Relationship between Neuroimaging Markers of Degenerative Change and Cognitive Decline in Mild Cognitive Impairment

An honors thesis for the department of Psychology

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Introduction

There has been considerable effort in recent years to characterize the earliest stages of Alzheimer's disease (AD) and the mechanisms that lead to its development. Recent research has identified amnestic mild cognitive impairment (MCI) as a potential intermediary stage between normal age related cognitive decline and AD, one that greatly increases the risk of developing dementia (Gauthier et al., 2006; Jack et al., 2010; Morris et al., 2001). Currently, Alzheimer's disease is the most common cause of dementia among older adults and the sixth leading cause of death in the U.S. (Brookmeyer et al., 2011). It is predicted to have an enormous impact on health care costs in the next several decades as the number of individuals with AD nearly triples from current estimates of 5.2 million in to an expected 13.8 million by 2050 (Alzheimer's Association, 2016). A preventative therapy targeting pre-symptomatic years would have an enormous public health impact: even a delay in onset of 5 years by 2025 could correspond to a drastic 42% reduction in disease prevalence (Alzheimer's Association, 2015). In order to slow the rapidly rising incidence rate of AD, it is important that clinical research geared towards treating or preventing the disease also consider MCI as a window for targeted treatment interventions.

It is estimated that 12-15% of amnestic MCI patients convert annually to AD, and within a three year period this conversion rate can be as high as 40.5% (Tabert et al., 2006). Thus, there is a high chance that individuals with MCI will convert to AD within a short period of time in comparison to healthy control subjects and the general aging population, who convert to AD at rates of about 1-2% per year (DeKosky & Marek, 2003; R C Petersen, 2004; Ronald C. Petersen et al., 2001; Tabert et al., 2006). In order to delay the onset of AD all biomarkers associated with the disease must be studied, especially in the MCI population. Certain vascular pathologies found in both MCI and AD, notably, white matter lesions (WML), may hold the key to delaying AD onset because the risk factors for these pathologies may be modifiable (Provenzano et al., 2013). In this study we examine changes in both vascular and neurodegenerative neuroimaging markers over two years and how these changes relate to cognition in individuals with MCI.

AD is strongly linked to a host of vascular risk factors, suggesting that this disease may be a multifactorial disorder that includes both vascular and neurodegenerative contributions (Breteler, 2000; Brickman, 2013; de la Torre, 2002). White matter damage is a common finding among older adults, and white matter lesions (WML), which are associated with vascular risk factors, have been implicated in AD development (M. M. B. Breteler et al., 1994). The rapid rate of conversion to AD in individuals with amnestic MCI may be influenced by (or may be a result of) WML, which has been shown to be present in increasing volume in MCI and AD as well as the normal elderly population; increasing volume of WML has been related to both cognition and clinical function in all of these populations (Au et al., 2006; M. M. Breteler et al., 1994; Brickman, 2013; Cees De Groot et al., 2000; Coutu, Goldblatt, Rosas, & Salat, 2015; De Groot et al., 2002; Prins & Scheltens, 2015; Prins et al., 2004). While the exact role of vascular and cerebrovascular contributions to brain aging and dementia is still unclear, WML may be an important potential biomarker of AD development and may be a mediating factor in the conversion from mild cognitive impairment to AD (Brickman, 2013; Lindemer et al., 2015; Provenzano et al., 2013).

One of the greatest challenges in studying MCI as a prodromal model of AD is trying to predict which individuals will undergo conversion to dementia. Impairment of memory is a characteristic cognitive deficit in MCI and often the earliest sign of AD onset. Patients with early

AD are impaired on tests of delayed recall as well as tests of new learning. Yet, memory is not the only cognitive process affected: individuals with early AD (and MCI) may also show deficits in language, executive function, attention, and others, and deficits in more than one domain are a better indicator of mild AD (Ronald C. Petersen et al., 2001). A variety of neuropsychological tests are useful in differentiating AD from healthy controls, but it would be more important to differentiate individuals with MCI from those with AD and MCI converters from non-converters for potential treatment targets. Neuropsychological testing may be useful in predicting individuals or tracking the progression of individuals who convert, when used in combination with measures of structural brain change. A real advantage of this current study is its examination of longitudinal changes in cognition, as well as it's consideration of multiple potential markers of brain change.

