).

Model 2: contains all terms in Model 1 plus one additional interaction term as below:

$$\begin{aligned} Y = {} & \beta_0 + b_0 + \beta_1 Time + b_1 Time + \beta_2 Age + \beta_3 Gender + \beta_4 (APOE - \varepsilon 4) \\ & + \beta_5 Cog.status + \beta_6 Education + \beta_7 WBV/ICV + \beta_8 WBV/ICV \times Time \\ & + \beta_9 Cog.status \times Time + \beta_{10} WBV/ICV \times Cog.status + \varepsilon \end{aligned} \tag{2.2}$$

Model 3: contains all terms in Model 2 plus one additional interaction term as below:

$$\begin{aligned} Y = {} & \beta_0 + b_0 + \beta_1 Time + b_1 Time + \beta_2 Age + \beta_3 Gender + \beta_4 (APOE - \varepsilon 4) \\ & + \beta_5 Cog.status + \beta_6 Education + \beta_7 WBV/ICV + \beta_8 WBV/ICV \times Time \\ & + \beta_9 Cog.status \times Time + \beta_{10} WBV/ICV \times Cog.status \\ & + \beta_{11} WBV/ICV \times Cog.status \times Time + \varepsilon \end{aligned} \tag{2.3}$$

Model 4: contains all terms in Model 3 plus one additional interaction term as below:

$$\begin{aligned} Y = {} & \beta_0 + b_0 + \beta_1 Time + b_1 Time + \beta_2 Age + \beta_3 Gender + \beta_4 (APOE - \varepsilon 4) \\ & + \beta_5 Cog.status + \beta_6 Education + \beta_7 WBV/ICV + \beta_8 WBV/ICV \times Time \\ & + \beta_9 Cog.status \times Time + \beta_{10} WBV/ICV \times Cog.status \\ & + \beta_{11} WBV/ICV \times Cog.status \times Time + \beta_{12} WBV/ICV \times Education + \varepsilon \end{aligned} \tag{2.4}$$

Moreover, as the literature indicates that the relationship between cognitive status and cognitive abilities may have differential associations across brain regions, 3 models were conducted to test this association: model I, II, and III looked for associations between proportionate hippocampus volume to ICV (HCV/ICV), and entorhinal cortex thickness, and ventricles volume proportionate to ICV (VEV/ICV) with ADAS-Cog 13 respectively. These models adjusted for all the covariates as previously described in Model 4, except that the WBV/ICV was replaced by the different regional brain variables.

Mixed models included both random intercepts and random slopes of time. The necessity of adding these random effects was confirmed by the Likelihood Ratio Test (LRT) comparing models with (1) random intercept, (2) random slopes, and (3) both random intercept and slopes models which confirmed that a model with random intercept and slope was the best model fit. In addition, looking at variance- covariance, and the correlation matrix of ADAS-Cog13 at different time-points, it revealed that the variance of cognitive scores were not constant over time, but that the ADAS-Cog13 correlation was approximately constant between different time-points. Thus different covariance structures were assessed: (1) compound symmetry with heterogeneous variances (CSH), (2) unstructured,

(3) and auto-regressive with and without heterogeneous variances. Model comparisons were assessed with LRTs or Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics (depending on whether the model was nested or non-nested). Comparing different covariance structures, in all cases but models I-III, the hybrid models with both random intercept and slope of time with unstructured covariance matrix and heterogeneous auto-regressive structure for within subjects errors were selected as the best fitting models. Models I-III also used the heterogeneous auto-regressive structure.

2.4.2 Latent class growth models

Due to the literature suggesting heterogeneity among MCI, a final analysis aimed to identify sub-classes of MCI based on latent class growth analysis. In this method, it is assumed that the population is composed of a mixture of distinct groups in which subjects follow the same pattern of change over time on a given variable. Provided that the direction and the magnitude of changes can vary independently from one another, latent class growth analysis models the heterogeneity in changes within the data by a finite set of unique polynomial functions each corresponding to a distinct trajectory (Andruff et al., 2009). Based on the type of the outcome variable (e.g discrete or continuous), specific probability distribution is used to estimate the model parameters. For instance, if the outcome of interest is continuous, a censored normal model distribution is used for parameters estimation. In fact, as the data are forced to group at the minimum and maximum of the scale (Jones et al., 2001), a censored distribution is used for modeling the scaled data. In addition, the outcome is linked with the time by means of a latent variable, y_{it}^{*j} which represents the predicted value of the outcome (y) for a given group or trajectory (j) at a specific time (t). Assuming a quadratic trend over time for subjects given the membership in group j:

$$y_{it}^{*j} = \beta_0^j + \beta_1^j X_{it} + \beta 2^j X_{it}^2 + \epsilon_{it}$$

where X is an independent variable of time or age, and ϵ_{it}, an error term, is normally distributed with mean zero and a constant variance σ^2. The link between the latent

variable and the observed but censored variable (y_{it}) is defined as follows (Nagin, 1999).

$$y_{it} = \begin{cases} S_{min} & y_{it}^{*j} < S_{min} \\ y_{it}^{*j} & S_{min} \leq y_{it}^{*j} \leq S_{max} \\ S_{max} & y_{it}^{*j} > S_{max} \end{cases}$$

Note that S_{min} and S_{min} represent the minimum and maximum scale of the outcome. Parameters of each trajectory are estimated by the Maximum Likelihood method given the number of groups and trajectory models of each group in advance based on the prior knowledge or the literature of the study. Moreover, the optimal number of groups and the best fitted shapes for each trajectory are assessed with Bayesian Information Criterion (BIC), and each individual is assigned to a group with respect to the maximum posterior probability of a group membership (Andruff et al., 2009).

In this study, a latent class growth curve model was applied to specify any probable sub-populations in the MCI group to explore the pattern of cognitive change in cognition among different MCI subdivisions. In addition to sMCI and pMCI, subjects with sCN status were also included in the analysis as a reference to assess the accuracy of the classification. Participants' performance of IADL assessed by FAQ was used to characterize the sub-classes among MCI subjects. After looking at baseline characteristics of these groups, two models were used to assess the new classification based on modeling the change in cognition among MCI subjects. Curve models with different number of groups and complexity of relationships (linear, quadratic, cubic) were conducted and compared to one another using censored normal models. The final model was selected based on significant trajectories shape, BIC, including at least 5% of the sample in each group (Andruff et al., 2009), and ease of interpretations.

3 Results

3.1 Descriptive analysis

Descriptive statistics of demographic characteristics and structural brain variables stratified by cognitive status at baseline are provided in Table 2. It is notable that groups were similar in demographic characteristics except for gender and education, such that men accounted for a larger proportion of participants in the sMCI and pMCI groups, and AD with the most impairments had the lowest mean years of education attained ($mean = 14.7$). Subjects in pMCI and AD groups were mostly carriers of at least one allele of APOE-ε4. In addition, baseline cognitive and functional abilities differed significantly between cognitive groups. pMCI and AD groups had larger average scores on baseline ADAS-Cog 13 and FAQ compared to subjects with sCN status, generally reflecting greater impairments. Moreover, structural brain variables revealed significant differences in global and regional brain measurements between groups: on average pMCI and AD groups had smaller whole brain and hippocampus volume, thinner entorhinal cortex, and larger ventricles volume at baseline compared with the control normal group. Although, cognitive groups did not differ significantly on baseline mean of intracranial volume representing the head size.

Table 2: Baseline characteristics

Characteristics	sCN	pCN	sMCI	pMCI	AD
No. participants	209	18	206	171	190
Male*, %	51.2	55.6	65.5	61.4	52.1
Age, years	75.7(5.0)	77.8(5.4)	74.8(7.6)	74.8(7.0)	75.3(7.5)
Education*, years	16.1(2.9)	15.7(2.8)	15.5(3.2)	15.8(2.9)	14.7(3.2)
APOE-ε4 carrier *, %	26	33.3	44.2	67.3	65.8
Average time of follow-up, month	38.2(12.2)	39.2(6.1)	30.2(15.0)	36.7(11.8)	21.2(8.6)
WBV*, cm^3	1006.2(101.3)	1014.3(87.2)	1007.2(106.5)	980.2(112.2)	952.3(107.7)
HCV*, cm^3	7.3(0.9)	6.8(1.0)	6.7(1.0)	6.0(1.0)	5.6(1.1)
VEV*, cm^3	35.2(20.1)	37.5(16.3)	42.6(24.1)	47.4(23.1)	50.3(25.3)
ERC*, cm	382.9(64.8)	349.3(94.3)	350.4(72.2)	303.1(70.8)	273.6(69.3)
ICV, cm^3	1532.9(156.3)	1594.5(157.8)	1573.3(159.0)	1573.3(176.0)	1547.5(181.8)
ADAS-Cog 13*	9.3(4.2)	12.0(4.0)	17.1(6.1)	21.3(5.3)	29.0(7.6)
FAQ*	0.1(0.4)	0.7(1.6)	2.7(3.6)	5.5(5.0)	13.1(6.8)

sCN: stable control normal, pCN: progressed control normal, sMCI: stable mild cognitive impairment, pMCI: progressed MCI, AD: Alzheimer's disease, HCV: hippocampus volume, ERC: entorhinal cortex, VEV: ventricles volume, ICV: intracranial volum, FAQ: functional abilities questionnaire.* $p < 0.01$, chiq- square and analysis of variance tests were used to explore the association between baseline characteristics and cognitive groups.

3.2 Baseline association

Associations between cognitive dysfunctions and each covariate at baseline were also assessed. Table 3 provides the results of the models which separately explored the effect of covariates on ADAS-Cog 13 while adjusting for centered age, gender, and cognitive status. Greater impairments in baseline mean cognition could be seen among APOE-ε4 carriers compared with non-carriers ($p < 0.02$). Controlling for head size, proportional brain volumetric variables such as whole brain, hippocampus, and ventricles volume (dividing by intracranial volume) were included in 3 separate models. It is notable that greater brain and hippocampus volume proportionate to the head size and thicker entrohinal cortex could be protective against cognitive impairments ($p < 0.0001$), while larger proportional ventricles volume was associated with greater baseline cognitive dysfunctions. Looking at the baseline effect of education on cognition, years of education significantly protected individuals from concurrent cognitive dysfunctions. For instance, men with sCN status,

who are 75 years of age on average experienced less impairment in cognitive abilities at baseline with each year of education attained ($\hat{\beta} = -0.19, p < 0.01$). However, one of the ADNI inclusion criteria was that years of education were incorporated into the classification of different cognitive groups. Thus education might influence the relationship between ADAS-Cog 13 and covariates. To overcome this probable influence, subjects with certain years of education who were on the cusp of two different classifications and were thus classified into one group based on their years of education were excluded from the study ($n = 108$). After excluding these subjects, education was not associated with baseline cognitive impairments adjusting for age and gender ($p > 0.05$). The rest of the analyses used these reduced data, after excluding these subjects ($n = 686$).