In a recent publication investigating the relationship between white matter changes, such as WML, and neuroimaging markers presumed to be altered due to primary AD neurodegenerative processes, Coutu et al (2015) observed strong significant pairwise correlations among five imaging measures of tissue degeneration: AD signature cortical thickness, hippocampal volume, ventricular volume, total WM volume and the volume of WMC. Factor analysis of all five measures yielded two significant factors across all groups, interpreted as the 'age- and vascular- associated' factor (Factor 1) and the 'neurodegenerative' factor (Factor 2), each contributing independently to AD development. Hippocampal volume, a traditional marker of neurodegenerative change in AD, was included in both factors, and the volume of white matter changes (presumably, WML) was of strong importance for Factor 1. The research performed by Coutu et al (2015) demonstrates the importance of understanding the primary measures that contribute to the development of Alzheimer's disease as well as those that may potentiate conversion from MCI to AD.

The objective of this study is to evaluate the hypothesis that white matter changes of presumed vascular origin are related to various cognitive deficits in MCI. The aim of this paper is to clarify the role of the 'age- and vascular- associated' factor proposed by Coutu on cognitive dysfunction in mild cognitive impairment, to infer the impact of WML on prodromal AD states. First, this research aims to determine whether changes in cognitive abilities, as measured by a neuropsychological testing scale sensitive and specific to Alzheimer's disease (the ADAS-Cog), are related to changes in brain imaging markers across two years in MCI. We hypothesize that 1) both neuroimaging factors will correlate strongly to cognitive dysfunction in MCI, at both time points, and that 2) the change in 'neurodegenerative' factor will be a stronger predictor of change in ADAS-Cog scores over time than the 'age- and vascular- associated' factor. Secondly, we aim to clarify the relationship between both neuroimaging factors and various domains of cognition affected in MCI. We will use factor analysis to elucidate any unique patterns of neuropsychological assessment scores in MCI, and use these factors in conjunction with neuroimaging measures to assess cognitive outcome. We hypothesize that different factors representing multiple cognitive domains sensitive to AD can be extracted from neuropsychological assessments, and that the 'neurodegenerative' neuroimaging factor will be a stronger predictor of cognitive dysfunction and decline across all neuropsychological factors.

Materials and Methods

Study Participants and MRI acquisition

Data from a total of 207 participants (N= 90 female, mean age = 71.66) were downloaded from the large publicly-available dataset Alzheimer's Disease Neuroimaging Initiative (ADNI, http://adni.loni.usc.edu). Full demographics information is provided in Table 1 and Table 2. This dataset included 67 cognitively-healthy elderly controls, 127 participants with MCI and 13 participants with AD, all of whom underwent whole-brain MRI scanning at four visits over a period of 12 months on a 3-Tesla GE Medical Systems scanner and had sagittal T1-weighted 3D spoiled gradient echo images available. This dataset was acquired using previously described ADNIGO and ADNI2 Core MRI and DTI protocols. Group designation of control, MCI, and probably AD was determined by ADNI based on the criteria of the National Institute of Neurological and Communicative Diseases and Stroke- Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). Neuropsychological assessment scores and diagnostic information were obtained from the visit closest in time to the MRI acquisition. Written informed consent was obtained from all participants or their representatives through ADNI. The study procedures were approved by institutional review boards of all participating institutions. For more information on ADNI please see: http://www.adni-info.org.

Neuroimaging Factors

Neuroimaging data used in this paper were processed as per Coutu et. al (2015). Automated subcortical and WMC segmentation from T_1- weighted MRI images using FreeSurfer (https://surfer.nmr.mgh.harvard.edu) provided measures of total WM volume, ventricular volume and hippocampal volume, which were all normalized to each subject's intracranial volume, as well as total volume of WMC, which was normalized by total WM volume (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002). The natural logarithm of the normalized volume of WMC was used. Cortical thickness measures in regions known to undergo cortical thinning in early AD (except for the hippocampus) were obtained from T1 weighted images using FreeSurfer (Dickerson et al., 2009). Factor scores were calculated for each participant using the factor structure of Coutu et al. (2015) at each time point from these volumetric and thickness measures.

Neuropsychological Assessments

The selected neuropsychological tests assessed a range of cognitive abilities affected by AD, MCI and normal aging. Two major cognitive domains being assessed are long-term memory, a classic indication of cognitive decline in AD, and executive function, which has been observed to decline in AD as well as vascular conditions (Buckner, 2004; Prins et al., 2005). Of the neuropsychological assessments chosen, the assessments known to measure changes in memory were the Alzheimer's Disease Assessment Scale Cognition (ADAS-Cog), the Rey Auditory Verbal Learning Test (RAVLT) immediate recall, delayed recall and recognition subscores, the Everyday Cognition test (ECOG), the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Tests sensitive to changes in executive function are the Functional Activities Questionnaire (referred to as Activities of Daily Living in ADNI) (FAQ), the Trail Making Test parts A and B, as well as certain components of the ADAS-Cog, MoCA, ECOG and MMSE. Neuropsychological assessments were administered to participants three times over a period of up to 24-48 months, at three of the following visits: screening, baseline,

month 3, month 6, annual, or 6 month interim. The two assessment scores chosen for analyses were those administered closest in date to the participant's chosen MRI scan dates. Additional details regarding the administration of these exams can be found at the ADNI Clinical Core site: http://adni.loni.usc.edu/about/centers-cores/clinical/.

The Alzheimer's Disease Assessment Scale- Cognition (ADAS-Cog) subscale is a modified form of the original ADAS (Rosen et. al, 1984), which includes 13 items that test a variety of cognitive domains often thought of as the core symptoms of AD: disturbances of memory, language, praxis, attention, orientation and others. The simplified ADAS-Cog may be a more efficient assessment of early AD or cognitive decline and is a good outcome measure used in clinical trials to determine improvement. In fact, the ADAS-Cog is the most widely used measure of cognition in clinical trials of AD (Connor & Sabbagh, 2008). We have chosen to focus on this assessment in this not only because it is a quality measure of clinical outcome, but also because it is very sensitive to AD and useful in assessing changes in cognition in MCI. Responsiveness in MCI can be increased when measures of executive function or functionality are added to the ADAS-Cog (Skinner et al., 2012). The ADAS-cog total score was used for this study, which was a composite measure of all domains assessed.

The Rey Auditory Verbal Learning Test (RAVLT) is a test of episodic verbal memory that assesses the ability to acquire a list of 15 words over the course of 5 trials (Rey, 1964). The test includes a measure of immediate recall, a short delayed recall trial following the presentation of a distractor list, a 30 minute long delayed recall trial, and a recognition trial following the short delayed recall trial. Only the immediate recall, 30 minute delayed recall, and recognition scores were used in analyses because these measures are inferred to represent components of short term and long term memory. In the present study we created a RAVLT 'long term memory' score by finding the difference between RAVLT immediate recall and delayed recall scores.

The Mini Mental State Exam (MMSE) is the most widely used screening test of cognitive functioning (Tombaugh & McIntyre, 1992). The original MMSE was designed to quantitatively estimate the severity of cognitive impairment and to document clinical change (Folstein, Folstein, & McHugh, 1975). This exam is a 30 point questionnaire with questions grouped into seven categories, each representing a different cognitive domain: Orientation to time, Orientation to place, Registration of three words, Attention and calculation, Recall of three words, Language, and Visual Construction. The maximum score for this test is 30, and a score of 23 or less is generally accepted as an indication of cognitive impairment.

The Montreal Cognitive Assessment (MoCA) is a 30-point assessment administered in 10 minutes. Eight major cognitive domains are tested: short term-memory is assessed in a recall task involving two learned trials of five nouns and a short delayed recall trial. Visuospatial abilities are assessed using a clock-drawing task and a drawing task (three-dimensional cube copy). Executive function is assessed using an adapted Trail Making B test, a phonemic fluency test and a verbal abstraction test. Attention was assessed using a target detection task, concentration using a serial subtraction task, and working memory using a digits forward and backward test. Language is assessed using a naming task with low-familiarity animals (lion, camel, and rhinoceros) and a sentence repetition/fluency task. The last domain was orientation to place and time of the exam. The MoCA has a sensitivity of 90% and a specificity of 78% for MCI when a cutoff score of 26 out of 30 was used, which is considerably more sensitive than the MMSE. This exam is one of the only known to reliably distinguish MCI from normal controls, while also

being highly sensitive to AD (Nasreddine et al., 2005).The final score (the simple sum of all tasks) was used in analyses.