Table 3: Baseline effects on ADAS-Cog13 by separate general linear models

Covariates	Estimated parameter (Standard error)	p-value
Education	-0.19(0.07)	0.01
APOE-ε4 Carrier, %	1.07(0.45)	0.02
WBV/ICV, %	-0.24(0.06)	<.0001
HC/ICV, %	-18.25(3.79)	<.0001
ERC, cm	-0.03(0.003)	<.0001
VEV/ICV, %	0.63(0.18)	0.001

HCV: hippocampus volume, ERC: entorhinal cortex, VEV: ventricles volume, ICV: intracranial volume. * p <0.05. HCV and VEV were proportional to ICV. Each variable was tested in a separate general linear model and adjusted for centered age, gender, and cognitive status.*$p < 0.05$, **$p < 0.01$, ***$p < 0.0001$.

3.3 Longitudinal association

Exploring the general patterns of cognitive abilities over time, Figure 1 displays the plots of ADAS-Cog 13 with a random 5% of participants along with their average over time. Subjects in pMCI and AD, on average, had greater rates of cognitive impairments over time compared to sCN and sMCI groups. In addition, generally patients with larger baseline cognitive scores were more likely to have larger rate of change in cognition over time. It is also evident that the rate of change in cognition differed from the general pattern for

different participants.

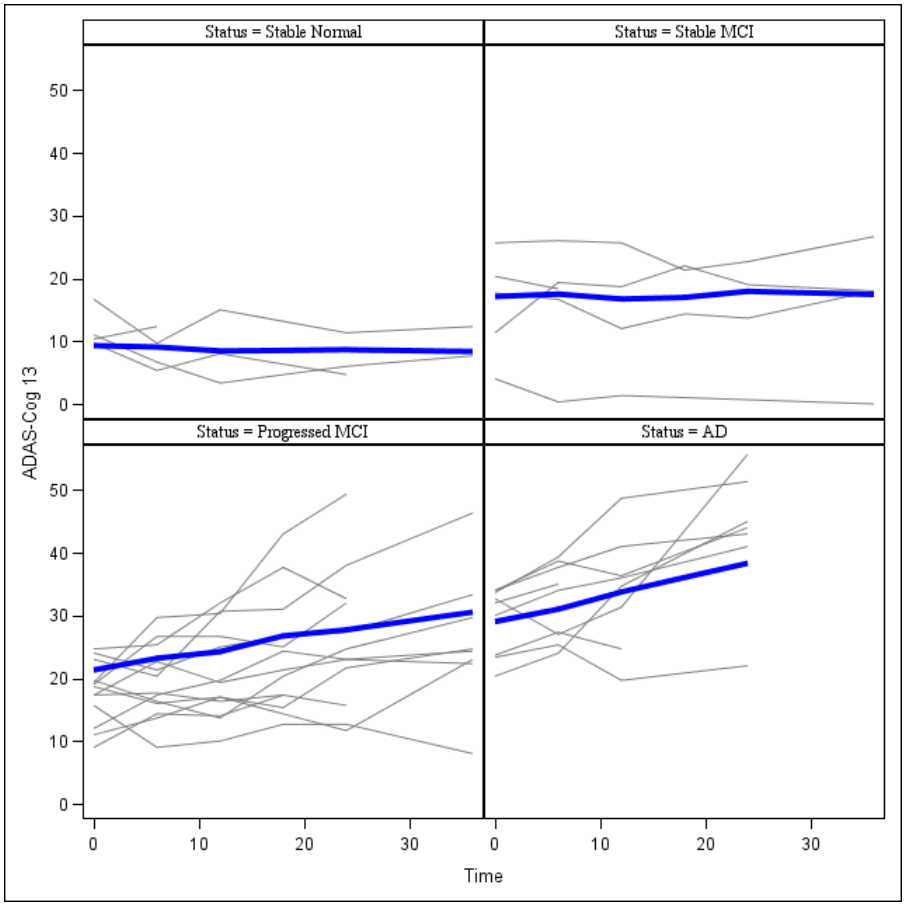

Figure 1: Time plot of cognitive dysfunctions of a 5% random sample of participants and average cognitive dysfunctions stratified by cognitive status

Figure 2 depicts the difference in average cognitive dysfunctions scores stratified by cognitive groups over time. It is clear that baseline and the overall trend of ADAS-Cog 13 was higher in groups with greater impairments, such that pMCI and AD groups with higher baseline mean scores also had steeper increases in mean cognitive impairments over time compared to other groups. Moreover, although both sCN and sMCI had almost a constant mean ADAS-Cog 13 over time, the average cognitive disabilities was remarkably higher among sMCI than sCN. Subjects in pCN group on average suffered from greater impairments in cognition both at baseline and over time compared to sCN. In pCN group, the rate of change in mean ADAS-Cog 13 was not constant over time, and it increased until it reached the sMCI mean levels of impairments. Regarding the patterns of mean

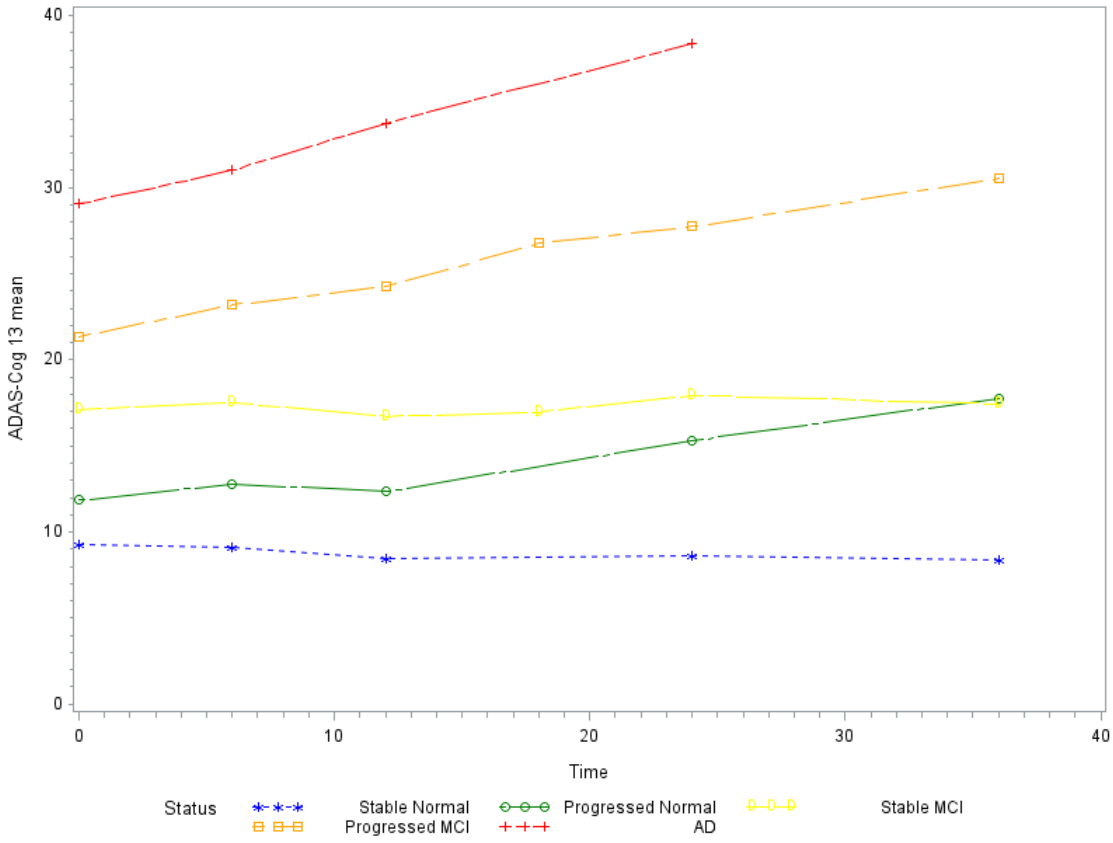

Figure 2: Time plot of mean cognitive dysfunctions stratified by cognitive status

cognition dysfunctions over time, the average cognitive dysfunctions increased linearly over time in almost all groups except for sCN and sMCI which had relatively stable mean ADAS-Cog 13 scores over time.

Further, we used mixed models with random intercept and random slope of time to investigate the change in cognitive abilities over time. According to the time plot displays in figure 1, patients with larger baseline cognitive scores were more likely to have larger rate of change in cognition over time. Thus, to reflect this variation in individuals, four models were fitted to the data to study the change in cognition over time.

To assess the adequacy of the fitted models, it is required to check the residuals for deviation from the model assumptions such as normality. Figure 3 displays three plots of the residuals for ADAS-Cog 13; residuals versus predicted mean values, the histogram of residuals, and the Q-Q plot of the residuals. The scatter plot of residuals versus predicted mean values is used to check the linearity assumption.