The Everyday Cognition (ECOG) exam was designed to assess functional abilities of all older adults, ranging from normal aging to mild or moderate dementia. The ECOG consists of 39 items with a four-point response option to capture the full variability in impairment. Response options include 1 = better or no change compared to 10 years earlier, 2 = questionable/occasionally worse, 3 = consistently a little worse, 4 = consistently much worse, and an "I don't know" option. These items assess several domains of everyday/real-world functioning relevant to neuropsychological domains: memory, language, semantic knowledge, visuospatial abilities, and three executive domains including planning, organization and divided attention (Farias et al., 2008). The exam can be administered to the patient/participant, or to a study partner. The total ECOG score from the participant's exam was used in analyses for this study.

The Functional Activities Questionnaire, or "Activities of Daily Living" (FAQ), is a standardized assessment of instrumental Activities of Daily Living (ADLs). It is a measurement of social function that is sensitive to the older population and samples more complex behavior than traditional ADL exams (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982). The questionnaire consists of a list of ten items, or 'activities' (i.e. writing checks, paying bills and keeping financial records). For each activity, four levels of performance ranging from dependence to independence are presented. The participant must rate their performance on one of the four levels: 3 = dependent, 2 = requires assistance, 1 = has difficulty but does by self, or 0 = normal. This exam has found to have 80.3% sensitivity and 87.0% specificity in differentiating MCI from AD. The total questionnaire score is the simple sum of scores for the individual activities, and this is the score that was used in analyses.

The Trail Making Test consists of two parts, Trails A and Trails B (Reitan and Wolfson, 1985). Part A is a test of motor processing speed and visual scanning. Part B also tests motor processing and visual scanning, but also is a measure of attentional set-shifting (a type of executive function). In part A participants are presented with an array of numbers on a page and asked to draw lines connecting the numbers in a sequential order. In Part B, the participant is presented with both numbers and letters and is asked to now draw connecting lines while alternating between letters and numbers, still in sequential order (i.e. 1-A-2-B…). Analyses for this study included the difference between the completion time from Part B and the completion time from Part A, referred to as "Trails Executive Function." This was done to isolate the executive function component of the Trail Making Test from the motor processing speed and attention set-shifting components.

Statistical Analysis

Statistical analyses were performed using JMP 12 PRO statistical software (SAS Institute Inc., Cary, NC, U.S.A.). A demographic representation of this population is presented in Table 1 (appendix) and Table 2. All statistical analyses focused on the MCI population only. All models reported are significant unless otherwise specified. All models presented are controlling for the following confounding variables: gender, education, age at baseline, average translation motion, average rotation motion, and any baseline measures associated with longitudinal outcomes. Bivariate relationships, uncontrolled for these confounding variables, are shown in all figures.

Neuroimaging Factors and Cognition

General linear models (including group, age at baseline, sex, education, measures of motion (translation and rotation) and baseline measures for any longitudinal models as covariates) were run between both neuroimaging Factor 1 ('age- and vascular- associated') and Factor 2 ('neurodegenerative') and ADAS-Cog scores. The aims of these analyses were to determine whether brain imaging markers were associated with cognitive scores cross-sectionally at two time points, whether these markers at time point 1 were associated with longitudinal changes in cognition, and whether longitudinal changes in brain imaging markers predict changes in cognitive abilities (as measured by the ADAS-Cog) over two years.

Neuropsychological Factor Analysis and relation to Neuroimaging Measures

Of all 207 subjects used in previous analyses, 169 of these subjects had results for all of the following neuropsychological assessments. These 158 subjects were therefore used in the factor analysis. Of this data set, 8 were diagnosed with AD at baseline, 104 were grouped as MCI and 46 were cognitively-healthy elderly controls. Subsequent analyses focused only on the MCI group.

A total of eight neuropsychological assessment variables were used in the factor analysis: RAVLT long term memory, RAVLT recognition memory, MMSE, MoCA, ADAS-Cog, FAQ, ECOG total, and Trails Executive Function. Factor analysis on correlation (performed with VARIMAX rotation) was used to determine whether these eight neuropsychological measures clustered into primary factors each representing different sources of correlation on imaging metrics. Resulting primary factors were then run in general linear models with the same covariates as above to determine whether these neuropsychological factors are associated with the 'age- and vascular- associated' factor and the 'neurodegenerative factor' both cross-sectionally and longitudinally. Additionally, the neuropsychological assessments with the highest loadings from each factor were correlated with the neuroimaging factors independent of other measures from the factor structure.

Results

Neuroimaging Factors and Cognition (ADAS-Cog 13)

Cross Sectional Analyses. In Model 1, associations between both neuroimaging Factor 1 and Factor 2 and ADAS-Cog score at baseline were tested to determine if relationships between neuroimaging measures and cognition exist cross-sectionally. We found significant negative associations between Factor 1 score and ADAS-Cog score at baseline (Spearman's rho $\rho = -0.2757$, p-value = 0.0017) and between Factor 2 score and ADAS-cog score at baseline (Spearman's rho $\rho = -0.3132$, p-value = 0.0003).

In Model 2, we investigated whether the negative correlations between both factors and cognition found in Model 1 remained significant at a time point two years later. Indeed, cross-sectional associations between Factor 1 and ADAS-Cog scores and between Factor 2 and ADAS-Cog scores two years post-baseline remained significant (Spearman's rho $\rho = -0.3698$, p-value < 0.0001 and Spearman's rho $\rho = -0.2557$, p-value = 0.0039, respectfully). The relationship between both factors and ADAS-Cog score at both time points is shown in Figure 1. See Table 4 for models.

Longitudinal Analyses. In Model 3, we examined the data longitudinally to determine whether associations existed between the change in neuroimaging factor scores per participant over two years and the corresponding change in ADAS-Cog scores. There was a significant negative association between change in Factor 1 scores and change in ADAS-cog scores, confirming that Factor 1 is strongly correlated with ADAS-Cog longitudinally (p-value < 0.0001). Similarly, the change in Factor 2 scores significantly negatively correlated with change in ADAS-Cog score (p-value = 0.0046). The bivariate relationship between the change in factor scores and the change in cognition can be seen in Figure 2. In Model 4, we examined whether there were significant associations between both neuroimaging factor scores at baseline and the change in ADAS-Cog scores over time. These associations were found to be non-significant for both factors. See Table 5 for models.

Neuropsychological Factor Analysis and relation to neuroimaging factors

Factor analysis on the eight neuropsychological measures yielded three significant factors (see Table 3). Factors 1 and 2 each included loadings from long term memory, MoCA and ADAS-cog scores. Neuropsychological Factor 1 otherwise included high loadings (> 0.4) from RAVLT recognition memory. Factor 2 included MMSE, FAQ and ECOG total scores, and factor 3 showed high loading for Trails Executive Function only. Based on the loadings for each factor, we named factor 1 "general cognition," factor 2 "clinical," and factor 3 "executive function."

Cross-Sectional Analyses. In Model 5 we determined whether the three neuropsychological factors were correlated with both two neuroimaging factors at baseline. Positive correlations between neuroimaging Factor 1 and the "general cognition" factor and the "clinical" factor and negative correlations with the "executive function" factor were all significant (p-value = 0.0157, p-value = 0.0040, p-value = 0.0398, respectively). Neuroimaging Factor 2, on the other hand, was significantly correlated with the "general cognition" factor and the "clinical" factor (p-value = 0.0035, p-value = 0.0122). The correlation between neuroimaging Factor 2 and the "executive function" factor was found to be non-significant. These significant relationships can be seen in Figure 2.

In Model 6 we determined whether the cross-sectional correlations found in Model 5 remained significant two years later. Indeed, all correlations were significant, and the correlation between neuroimaging Factor 2 and the "executive function" factor was also significant at this time point (p-value = 0.0011) (see Table 7). Cross sectional relationships between the two neuroimaging factors and neuropsychological factors at both time points can be seen in Figure 3. See models in Table 6.