In order to determine whether the linearity assumption held, the scatter plot of residu-

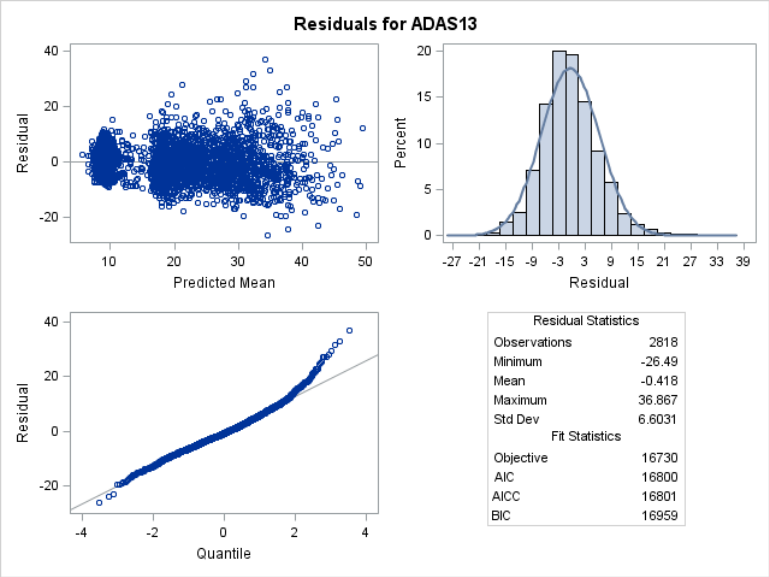

Figure 3: Residual plots for ADAS-Cog 13

als was reviewed. Although the linearity assumption did not appear to be grossly violated generally (no systematic pattern), the plot appears to be approximately divided in two parts. Looking at the cognitive status of subjects assigned to these two parts and of those who were located in between, it was realized that mostly, individuals in the pCN group were placed between two clusters. Therefore, it can be concluded that the small number of subjects in the pCN group might explain a division in the scatter plot. In addition, the residuals histogram and Q-Q plot depict a moderate violation from normality assumption. The histogram shows a slightly skewness to the right, and Q-Q plot also displays a modest departure from a straight line particularly at the right end. Nevertheless, after applying different transformation methods such as logarithmic and square root transformation, a square root transformation of the ADAS-Cog 13 brought the distribution of the data towards normality (Figure 4).

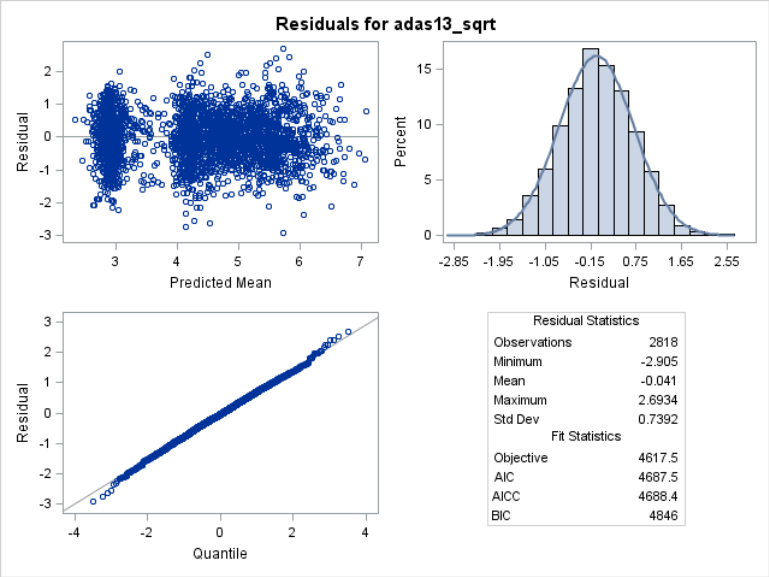

Figure 4: Residual plots for ADAS-Cog 13 with square root transformation

The estimated parameters with standard errors for four models of non-transformed outcome are displayed in Table 4. In addition, due to the moderate violation of the normality assumption, the estimated parameters of Model 3 with non-transformed and transformed outcome were also provided in Table 5 for the comparison. The results were interpreted regarding the adjustment for baseline characteristics and other included variables, and sCN was considered as a reference group. In Model 1, it is evident that baseline cognitive dysfunction was higher in all groups except for pCN relative to sCN. At baseline, individuals with greater WBV/ICV might show less impairment in cognition regardless of their cognitive status ($\hat{\beta} = -0.28, p < 0.0001$), and the decrease in WBV/ICV accelerated the rate of decline in cognitive abilities over time ($\hat{\beta} = -0.01, p < 0.0001$). Indeed, while mean ADAS-Cog 13 increased over time in all groups (which represents a decline in cognition over time), the rate was steeper among subjects in pMCI and AD groups compared to sCN with the same baseline characteristics ($\hat{\beta}_{pMCI} = 0.27 + 0.81 = 1.08, \hat{\beta}_{AD} = 0.36 + 0.81 = 1.17$). In Model 1, it was assumed that baseline and the longitudinal effect of brain volume across different groups were the same.

After including the interaction between brain volume and cognitive status in Model 2, sMCI baseline cognition was no longer significantly different from sCN. This implies

that the effect of brain volume on baseline mean ADAS-Cog 13 was similar among sMCI, and sCN groups. However, participants in the pMCI and AD groups with smaller brain volume had lower cognitive impairment at baseline ($\hat{\beta}_{pMCI} = -0.35, p < 0.05 \hat{\beta}_{AD} = -0.68, p < 0.0001$). Model 3 tested the difference in the effect of brain volume on the rate of cognitive abilities over time across cognitive groups by adding an interaction term between WBV/ICV, cognitive status, and time. It is clear that in the pMCI and AD groups, the effect of brain volume on the rate of change in average ADAS-Cog 13 differed from subjects in other groups. In fact, the magnitude of brain volume effect on the rate of change in cognition was larger among pMCI and AD compared to other groups ($|-0.01 - 0.02| = 0.03$). Therefore, it seems that greater proportional brain volume might have the greater moderating effect on the rate of cognitive impairments over time in pMCI and AD groups.

Studying the effect of education on cognitive abilities, it can be seen that in the first three models, individuals with the same baseline characteristics and the same proportional brain volume but higher education attainments, on average, experienced less impairments in cognitive abilities at the baseline ($\hat{\beta} = -0.16, p < 0.05$), from Models 1-3. However, education might not moderate the relationship between whole brain volume and ADAS-Cog 13, as the estimated coefficient of interaction between education and whole brain volume was not significant ($p > 0.05$), Model 4.

In summary, subjects who were already impaired at baseline (in sMCI, pMCI, and AD groups) had greater impairment in cognition relative to sCN participants at baseline. While baseline impairment level was highest among pMCI and AD patients with smaller brain volume, brain volume had a similar effect on the initial cognitive impairment among sCN, pCN, and sMCI subjects. In addition, cognitive abilities declined over time in all groups but with the steeper rate among pMCI and AD patients. Importantly, decrease in brain volume accelerated the rate of decrease in cognition over time, however, the brain volume effect on the rate of decline was higher among pMCI and AD subjects. In all models, centered age, gender, and APOE-ε4 carrier status did have any effect on mean ADAS-Cog 13 (results not shown).

Table 4: Modeling change in ADAS-Cog 13 over time in different clinical groups

	Model 1	Model 2	Model 3	Model 4
Covariates	Estimated parameters (standard error)			
Cognitive status				
pCN	1.95(1.41)	7.42(22.07)	9.93(22.31)	9.80(22.32)
sMCI	7.69(0.63)***	12.50(8.31)	10.97(8.54)	10.71(8.56)
pMCI	11.01(0.67)***	33.72(8.42)***	27.51(8.64)**	26.97(8.70)**
AD	18.35(0.66)***	60.96(8.01)***	55.69(8.13)***	55.86(8.13)***
Time	0.81(0.14)***	0.85(0.14)***	0.35(0.21)	0.35(0.21)
Education	-0.16(0.07)*	-0.16(0.07)*	-0.16(0.07)*	0.33(0.82)
WBV/ICV, %	-0.28(0.05)***	-0.04(0.08)	-0.09(0.08)	0.03(0.21)
WBV/ICV*Time	-0.01(0.002)***	-0.01(0.002)***	-0.01(0.003)	-0.01(0.003)
Cognitive status* WBV/ICV				
pCN		-0.08(0.34)	-0.12(0.35)	-0.12(0.35)
sMCI		-0.07(0.13)	-0.04(0.13)	-0.04(0.13)
pMCI		-0.35(0.13)*	-0.25(0.14)	-0.24(0.14)
AD		-0.68(0.13)***	-0.59(0.13)***	-0.59(0.13)***
Cognitive status*Time				
pCN	0.11(0.05)*	0.11(0.05)*	-0.43(0.74)	-0.44(0.74)
sMCI	0.07(0.03)*	0.07(0.03)*	0.35(0.37)	0.34(0.37)
pMCI	0.27(0.02)***	0.25(0.03)***	1.28(0.33)**	1.27(0.33)**
AD	0.36(0.03)***	0.30(0.03)***	1.73(0.42)***	1.73(0.42)***
Cognitive status * WBV/ICV * Time				
pCN			0.01(0.01)	0.01(0.01)
sMCI			-0.004(0.01)	-0.004(0.01)
pMCI			-0.017(0.005)**	-0.016(0.005)**
AD			-0.023(0.007)**	-0.023(0.007)**
WBV/ICV*Education				-0.01(0.01)

sCN: stable control normal, pCN: progressed control normal, sMCI: stable mild cognitive impairment, pMCI: progressed MCI, AD: Alzheimer's disease, WBV: whole brain volume, ICV: intracranail volume. *$p < 0.05$, **$p < 0.01$, ***$p < 0.0001$. sCN was the reference group in all models.WBV was proportional to ICV for controlling the head size. Each model adjusted for centered age, gender, and APOE-ε4.

To assess whether the association between cognitive abilities and the brain measurements would change after transforming the outcome, all four mixed models in Table 4 were conducted again replacing the ADAS-Cog 13 with its square root. The results re-

vealed that the estimated coefficients of each term in Model 1 and Model 2 remained approximately the same regarding a significance level and direction of effects (the sign of coefficients), however, in Model 3 and Model 4, the effect of the brain volume on the rate of change in cognition in the pMCI and AD groups were no longer significant after transforming the outcome. Table 5 provides information on the estimated parameters and their standard errors in Model 3 with and without transforming the ADAS-Cog 13. The estimated coefficients which differ from one another in terms of a significance level are specified in bold. In general, the results were consistent with respect to the significance level and the direction of effects in the four models regardless of whether the outcome was transformed or non-transformed except for a small number of estimated parameters. Moreover, due to the complexity of computation of back-transformed coefficients and different scales of non-transformed and transformed estimated effects, we cannot compare the magnitude of estimated effects. Thus, regarding the general consistency in the results and also for the ease of interpretations, the findings were presented without transforming the outcome. However, explaining the effect of the brain volume on the rate of change in ADAS-Cog 13 in different cognitive groups must be reported cautiously and with more considerations.