Longitudinal Analyses. In Models 7 and 8 we examined the data longitudinally, in the same manner as Models 3 and 4. In Model 7 we aimed to determine whether associations existed between the change in neuroimaging Factor 1 and 2 scores per participant over two years and the corresponding change in the neuropsychological factor scores. Change in neuroimaging Factor 1 had significant positive correlations with the "general cognition" and "clinical" factors (p-value = 0.0030, p-value = 0.0035, respectively). Change in neuroimaging Factor 1 had a significant negative correlation with the "executive function" factor (p-value = 0.0457). Change in neuroimaging Factor 2 had a significant negative correlation with the "executive function" factor (p-value = 0.0101). Correlations between neuroimaging Factor 2 and "general cognition" and "clinical" factors were found to be nonsignificant. These relationships between change in

neuroimaging factor scores and change in the three neuropsychological factor scores can be seen in Figure 3.

In Model 8 we examined whether associations between neuroimaging factors at baseline and change in neuropsychological factors exist. None of the correlations were found to be significant, yet correlations between neuroimaging Factor 2 at baseline and change in both "clinical" and "executive function" scores were trending towards significance (p-value = 0.0528, p-value = 0.0597). See Table 7 for models.

In Model 9 the neuropsychological measures providing the highest loading to each of the three neuropsychological factors were run in general a linear model with both the 'age- and vascular-associated' and 'neurodegenerative' factors, to further explore how these neuroimaging factors directly relate to the strongest measures of cognition and function. Recognition memory score ("general cognition" factor), MMSE ("clinical" factor), and trails executive function ("executive function" factor) were the highest loadings. The change in recognition memory was significantly correlated with the change in neuroimaging Factor 1 only (p-value = 0.0003). The change in MMSE score, as well as the change in trials executive function, was significantly correlated with change in both neuroimaging Factor 1 and Factor 2. Interestingly, neuroimaging Factor 2 measures at baseline (time point 1), instead of the change over two years, were significantly correlated with the change in both MMSE and Trails executive function scores (p-value = 0.0195, p-value = 0.0081). This finding is in contrast to that of Model 8. This model can be seen in Table 8 and the significant relationships in Figure 4.

In Model 10 we examined whether all neuroimaging measures together (WM volume, ventricular volume, WML volume, hippocampal volume, and cortical thickness) would be able to predict cognition changes longitudinally, given that the two classes of degenerative change were not able to separately predict cognitive changes. While there was no predictive power of all neuroimaging measures on changes in the general cognition factor, there was a significant correlation between the sum of the neuroimaging factors and changes in both the clinical and the executive function factors (p-value = 0.0134, p-value = 0.0271). This model can be seen in Table 9 and the significant relationships in Figure 5.

Discussion

Our principal finding was that within a relatively large population of older adults with MCI both the 'age- and vascular- associated' and 'neurodegenerative' neuroimaging factors can be used to assess cognitive dysfunction and decline over several years. Our results confirm the relevance of studying white matter changes in mild cognitive impairment, as this vascular-associated pathology may suggest a secondary, concurrent pathway to AD development.

The ADAS-Cog has been shown to be a reliable measure for clinical outcome in AD, assessing cognitive decline and differentiating AD patients from the normal population. The population of interest, however, is those with mild cognitive impairment as these individuals may hold the key to understanding the factors contributing to the development of dementia. Our findings suggest that the utility of the ADAS-Cog may extend beyond identifying individuals with Alzheimer's disease: when looked at in conjunction with neuroimaging measures, the ADAS-Cog is sensitive

to cognitive changes in mild cognitive impairment as well. As seen in Figure 1, changes in both the 'age- and vascular- associated' factor (Factor 1) and the 'neurodegenerative' factor (Factor 2) are directly related to changes in cognition: as both of these brain measures worsen, cognition in the various domains measured by the ADAS-Cog worsens. However, neither neuroimaging factor at baseline was related to change in cognition, suggesting that these brain imaging measures alone may not be able to predict cognitive decline in MCI, when measured by this metric. Therefore, analyzing these two classes of brain change may be useful in tracking an MCI individual's decline, but these measures are not sufficient enough for a predictive relationship.

Out of the eight neuropsychological assessments chosen, we found these assessments can be grouped into three classes representing different outcomes of disease progression: general cognition, clinical outcome and executive function. Nearly all cross-sectional correlations at both time points were significant for all three factors, suggesting that these brain measures used are strongly associated with most psychological measures in MCI (the only exception being neuroimaging Factor 2 and Executive Function Factor at baseline).

The 'age- and vascular- associated' factor, which consists of WMC volume, WM volume, ventricular volume and hippocampal volume measures, is strongly related to assessments of general cognition and clinical outcome. Increased WMC volume and ventricular volume, and simultaneous decrease in WM and hippocampal volumes over time negatively affect cognition and clinical outcome – this is important because it suggests that vascular-associated changes in the brain, not traditional neurodegenerative changes, are highly important in MCI progression. However, since hippocampal volume is also included in the 'age-and-vascular' factor, it is likely that vascular measures are the best indication of disease progression when used in conjunction with certain neurodegenerative measures. Decline in hippocampal volume and cortical thickness, the classic neurodegenerative measures strongly associated with AD, were found to negatively affect executive function only, but changes in vascular-associated measures did not.

The findings from examining the relationship between the change in highest loadings from the three neuropsychological factors (RAVLT recognition memory, MMSE and Trails executive function) and change in neuroimaging measures validated the results from Model 7: neuroimaging Factor 1 affects measures of cognition, clinical outcome, and Factor 2 affects measures of executive function. However, when only looking at highest loadings, changes in neuroimaging Factor 1 are also related to changes in Trails executive function, and changes in Factor 2 were also linked to changes in MMSE; these findings suggest that while the factor structure is useful in broadly assessing change in the three chosen areas of cognitive/functional decline, it may not have the same sensitivity as individual assessments.

Our findings suggest these degenerative changes in the 'age- and vascular- associated' factor and the 'neurodegenerative' factor are useful in assessing the progression of cognitive impairment, clinical outcome, and executive function. We also found that baseline measures of these two factors alone were not able to significantly predict the change in neuropsychological factor scores at a time point two years later. However, our results suggest that by using the baseline values of all five brain imaging measures in conjunction, one might be able to predict the change in clinical outcome and executive function in MCI over several years, but not the change in general cognition. More generally, it seems that cognitive measures change as a result of a change in neuroimaging markers, and otherwise stay stable.

Measures of cognitive change in the form of neuropsychological testing, while they may be sensitive to dementia, are not sufficient alone to predict conversion from MCI to dementia. These neuropsychological assessments and measures of white matter volume together could be used diagnostically to assess decline in the individuals that eventually convert to dementia. However, since many older adults who have white matter changes present do not develop dementia, the relationship between these two must be further investigated.

Prior work has discovered that both white matter lesions are highly prevalent in individuals with AD, especially in comparison to non-demented older adults. It is interesting to note that this finding also extends to MCI samples. There have been many studies finding associations between WML volumes and cognitive dysfunction; however, these studies have mostly been of a cross sectional nature and have not examined the impact of WML/WMC on cognition distinctly from other common magnetic resonance imaging measures of structural brain changes. Hence, a real advantage of this study is its longitudinal design as well as it's consideration of several other potential markers of brain change as a prodromal disease state.

Early detection of Alzheimer's disease is imperative to the possibility of a pre-symptomatic diagnosis and treatment, perhaps during the development of mild cognitive impairment. It is important, therefore, that multiple avenues of AD pathogenesis are explored fully in order to characterize this transitionary phase. Our finding that both neuroimaging factors, which represent traditional neurodegenerative changes in the brain as well as vascular-related changes, contribute strongly to cognitive and clinical decline is an important one because it suggests that not only is cognitive dysfunction related to degeneration of the hippocampus and widespread cortical atrophy, but that these cognitive changes are likely be mediated by changes in white matter, such as the development of WML and ventricular enlargement. A caveat here is that the same factor that included WMLs also included other features considered more primary to AD including ventricular enlargement and hippocampal atrophy. We interpret the factor results as being suggestive that these 'classical' features have been misinterpreted and are in fact at least to some degree tied to poor vascular health. This may explain why 'classical' features such as hippocampal volume cluster with vascular-associated measures, such as WML. All mechanistic interpretations are, however, speculative and require additional research.