Table 5: Modeling change in ADAS-Cog 13 over time with and without square root transformation

	Model 3 with non-transformed outcome	Model 3 with transformed outcome
Covariates	Non-transformed	Transformed
Cognitive status	estimated parameter(standard error)	estimated parameter (standard error)
pCN	10.90(21.77)	1.06(2.66)
sMCI	10.97(8.54)	1.52(1.02)
pMCI	27.51(8.64)**	3.16(1.03)**
AD	55.69(8.12)***	5.62(0.96)***
Time	**0.35(0.21)**	**0.06(0.02)****
Education	-0.16(0.07)*	-0.02(0.01)**
WBV/ICV	-0.09(0.08)	-0.01(0.01)
WBV/ICV*Time	**-0.01(0.003)**	**-0.001(0.0004)****
Cognitive status*WBV/ICV		
pCN	-0.14(0.34)	-0.01(0.04)
sMCI	-0.04(0.13)	-0.01(0.02)
pMCI	-0.25(0.14)	-0.03(0.02)
AD	-0.59(0.13)***	-0.05(0.02)**
Cognitive status*Time		
pCN	-0.50(0.73)	-0.08(0.08)
sMCI	0.35(0.37)	0.02(0.04)
pMCI	**1.28(0.33)****	**0.06(0.04)**
AD	1.73(0.42)***	0.09(0.04)*
Cognitive status*WBV/ICV* Time		
pCN	0.01(0.01)	0.002(0.001)
sMCI	-0.004(0.01)	-0.0001(0.001)
pMCI	**-0.02(0.01)****	**-0.001(0.001)**
AD	**-0.02(0.01)****	**-0.001(0.001)**

sCN: stable control normal, pCN: progressed control normal, sMCI: stable mild cognitive impairment, pMCI: progressed MCI, AD: Alzheimer's disease, WBV: whole brain volume, ICV: intracranail volume. $*p < 0.05$, $**p < 0.01$, $***p < 0.0001$. sCN was the reference group in two models.WBV was proportional to ICV for controlling the head size. Each model adjusted for centered age, gender, and APOE-$\varepsilon 4$. The estimated parameters with the red color display the difference between two models in terms of the significance level.

3.4 Cognitive change and brain regions

Table 6 displays 3 models which studied the effect of structural brain variables (such as hippocampus and ventricles volume and entorhinal thickness) on baseline ADAS-Cog

13 among subjects with different cognitive status compared with sCN individuals. Each brain variable was tested in a separate model: Model I included proportional hippocampus volume, Model II and III studied entorhinal cortex thickness and proportional ventricles volume respectively. Each model also controlled for demographic and genetic characteristics as previously described. On average subjects in sMCI and AD groups who shared the same baseline characteristics but had a greater proportional hippocampus experienced lower cognitive dysfunction at baseline compared to sCN. AD subjects with thicker entorhinal cortex showed less impairments in mean cognitive abilities at initial levels. Participants with AD who had larger ventricle volume proportionate to the head size had significantly greater mean scores on ADAS-Cog 13 compared to sCN adjusting for other covariates. However, volumetric or thickness measurements of the brain showed similar effect on the rate of change in mean cognitive abilities across all groups except for pMCI subjects with respect to their VEV/ICV. Indeed, ventricles enlargement had a greater effect on the rate of increase in ADAS-Cog 13 scores (greater impairment) among pMCI patients relative to individuals with different cognitive status with the same attributes ($\hat{\beta} = 0.04, p < 0.05$).

Table 6: Longitudinal effect of structural brain variables on ADAS-Cog 13

Covariates	Model I	Model II	Model III
Cognitive status	HCV/ICV	ERC	VEV/ICV
pCN	0.53(8.78)	-1.08(4.28)	-1.19(3.61)
sMCI	18.50(4.16)***	12.58(2.53)***	8.13(1.32)***
pMCI	15.98(4.15)**	13.55(2.28)***	10.00(1.49)***
AD	25.95(3.76)***	22.60(2.26)***	15.30(1.38)***
Time	0.13(0.11)	-0.02(0.08)	-0.05(0.03)
Brain variable	-6.29(6.06)	-0.004(0.004)	0.62(0.35)
Brain variable*Time	-0.30(0.23)	0.00003(0.0002)	0.02(0.01)
Cognitive status*Brain variable			
pCN	3.96(19.83)	0.01(0.01)	1.58(1.44)
sMCI	-25.69(9.29)*	-0.01(0.01)	-0.04(0.46)
pMCI	-11.86(9.90)	-0.01(0.01)	0.53(0.50)
AD	-20.62(8.82)*	-0.01(0.01)*	1.15(0.45)*
Cognitive status*Time			
pCN	0.43(0.30)	0.41(0.19)*	0.12(0.13)
sMCI	0.12(0.17)	0.05(0.12)	0.02(0.06)
pMCI	0.16(0.16)	0.35(0.10)**	0.15(0.06)*
AD	0.07(0.17)	0.32(0.12)*	0.28(0.07)***
Cognitive status*Brain variable * Time			
pCN	-0.76(0.72)	-0.001(0.001)	0.004(0.04)
sMCI	-0.16(0.40)	0.0001(0.0003)	0.02(0.02)
pMCI	0.34(0.40)	-0.0001(0.0003)	0.04(0.02)*
AD	0.87(0.44)	0.0004(0.0004)	0.02(0.02)

sCN: stable control normal, pCN: progressed control normal, sMCI: stable mild cognitive impairment, pMCI: progressed MCI, AD: Alzheimer's disease, HCV/ICV: proportional hippocampus volume to ICV, ERC: entorhinal cortex, VEV/ICV: proportional ventricles volume to ICV, ICV: intracranial volume. * p <0.05. Model I, II, and III test the effect of each structural brain variable on ADAS-Cog 13 separately. Each model adjusted for centered age, gender, APOE-ε4, and education.

3.5 MCI sub-groups

Based on model fit statistics as described in the statistical analysis section, a model with 3 groups and linear trends in all groups was selected as a best fitting model in the latent class growth analysis. Figure 5 depicts the pattern of mean scores on FAQ of each group where the dashed and solid lines represented predicted and actual trend of mean FAQ scores over time. Regarding the initial levels and trends of FAQ over time (greater scores on FAQ represents greater impairment in IADL performance), groups were labeled as normal, mildly impaired and impaired in terms of their performance of IADL. It is notable that subjects in mildly impaired and impaired groups with greater mean scores at baseline showed an increase in level of difficulties of performing IADL over time, although subjects in the normal group had the lowest scores on FAQ and preserved the same level of activities over time.

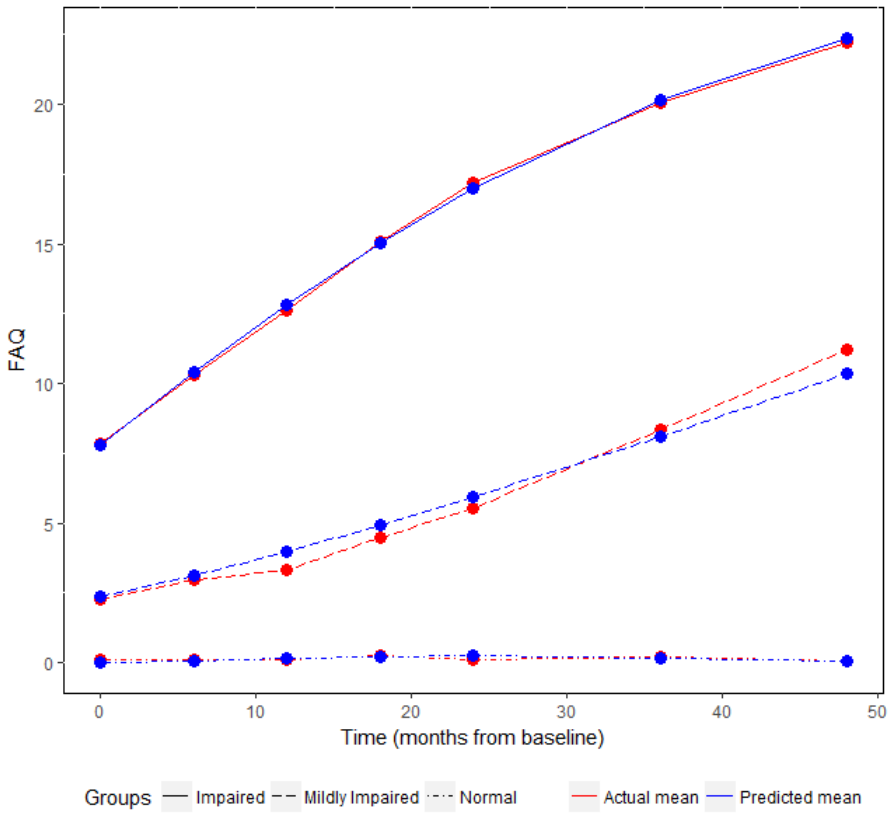

Figure 5: FAQ trajectories over time

Table 7 provides information on the distribution of subjects with different cognitive

status (which were defined based on changes in status over time as presented in previous sections) over these 3 IADL-based groups. While there was some concordance between cognitive status and IADL-based groups, the distribution suggests that the FAQ trajectories were also contributing complementary information. For instance, 35 individuals with sMCI based on cognitive status were identified as part of the normal FAQ trajectory group. In total, approximately 25% of the FAQ trajectory groups were discordant with the cognitive status groups.

Table 7: Distribution of sCN and MCI subjects over different groups

Group	Cognitive status			
	sCN	sMCI	pMCI	Total
Normal	187	35	0	222
Mildly impaired	10	89	56	155
Impaired	0	25	85	110
Total	197	149	141	487

Table 8 presents baseline characteristics of subjects in different IADL-based groups. It is evident that groups differed in baseline attributes except for age, gender, and education. For example, not only did mildly impaired and impaired groups have greater baseline mean scores on ADAS-Cog 13 and FAQ compared to the normal IADL-based group, but they were also different from one another in baseline mean ADAS-Cog 13 and FAQ. Generally groups also differed in their baseline mean of structural brain variables, although they only differed from one another in baseline mean of hippocampus volume.

Table 8: Baseline characteristics stratified by groups based on functional abilities

Group	Normal	Mildly impaired	Impaired
Variable	Mean (standard deviation)		
Age	75.9(5.5)	74.8(6.9)	74.4(7.6)
Male, %	41.2	35.3	23.5
Education attainment, year	16.0(2.9)	15.9(3.1)	16.0(2.8)
APOE-ε4 carrier*, %	28.4	40.4	31.2
ADAS-Cog 13**	10.1(4.8)	18.5(5.8)	21.8(5.8)
FAQ**	0.1(0.4)	2.1(2.2)	8.0(5.1)
WBV*, cm^3	1006.8(102.2)	1005.1(104.7)	975.3(115.3)
HCV**, cm^3	7.2(0.9)	6.4(1.1)	6.1(0.9)
VEV * , cm^3	35.4(19.5)	44.6(23.4)	50.4(27.3)
ERC*, cm	379.3(65.5)	321.6(72.5)	310.1(73.5)

HCV: hippocampus volume, ERC: entorhinal cortex, VEV: ventricles volume. * General difference between groups accounting for each variable, ** both general and paired difference between groups accounting for each variable, p < 0.05

Further, to assess if the classification of individuals based on their performance of IADL could improve the characterization of MCI subjects, Table 9 provided information on two models: Model 1 explored the change in ADAS-Cog 13 among individuals with different cognitive status (as previously presented in section 2.4), while Model 2 studied the change in ADAS-Cog 13 over IADL-based groups identified from the latent class growth analysis. Both models adjusted for centered age, gender, education, and APOE-ε4 carriers. As presented in Table 9, most of the estimated parameters in both models were similar in terms of magnitudes and significance except for the coefficients of interaction terms with time. For instance, while the rate of increase in mean ADAS-Cog 13 over time was significant among subjects in the impaired IADL-based group ($\hat{\beta} = 0.97, p = 0.002$), it was small and non-significant among sMCI participants ($\hat{\beta} = 0.37, p = 0.27$). These results were expected, since there was an overlap between sMCI and pMCI over IADL groups. Comparing models, the -2 log likelihood statistics of Model 1 was smaller than Model 2 (12521 vs 12575) which indicated that Model 1 fitted the data better than Model 2.

Table 9: Comparison between two different classification of MCI group

Model 1 (Status)			Model 2 (IADL-based group)		
Covariates			Covariates		
Group	Estimated parameter (SE)	p-value	Group	Estimated parameter (SE)	p-value
sMCI	11.03(7.56)	0.14	Mildly impaired	11.84(7.81)	0.13
pMCI	27.52(7.69)**	0.0004	Impaired	23.85(8.21)**	0.004
Time	0.34(0.19)	0.07	Time	0.32(0.18)	0.08
Education	-0.22(0.07)**	0.004	Education	-0.23(0.08)**	0.003
WBV/ICV	-0.07(0.07)	0.35	WBV/ICV	-0.07(0.07)	0.31
WBV/ICV*Time	-0.01(0.003)	0.06	WBV/ICV*Time	-0.005(0.003)	0.08
Group*WBV/ICV			Group*WBV/ICV		
sMCI	-0.05(0.12)	0.70	Mildly impaired	-0.06(0.12)	0.6
pMCI	-0.25(0.12)*	0.04	Impaired	-0.20(0.13)	0.12
Group*Time			Group*Time		
sMCI	0.37(0.33)	0.27	Mildly impaired	0.98(0.30)**	0.001
pMCI	1.26(0.29)***	<.0001	Impaired	1.18(0.35)**	0.001
Group*WBV/ICV * Time			Group*WBV/ICV* Time		
sMCI	-0.005(0.01)	0.38	Mildly impaired	-0.01(0.005)*	0.01
pMCI	-0.02(0.005)**	0.001	Impaired	-0.01(0.01)*	0.01

HCV: hippocampus volume, ERC: entorhinal cortex, VEV: ventricles volume, ICV: intracranial volume. * p <0.05. HCV and VEV were proportional to ICV. Each model studies the change on ADAS-Cog 13 over time adjusting for centered age, gender, APOE-ε4, and education. Model 1 included cognitive status, while Model 2 was built based on IADL-based groups. Both models adjusted for centered age, gender, education, and APOE-ε4 carriers.

4 Discussion

This study explored the association between global and regional structural brain measurements and cognitive abilities across different groups with stable or progressed cognitive status. The results show that cognitive abilities decreased over time in all groups, and the rate of decline was greater among individuals in all groups relative to sCN participants. It was also revealed that brain volume affected the rate of change in cognition across all groups. Importantly, the rate of decline in cognition over time among pMCI and AD subjects differed from other groups, such that greater proportional brain volume might have the greater moderating effect on rate of cognitive impairments over time in pMCI and AD groups. Moreover, at baseline, cognition was associated with entorhinal cortex thickness and ventricles volume in the AD group, but it was correlated with hippocampus volume in sMCI and AD groups. Of all five groups, in the pMCI group, ventricles enlargement showed a greater effect on the rate of decline in cognitive abilities over time relative to other groups.

Looking at baseline differences between all groups with the sCN group, we concluded that subjects in all groups except for the pCN group showed greater baseline cognitive dysfunctions relative to sCN. In addition, decline in cognitive abilities in sMCI were slightly steeper than sCN individuals over time. In contrast to our findings, Jack Jr et al. (2008) observed a constant pattern in cognitive abilities in the CN group and very slight increase in cognition in the sMCI over time. This inconsistency in results can be explained by different psychological tests which were used in assessing cognition over time. While we used ADAS-cog 13 which is commonly used in clinical trials to detect changes in cognition over time, Jack Jr et al. (2008) used MMSE, which has been shown to be poor in detecting changes over time. Moreover, we included brain volume in the models. In contrast, previous authors assessed the pattern of decline in cognition and brain volume in separate models.

Our findings on the baseline and longitudinal association between cognitive abilities and structural brain variables are consistent with the literature. This study revealed that both baseline and rate of decline in cognition depended on WBV/ICV in participants

with AD, and the impact of brain volume on rate of decline in cognition among AD individuals was different from other groups. AD patients with smaller proportional brain volume had greater initial score on ADAS-Cog 13 implying greater impairment. They also experienced steeper decline in cognition over time compared to their counterpart with greater WBV/ICV. Similarly, Nestor et al. (2008) and Ridha et al. (2008) detected that lower cognitive functioning was associated with smaller brain volume among AD patients. Evans et al. (2010) declared that change in whole brain and ventricles volume correlated with change in cognition in MCI and AD individuals comparing two time points (over a year). However, the authors tested the change in general cognition in MCI including both converters and non-converters in the same group. In contrast, this study was able to assess changes in cognition for stable MCI separately from MCI who progress to AD.

In this current study, AD participants showed decline in their cognitive abilities over time with the different rate depending on their whole brain but not their ventricles volume. We also detected the decreasing pattern in cognition over time relating to whole brain and ventricles volume among pMCI subjects but not in the sMCI. Similar to our study, Jack Jr et al. (2008) also found that general cognitive abilities decreased noticeably over time in the pMCI group, however, the authors did not control for the effect of structural brain measurements on cognitive abilities.

Our study did not detect any association between hippocampus volume and entorhinal cortex thickness and cognitive dysfunction over time. However, sMCI and AD individuals with greater hippocampus and AD subjects with thicker entrohinal cortex displayed less cognitive dysfunction at baseline compared with sCN individuals. We did not see any baseline association between ADAS-Cog 13 and any brain regions among pMCI individuals. Results are in contrast to a study by Jack Jr et al. (1999) in which authors reported the association between baseline hippocampus atrophy and risk of progression to AD among MCI. However, our study was focused on describing characteristics of different cognitive status groups, rather than predicting those who progress to AD. Indeed, in our study, we explored the effect of regional brain measurements on general cognitive abilities. Thus, this inconsistency between studies implies that hippocampus may affect specific domains

of cognitive abilities which may contribute to progression to AD. This is supported by a study by Mungas et al. (2005) in which longitudinal change in hippocampus volume was associated with changes in memory.

Our secondary objective was to explore the effect of education on cognitive dysfunction. We detected that after controlling for individual differences in age, gender, APOE-ε4 carrier status, and cognitive status, education was associated with initial cognitive abilities. Indeed, participants with higher education displayed less impairment in baseline cognition. In addition, similar to a study by Wilson et al. (2009) education in our study did not affect decline in cognition over time. Moreover, education did not moderate the association between whole brain volume and ADAS-Cog 13 in this study. In contrast, Perneczky et al. (2009) revealed that education modified the association between change in brain pathology and cognitive abilities in AD. However, the authors examined the relationship between medial temporal lobe atrophy (a part of the brain) and general cognition among AD. Whole brain volume as well as regional brain volume was assessed in this study. Thus, the inconsistent findings may stem from the fact that education attainment might affect particular brain regions and their relationship with cognitive changes. In addition, global or regional brain measurements may be associated with sub-domains of cognitive abilities rather than general cognition, or we may need to adjust for other factors to see the effect of education. Importantly, the ADNI1 inclusion criteria adjusted for education in their calculation of the logical memory II sub-scale from the Wechsler Memory Scale. Thus, in order to avoid inflating the effect of education on ADAS-Cog 13 in our analysis, we excluded individuals in which their particular years of education attainment affected the cutoff scores on the memory test. As this was a relatively small proportion of our sample size (14%), this is unlikely to affect our results.

Our third objective was to find a methodology to better characterize MCI sub-classes. Using a latent class growth curve model, we classified MCI individuals into three groups based on their performance of IADLs: normal, mildly impaired, and impaired. Participants in the mildly impaired group differed from normal and impaired subjects both at initial levels and over time. In addition, IADL-based groups were different from one another

based on baseline ADAS-Cog 13, FAQ, and structural brain measurements. IADL-based group showed concordance with groups based on cognitive status (stable or progressed) but also provided some complementary information regarding their FAQ trajectories. Although this classification did not perfectly match with cognitive groups, it detected some interesting results studying change in cognitive abilities over different IADL-based and cognitive status groups in two separate models. Estimated parameters were approximately the same in the two models at baseline regarding their magnitude and significance level, and inconsistency between the models were observed for estimation of ADAS-Cog 13 over time. Notably, both pMCI and impaired groups in the two models showed larger baseline impairment in cognition relative to reference groups (sCN/ normal), and they had steeper decline in cognition over time.

Although a model including IADL-based groups was not statistically preferable to a model including cognitive status which classified MCI individuals based on the progression of the disease, the latter classification requires the follow-up of participants for a longer period of time. Moreover, baseline and FAQ trajectories of IADL-based groups depicted that subjects in the mildly impaired group had the initial mean scores on FAQ around 2 which did not match clinical criteria of functional impairments (FAQ $\geq$ 9 is regarded as impaired (Pérès et al., 2008)). However, their IADL performance impaired gradually over time until it reached the clinical criteria of FAQ$\geq$ 9. In addition, about 60% of pMCI subjects were classified in the impaired group with baseline mean FAQ scores of 8, which is close to the clinical criteria. Thus, although these two groups did not meet the FAQ criteria at baseline, there is not a consensus on cutoff points for FAQ to specify functional impairments. Our results imply that baseline functional assessments may help to distinguish at-risk individuals at an earlier stage. Results are consistent with previous studies examining the role of functional assessment and its association with conversion to AD (Pérès et al., 2008; Rozzini et al., 2007; Burton et al., 2009).

In this study, we directly investigated the relationship between cognitive abilities and structural brain measurements and the effect of brain variables on the rate of change in cognition over time across groups with distinct cognitive status. However, this study

also has some limitations. Firstly, MCI group just contained participants with amnestic MCI, and we did not explore subjects at an earlier stage of disease such as exploring subjects at transitional stages between cognitively normal and MCI. Secondly, we focused on the association between general cognitive abilities and global brain volume, as well as three specific regional brain measurements. Over some groups, we saw a similar effect of these structural brain variables on cognition, which is in contrast with the literature. These inconsistencies might be because the general cognition or its sub-domains may be associated with particular brain regions distinctly over different AD stages. Thirdly, to meet the normality assumption, we used square root transformation to adjust for the normality of the outcome. Despite the fact that the transformed data were technically a better fit, the results were generally consistent in terms of the significance level and the direction regardless whether the outcome was transformed or not. In addition, due to the complexity of the models, it was complicated to back-transform the estimated parameters and compare them with non-transformed estimations with respect to their magnitudes. Lastly, in characterizing MCI participants, we used FAQ scores to assess general IADL performance, although sub-domains of IADL (such as financing) as well as other factors (such as executive functioning) or combination of these factors may more precisely distinguish between MCI individuals, and especially those at-risk of progression to AD. Further research is needed to clarify the association between general and sub-domains of cognitive abilities and structural brain variables and their effect on changes in cognition over time across AD stages, particularly at earlier stage.

In conclusion, this study reveals that cognitive abilities decreased over time across different groups with stable or progressed cognitive status, and the rate of decline in cognition was greater in all groups relative to sCN participants. Importantly, the rate of change in cognition depended on whole brain volume across all groups. However, it had a greater effect in the pMCI and AD groups compared to the sCN group. Indeed, the rate of decline in cognitive abilities was accelerated with the greater magnitude by decrease in brain volume among individuals in the pMCI and AD groups relative to sCN participants. Ventricle enlargement in the pMCI group also accelerated the rate of decline in

cognitive abilities with the greater magnitude compared to the sCN group. Results highlight the importance of different brain regions on cognition. Future research should further investigate these differential effects. In addition, baseline cognition was associated with both entorhinal cortex thickness and ventricles volume in AD group, and it was affected differently by hippocampus volume both in sMCI and AD groups. Lastly, based on assessment of functional abilities at baseline, this study demonstrated an efficient methodology to identify MCI subjects who are most at-risk for cognitive impairment progression in hopes to be better equipped to slow or stop cognitive impairment progression.

5 SAS codes

```
libname t 'C:\Users\Fatemeh\Dropbox\SAS results';
/* Extract the data were collected throughout ADNI1   */
data t.adni_1;
set t.adnimerge;
where colprot='ADNI1';
Time=m;

Entorhinal=Entorhinal*0.1;
Entorhinal_bl=Entorhinal_bl*0.1;
Fusiform=Fusiform*0.001;
Fusiform_bl=Fusiform_bl*0.001;
Hippocampus=Hippocampus*0.001;
Hippocampus_bl=Hippocampus_bl*0.001;
ICV=ICV*0.001;
ICV_bl=ICV_bl*0.001;
MidTemp=MidTemp*0.001;
MidTemp_bl=MidTemp_bl*0.001;
Ventricles=Ventricles*0.001;
Ventricles_bl=Ventricles_bl*0.001;
WholeBrain=WholeBrain*0.001;
WholeBrain_bl=WholeBrain_bl*0.001;

if icv not in (., 0) then do;
bv=100*wholebrain/icv;
hipo=100*hippocampus/icv;
ven=100*ventricles/icv;
end;
if dx in (1,7,9) then tr=1;
```

```
else if dx in (2,4,8) then tr=2;
else if dx in (3,5,6) then tr=3;

if dx_bl in (3,4) then dx_b=2;
else if dx_bl=1 then dx_b=1;
else if dx_bl=5 then dx_b=3;

if apoe4 in (1, 2)then apoe4=1;
else if apoe4=0 then apoe4=0;

run;

** Creating a variable illustrates participants' cognitive status\\
data dx;
        set t.adni_1;
        where dx ne .;
        keep rid dx_bl dx_b time dx tr;
run;

**Create a dummy variable st: st=1 stable st=0 unstable for\\
 each subject for each visit
proc sort data=dx;
by rid;
run;
data tt;
set dx;
by rid;
if dx_b ne tr then st=0;
else st=1;
```

```
run;

/** Calculate the min of st for each
 subject over all visits (a time-invariant variable)**/
proc sort data=tt;
by rid;
run;
proc summary data=tt min;
by rid;
var st;
output out=mtt(drop=_type_ _freq_) min=mst;
run;

/** Add mst to the main data to the desired variable **/
proc sort data=mtt;
by rid;
run;
proc sort data=dx;
by rid;
run;
data dx_track;
merge dx mtt;
by rid;
run;
proc contents data=dx_track; run;
/**Making the new variable "STATUS" with 6 levels**/
data dx_track;
set dx_track;
     if mst=1 and dx_b=1 then status=1;
```

```
else if mst=0 and dx_b=1 then status=2;
else if mst=1 and dx_b=2 then status=3;
else if mst=0 and dx_b=2 then status=4;
else if mst=1 and dx_b=3 then status=5;
else if mst=0 and dx_b=3 then status=6;
run;

proc sort data=dx_track;
by rid;run;

proc sort data=t.adni_1;
by rid;run;

data t.adni_1;
merge t.adni_1 dx_track(keep= rid status);
by rid;
run;

/* Removing subjects who revert back to CN, MCI, or AD */

proc sort data=t.adni_1;
by rid dx_bl time;run;

data t.adni_f;
set t.adni_1;
if rid in (112,168,188,205,384,422,443,551,668,669,722,
1092,1168,1188,1245,1352,1408, 429,1241,162,167,
1009,138,702,699) then delete;
run;
```

```
/* Assigning  a random number to each subject */
proc sort data=t.adni_f;
by rid ;
run;

data t.adni_f;
set t.adni_f;
by rid ;
if (first.rid=1) then U=ranuni(23407);
retain U;
run;

/*Excluding subjects with memory scores equal to cutoff points **/
data test1;
set t.neurobat;
where colprot='ADNI1' and viscode not in ('f','uns1');
keep rid viscode ldeltotal ;
run;

data test1;
set test1;
if viscode='bl' then delete;
run;
data test1;
set test1;
if viscode='sc' then viscode='bl';
run;
```

```
data t.adni_f;
set t.adni_f;
ch=rid;run;

proc sort data=t.adni_f;
by rid viscode;
run;

proc sort data=test1;
by rid viscode;
run;

data edu;
merge t.adni_f test1(keep= rid viscode ldeltotal);
by rid viscode;
run;
data edu;
set edu;
where rid=ch;run;

data test;
set edu;
where time=0;
if LDELTOTAL in (8,9)and mmse>=24 and mmse<=30
and pteducat>=16 then delete=1;
else if LDELTOTAL in (2,3) and mmse>=24 and mmse<=30
and pteducat>=0 and pteducat<=7 then delete=1;
else if LDELTOTAL in (5,4) and mmse>=24 and mmse<=30
and pteducat>=8 and pteducat<=15 then delete=1;
```

```
run;

proc sort data=test;
by rid;
run;
proc sort data=edu;
by rid;
run;
data test0;
merge edu test(keep=rid delete);
by rid;
run;

data test_1;
set test0;
where delete=.;
run;

data test_1;
set test_1;
where status ne . and time ne .;
run;

data t.adni_r;
set test_1;
drop delete;
run;

/**Discriptive analysis**/
```

```
proc sort data=t.adni_f;
by rid dx_bl status time;run;

proc freq data=t.adni_f;
tables status*time/nocol norow nopercent missing;
run;
proc freq data=t.adni_f;
where time=0;
/**apoe4*status***/
tables ptgender*status/norow nopercent missing chisq ;
run;
proc anova data=t.adni_f;
where time=0;
class status;
/**education, adas13, faq, whole brain,
 hippocampus, ventricles, entorhinal**/
model age=status;
means status;
means status/tukey;
run;
/***Centering age at grand mean****/
proc means data=t.adni_f;
where time=0;
var age;
run;
data t.adni_f;
set t.adni_f;
c_age=age-75.2;
run;
```

```
proc means data=t.adni_r;
where time=0;
var age;
run;
data t.adni_r;
set t.adni_r;
c_age=age-75.3;
run;

/*** Baseline association ***/
proc glm data=t.adni_f;
where time=0 and v1='1.5 Tesla MRI';
class status(ref='1') ptgender(ref='Male');
/***apoe4, whole brain, hippocampus, ventricles, entorhinal**/
model adas13=c_age ptgender  pteducat status /ss3 solution;
run;
/**Time plot of mean ADAS-Cog 13**/
proc sort data=t.adni_r;
by  status time;
run;
proc means data=t.adni_r mean nway noprint;
where v1='1.5 Tesla MRI';
class status time;
var adas13;
output out=ad mean=ad_mean;
run;
ods listing gpath="C:\Fatemeh\Latex";
 axis1 label = (angle=90 "Time(month)" f= 'times new roman');
 axis2 label = (angle=90 "ADAS-Cog 13 mean" f= 'times new roman');
```

```
symbol1 i = j value = star  c = blue  h = 1 line = 1 width = .8 l=2;
symbol2 i = j value = circle  c = green  h = 1 line = 1 width = .8 l=10;
symbol3 i = j value =diamond   c =yellow h = 1 line = 1 width = .8 l=18;
symbol4 i = j value = square   c = orange h = 1 line = 1 width = .8 l=26;
symbol5 i = j value = plus   c = red   h = 1 line = 1 width = .8 l=30;
proc gplot data=ad;
where time<=36;
plot ad_mean*time=status/vaxis=axis2;
run;
 proc sgpanel data=t.adni_r noautolegend;
 where time<=36 and u>0.95  ;
 panelby Status/   rows=2 columns=3 ;
series x=time y=adas13/group=rid lineattrs=(color=grey
pattern=1 thickness=1);
series x=time y=ad_mean/ LineAttrs= (pattern=1 color="blue"
 thickness=4);
format status status.;
 rowaxis  label="ADAS-Cog 13";
run;
/**Covariance structure ***/
proc mixed data=t.adni_r  covtest  method=ml maxiter=1000 maxfunc=5000 ;
where v1='1.5 Tesla MRI';
 class  m status(ref='1') ptgender(ref='Male')  apoe4(ref='0');
 model adas13= c_age ptgender  apoe4 status time pteducat bv bv*time
 status*time status*bv status*bv*time;
 repeated m/subject=rid  rcorr ;
ods output FitStatistics=FitFix (rename=(value=Fix))
FitStatistics=FitFixp;
 run;
```

```
 proc mixed data=t.adni_r covtest  method=ml maxiter=1000 maxfunc=5000 ;
where v1='1.5 Tesla MRI';
 class  m status(ref='1') ptgender(ref='Male')  apoe4(ref='0');
 model adas13= c_age ptgender  apoe4 status time pteducat
 bv bv*time  status*time status*bv status*bv*time;
 random int  /subject=rid ;
 repeated m/subject=rid  rcorr ;
ods output FitStatistics=Fitmix (rename=(value=mix))
FitStatistics=Fitmixp;
 run;
 proc mixed data=t.adni_r covtest  method=reml maxiter=1000 maxfunc=5000 ;
where v1='1.5 Tesla MRI';
 class  m status(ref='1') ptgender(ref='Male')  apoe4(ref='0');
 model adas13= c_age ptgender  apoe4 status time pteducat
  bv bv*time  status*time status*bv status*bv*time;
 random int  /subject=rid ; /***time, int time**/
 repeated m/subject=rid  rcorr ;
 /*Fitint, Fittime, Fitinttime**/
ods output FitStatistics=Fitmix (rename=(value=mix))
FitStatistics=Fitmixp;
 run;

ods csv file='C:\Fatemeh\SAS analysis\model comparison.csv';
 data fits;
merge FitFix Fitmix Fitint Fittime Fitinttime;
by descr;
run;
ods csv close;
```

```
 proc mixed data=t.adni_r covtest  method=reml maxiter=1000 maxfunc=5000 ;
where v1='1.5 Tesla MRI';
 class  m status(ref='1') ptgender(ref='Male')  apoe4(ref='0');
 model adas13= c_age ptgender  apoe4 status time pteducat
  bv bv*time  status*time status*bv status*bv*time;
 random int  time/subject=rid  type=un; /***time, int time**/
 /** un,csh, arh(1), toeph(1)**/
 repeated m/subject=rid type=ar(1) rcorr ;
 run;
 /** Latent class growth curve analysis **/
 data adni;
set t.adni_r;
     if time=0  then t=1;
else if time=6  then t=2;
else if time=12 then t=3;
else if time=18 then t=4;
else if time=24 then t=5;
else if time=36 then t=6;
else if time=48 then t=7;
else t=.;
run;

data adni;
set adni;
where t ne . ; run;
proc sort data=adni;
by rid status t  ;
run;
proc transpose data=adni out=t.faq prefix=fa;
```

```
by rid status ;
var faq;
id t;
run;

proc transpose data=adni out=t prefix=t;
by rid  ;
var time;
id time;
run;

data t;
set t;
m1=t0; m2=t6; m3=t12;
m4=t18; m5=t24; m6=t36; m7=t48;
drop _NAME_;
run;

proc sort data=t.faq;
by rid;
run;
proc sort data=t;
by rid;
run;
data t.faq;
merge t.faq(drop=_NAME_) t;
by rid;
run;
```

```
proc traj data=t.faq out=out outstat=os outplot=op;
where status not in (2,5);
id rid;
var fa1-fa7;
Indep m1-m7;
Model cnorm;
min 0;
max 30;
Ngroups 3;
order   1 1 1  ;
run;
 %trajplot ( op, os, ,,'FAQ',' Time(month)');
```

References

Alzheimer's Association. (n.d.). *What is Alzheimer's?* (Tech. Rep.). (Retrived from `http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp`)

Andruff, H., Carraro, N., Thompson, A., Gaudreau, P., & Louvet, B. (2009). Latent class growth modelling: a tutorial. *Tutorials in Quantitative Methods for Psychology*, *5*(1), 11–24.

Backman, L., Jones, S., Berger, A. K., Laukka, E. J., & Small, B. J. (2004). Multiple cognitive deficits during the transition to Alzheimer's disease. *Journal of Internal Medicine*, *256*, 195–204.

Burton, C. L., Strauss, E., Bunce, D., Hunter, M. A., & Hultsch, D. F. (2009). Functional abilities in older adults with mild cognitive impairment. *Gerontology*, *55*(5), 570–581.

Busse, A., Hensel, A., Guhne, U., Angermeyer, M., & Riedel-Heller, S. (2006). Mild cognitive impairment long-term course of four clinical subtypes. *Neurology*, *67*, 2176–2185.

Cardenas, V., Chao, L., Studholme, C., Yaffe, K., Miller, B., Madison, C., ... Weiner, M. (2011). Brain atrophy associated with baseline and longitudinal measures of cognition. *Neurobiology of Aging*, *32*(4), 572–580.

Chertkow, H., Feldman, H., Jacova, C., & Massoud, F. (2013). Definitions of dementia and predementia states in alzheimer's disease and vascular cognitive impairment: consensus from the canadian conference on diagnosis of dementia. *Alzheimer's Research and Therapy*, *5(Suppl 1)*(S2).

Connor, D., & Sabbagh, M. (2008, November). Administration and scoring variance on

the ADAS-Cog. *Journal of Alzheimer's Disease*, *15*(3), 461–464.

Cosentino, S., Scarmeas, N., Helzner, E., Glymour, M., Brandt, J., Albert, M., ... Stern, Y. (2008). Apoe $\varepsilon 4$ allele predicts faster cognitive decline in mild alzheimer disease. *Neurology*, *70*(19 Part 2), 1842–1849.

Courchesne, E., Chisum, H. J., Townsend, J., Cowles, A., Covington, J., Egaas, B., ... Press, G. (2000, September). Normal brain development and aging: quantitative analysis at in vivo mr imaging in healthy volunteers. *Radiology*, *216*(3), 672–682.

Curran, P., Obeidat, K., & Losardo, D. (2010). Twelve frequently asked questions about growth curve modeling. *Journal of Cognition and Development*, *11*(2), 121–136.

Driscoll, I., Davatzikos, C., An, Y., Wu, X., Shen, D., Kraut, M., & Resnick, S. (2009). Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology*, *72*(22), 1906–1913.

Evans, M., Barnes, J., Nielsen, C., Kim, L., Clegg, S., Blair, M., ... Alzheimer's Disease Neuroimaging Initiative (2010). Volume changes in alzheimer's disease and mild cognitive impairment: cognitive associations. *European Radiology*, *20*(3), 674–682.

Farias, S. T., Mungas, D., Reed, B. R., Harvey, D., & DeCarli, C. (2009). Progression of mild cognitive impairment to dementia in clinic-vs community-based cohorts. *Archives of neurology*, *66*(9), 1151–1157.

Fischer, C. (2002, June). A clinician's guide to interpreting cognitive measures in clinical trials for alzheimer's disease. *Bulletin of Canadian Psychiatric Association*, *34*(3), 16–18.

Fitzmaurice, G. M., Laird, N. M., & Ware, J. H. (2012). *Applied longitudinal analysis* (Vol. 998). John Wiley & Sons.

Franklin, B., Creighton, H., & Beach, B. (2014, November). *Rising from the ashes: The role of older workers in driving eurozone recovery* (Tech. Rep.). International Longevity Centre-UK. Retrieved from International Longevity Centre-UK Web site: `www.ilcuk.org.uk/files/ILC_Rising_from_the_ashes_(final).pdf`.

Harada, C. N., Natelson Love, M. C., & Triebeld, K. (2013). Normal cognitive aging. *Clinics in Geriatric Medicine*, *29*(4), 737–752. (Doi: 10.1016/j.cger.2013.07.002)

Ho, A., Hua, X., Lee, S., Leow, A., Yanovsky, I., Gutman, B., ... the Alzheimer's Disease Neuroimaging Initiative Laboratory of Neuro Imaging (2010). Comparing 3 T and 1.5 T MRI for tracking Alzheimer's Disease progression with tensor-based morphometry. *Human Brain Mapping*, *31*(4), 499–514.

Jack Jr, C., Barnes, J., Bernstein, M., Borowski, B., Brewer, J., Clegg, S., ... Weiner, M. (2015). Magnetic resonance imaging in ADNI. *Alzheimer's and Dementia the journal of the Alzheimer's Association*, *11*(7), 740–756.

Jack Jr, C., Bernstein, M. A., Borowski, B. J., Gunter, J. L., Fox, N. C., Thompson, P. M., ... the Alzheimer's Disease Neuroimaging Initiative (2010, May). Update on the magnetic resonance imaging core of the alzheimer's disease neuroimaging initiative. *Alzheimer's and Dementia the journal of the Alzheimer's Association*, *6*(3), 212–220.

Jack Jr, C., Petersen, R. C., Xu, Y. C., O'Brien, P. C., Smith, G. E., Ivnik, R. J., ... Kokmen, E. (1999). Prediction of ad with mri-based hippocampal volume in mild cognitive impairment. *Neurology*, *52*(7), 1397–1397.

Jack Jr, C., Weigand, S. D., Shiung, M., Przybelski, S. A., O'Brien, P., Gunter, J., ... Petersen, R. (2008). Atrophy rates accelerate in amnestic mild cognitive impairment. *Neurology*, *70*(19 Part 2), 1740–1752.

Jacqmin-Gadda, H., Fabrigoule, C., Commenges, D., & Dartigues, J. (1997). A 5-year longitudinal study of the mini-mental state examination in normal aging. *American Journal of Epidemiology*, *145*, 498–506.

Jekel, K., Damian, M., Wattmo, C., Hausner, L., Bullock, R., Connelly, P., ... Frolich, L. (2015). Mild cognitive impairment and deficits in instrumental activities of daily living: a systematic review. *Alzheimer's Research & Therapy*, *7*(17), 1–20. (DOI 10.1186/s13195-015-0099-0)

Jones, B. L., Nagin, D. S., & Roeder, K. (2001). A sas procedure based on mixture models for estimating developmental trajectories. *Sociological methods & research*, *29*(3), 374–393.

Karp, A., Kareholt, I., Qiu, C., Bellander, T., Winblad, B., & Fratiglioni, L. (2004). Rela-

tion of education and occupation-based socioeconomic status to incident Alzheimer's Disease. *American Journal of Epidemiology*, *159*(2), 175–183.

Kimbler, K. J. (2013). Everyday problem solving and instrumental activities of daily living: Support for domain specificity. *Behavioral Sciences*, *3*(1), 170–191.

Koepsell, T. D., & Monsell, S. E. (2012). Reversion from mild cognitive impairment to normal or near-normal cognition risk factors and prognosis. *Neurology*, *79*(15), 1591–1598.

Lindsay, J., Laurin, D., Verreault, R., Hébert, R., Helliwell, B., Hill, G., & McDowell, I. (2002). Risk factors for alzheimer's disease: a prospective analysis from the canadian study of health and aging. *American Journal of Geriatric Pharmacotherapy*, *156*(5), 445–453.

Lipnicki, D., Sachdev, P., Crawford, J., Reppermund, S., Kochan, N., Trollor, J., ... Brodaty, H. (2013). Risk factors for late-life cognitive decline and variation with age and sex in the sydney memory and ageing study. *PLoS ONE*, *8*(6), e65841. (doi:10.1371/journal.pone.0065841)

Manning, E., Barnes, J., Cash, D., Bartlett, J., Leung, K., Ourselin, S., & Fox, N. (2014, May). APOEε4 is associated with disproportionate progressive Hippocampial atrophy in AD. *PLoS ONE*, *9*(5). (e97608) doi: 10.1371/journal.pone.0097608

Marshall, G., Olson, L., Frey, M., Maye, J., Becker, J. A., Rentz, D., ... Initiative, A. D. N. (2011). Instrumental activities of daily living impairment is associated with increased amyloid burden. *Dementia and Geriatric Cognitive Disorders*, *31*(6), 443–450. (doi: 10.1159/000329543)

Milanovic, Z., Pantelic, S., Trajkovic, N., Sporis, G., Kostic, R., & James, N. (2013). Age-related decrease in physical activity and functional fitness among elderly men and women. *Clinical Interventions in Aging*, *8*, 549–556.

Mohs, R., Knopman, D., Petersen, R., Ferris, S., Ernesto, C., Grundman, M., ... the Alzheimer's Disease Cooperative Study (1997). Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the alzheimer's disease assessment scale that broaden its scope. *Alzheimer Disease Associated Dis-*

orders, *11*(2), 13–21.

Mungas, D., Harvey, D., Reed, B., Jagust, W., DeCarli, C., Beckett, L., ... others (2005). Longitudinal volumetric mri change and rate of cognitive decline. *Neurology*, *65*(4), 565–571.

Nagin, D. S. (1999). Analyzing developmental trajectories: A semiparametric, group-based approach. *Psychological methods*, *4*(2), 139.

Nestor, S. M., Rupsingh, R., Borrie, M., Smith, M., Accomazzi, V., Wells, J. L., ... Initiative, A. D. N. (2008). Ventricular enlargement as a possible measure of alzheimer's disease progression validated using the alzheimer's disease neuroimaging initiative database. *Brain*, *131*(9), 2443–2454.

Perneczky, R., Wagenpfeil, S., Lunetta, K. L., Cupples, L. A., Green, R. C., DeCarli, C., ... Kurz, A. (2009). Education attenuates the effect of medial temporal lobe atrophy on cognitive function in alzheimer's disease: the mirage study. *Journal of Alzheimer's Disease*, *17*(4), 855–862.

Petersen, R., Aisen, P., Beckett, L., Donohue, M., Gamst, A., Harvey, D., ... Weiner, M. (2010). Alzheimer's disease neuroimaging initiative (adni), clinical characterization. *Neurology*, *74*, 201–209.

Petersen, R., Doody, R., Kurz, A., Mohs, R., Morris, J., Rabins, P., ... B., W. (2001). Current concepts in mild cognitive impairment. *Archives of Neurolgy*, *58*(12), 1985–1992. (doi:10.1001/archneur.58.12.1985)

Pfeffer, R. I., Kurosaki, T. T., Harrah, C. H. J., Chance, J. M., & Filos, S. (1982). Measurement of functional activities in older adults in the community. *Gerontology*, *37*(3), 323–329.

Plassman, B., Williams, J., Holsinger, T., & Benjamin, S. (2010). Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Annals of Internal Medicine*, *153*, 182–193.

Pérès, K., Helmer, C., Amieva, H., Orgogozo, J., Rouch, I., Dartigues, J. F., & Barberger-Gateau, P. (2008). Natural history of decline in instrumental activities of daily living performance over the 10 years preceding the clinical diagnosis of dementia:

A prospective population-based study. *Journal of the American Geriatrics Society*, *56*(1), 37–44.

Ridha, B. H., Anderson, V. M., Barnes, J., Boyes, R. G., Price, S. L., Rossor, M. N., ... others (2008). Volumetric mri and cognitive measures in alzheimer disease. *Journal of neurology*, *255*(4), 567–574.

Risacher, S. L., Shen, L., West, J. D., Kim, S., McDonald, B. C., Beckett, L. A., ... others (2010). Longitudinal mri atrophy biomarkers: relationship to conversion in the adni cohort. *Neurobiology of aging*, *31*(8), 1401–1418.

Ritchie, S., Dikie, D., Cox, S., Valdes Hernandez, M., Corley, J., Royle, N., ... Deary, I. (2015). Brain volumetric changes and cognitive aging during eight decades of life. *Human Brain Mapping*, *36*, 4910–4925.

Roberts, R., & Knopman, D. S. (2013). Classification and epidemiology of MCI. *Clinics in Geriatric Medicine*, *29*(4), 753–772.

Ronnlund, M., Nyberg, L., Backman, L., & Nilsson, L. (2005). Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study. *Psychology and Aging*, *20*(1), 3–18.

Rosen, W., Mohs, R., & Davis, K. (1984, November). A new rating scale for Alzheimer's disease. *The American Journal of psychiatry*, *141*(11), 1356–1364.

Royle, N., Booth, T., Valdés Hernández, M., Penke, L., Murray, C., Gow, A., ... Wardlaw, J. (2013). Estimated maximal and current brain volume predict cognitive ability in old age. *Neurobiol Aging*, *34*, 2726–2733.

Rozzini, L., Chilovi, B., Conti, M., Bertoletti, E., Delrio, I., Trabucchi, M., & Padovani, A. (2007). Conversion of amnestic Mild Cognitive Impairment to dementia of Alzheimer type is independent to memory deterioration. *International Journal of Geriatric Psychiatry*, *22*(12), 1217–1222.

Scahill, R., Frost, C., Jenkins, R., Whitwell, J., Rossor, M., & Fox, N. (2003). A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Archive of Neurology*, *60*(7), 989–994.

Sluimer, J. D., van der Flier, W. M., Karas, G. B., Fox, N. C., Scheltens, P., Barkhof, F., & Vrenken, H. (2008). Whole-brain atrophy rate and cognitive decline: longitudinal MR study of memory clinic patients. *Radiology*, *248*(2), 590–598.

Sperling, R., Aisen, P., Beckett, L., Bennett, D., Craft, S., Fagan, A., ... Phelps, C. (2011). Toward defining the preclinical stages of alzheimer's disease: Recommendations from the national institute on aging-alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. *Alzheimer's and Dementia the journal of the Alzheimer's Association*, *7*(3), 280–292.

United Nations, Department of Economic and Social Affairs, Population Division . (2017). World population prospects: The 2017 revision, key findings and advance tables [Computer software manual]. (Working Paper No. ESA/P/WP/248)

Whitwell, J., Crum, W., Watt, H., & Fox, N. (2001, September). Normalization of cerebral volumes by use of intracranial volume: Implications for longitudinal quantitative mr imaging. *American Journal of Neuroradiology*, *22*(8), 1483–1489.

WHO. (2015, September). *Aging and health.* Retrieved from World Health Organization Website :`http://www.who.int/mediacentre/factsheets/fs404/en/`. (Fact sheet No. 404)

WHO. (2017, May). *Dementia.* Retrieved from World Health Organization Website :`http://www.who.int/mediacentre/factsheets/fs362/en/`. (Fact sheet 362)

Wilson, R., Hebert, L., Scherr, P., Barnes L.L. and Mendes de Leon, C. F., & Evans, D. (2009). Educational attainment and cognitive decline in old age. *Neurology*, *72*(5), 460–465.

Zanetti, O., Solerte, S., & Cantoni, F. (2009). Life expectancy in Alzheimer's disease (AD). *Archives of Gerontology and Geriatrics*, *49*(1), 237–243.