The implications of Alzheimer's disease consisting of a vascular component are wide reaching, as is the implication that vascular-related brain changes affect decline in cognition, clinical outcome, and executive function measures in MCI, potentially more so than neurodegenerative changes. Support for this vascular-related theory of AD development promotes the discovery of novel therapeutic interventions or possible treatments, it allows for a more complete characterization of the disease state and pre-disease states and may allow for a diagnosis of Alzheimer's to be given several years before the most severe symptoms of AD become apparent. An early diagnosis of AD, or at least the ability to identify the timeframe during which an individual will convert from MCI to AD, would be of tremendous importance in designing interventions to delay the onset of AD and treat the underlying pathology before the emergence of cognitive decline. More research is required to determine if a predictive relationship between vascular-related changes and cognitive/function decline indeed exists.

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Appendix

Table 1 *Demographics for all MCI participants.*

	Baseline	Time Point 2
All ADNI, n = 207		
MCI, n = 127		
Participants (female)	127 (57)	-
Education (years)	16.62 (0.23)	-
Age (years)	70.62 (0.63)	72.59 (0.63)
Factor 1	-0.13 (0.09)	-0.30 (0.10)
Factor 2	0.77 (0.07)	0.61 (0.08)
ADAS-Cog	13.72 (0.58)	14.81 (0.86)

Standard errors are shown in parentheses. (MCI: mild cognitive impairment; ADAS-Cog: Alzheimer's Disease Assessment Scale, Cognition)

Table 2 *Demographics for all participants.*

	Dementia	MCI	CN
All ADNI, n = 158			
Participants (female)	8 (1)	104 (46)	46 (21)
Education (years)	16.63 (0.94)	16.57 (0.26)	16.83 (0.34)
Age (years)	72.6 (2.19)	70.30 (0.69)	72.96 (1.18)
Factor 1	-0.51 (0.19)	-0.10 (0.11)	-0.02 (0.14)
Factor 2	0.11 (0.31)	0.76 (0.08)	1.00 (0.10)
MMSE	23.75 (0.86)	28.23 (0.17)	29.35 (0.16)
FAQ	10.88 (1.79)	2.55 (0.37)	0.22 (0.10)
ECOG	2.32 (0.21)	1.76 (0.04)	1.30 (0.04)
MoCA	17.63 (2.17)	23.99 (0.34)	26.04 (0.44)
ADAS-Cog	30 (3.20)	13.88 (0.67)	9.28 (0.72)
RAVLT immediate	23.13 (2.58)	39.08 (1.18)	45.74 (1.59)
RAVLT delayed recall	5.75 (1.32)	7.21(0.48)	4.17 (0.65)
RAVLT recognition memory	9 (0.96)	11.38 (0.34)	13 (0.32)
RAVLT long term memory	17.38 (2.43)	31.87 (1.15)	41.57 (1.57)
Trail Making Test A	52.13 (14.19)	34.56 (1.22)	29.72 (1.50)
Trail Making Test B	175.13 (27.28)	98.86 (5.70)	75.85 (4.96)
Trails executive function	123 (19.26)	64.30 (5.06)	46.13 (4.19)
General Cognition Factor	-0.91 (0.24)	-0.12 (0.09)	0.31 (0.09)
Clinical Factor	-1.94 (0.44)	-0.04 (0.06)	0.53 (0.08)
Executive Function Factor	0.63 (0.34)	0.02 (0.11)	-0.15 (0.09)

Standard errors are shown in parentheses. (MCI: Mild Cognitive Impairment; CN: Controls; MMSE: Mini Mental State Exam; FAQ: Functional Activities Questionnaire; ECOG: Everyday Cognition; MoCA: Montreal Cognitive Assessment; ADAS-Cog: Alzheimer's Disease Assessment Scale, Cognition; RAVLT: Rey Auditory Verbal Learning Test;

Table 3 *Factor analysis of neuropsychological assessments sensitive to general cognitive decline, MCI, or AD.*

Parameters	**General Cognition Factor**	**Clinical Factor**	**Executive Function Factor**
ADNI, n=158			
RAVLT recognition	**0.837**	0.159	-0.128
memory	**0.606**	**0.506**	-0.053
RAVLT long-term memory	0.369	**0.639**	-0.135
MMSE	**0.470**	**0.625**	-0.289
MoCA	**-0.646**	**-0.561**	0.298
ADAS-Cog	-0.163	-0.276	**0.947**
Trails executive function	-0.395	**-0.466**	0.244
FAQ	-0.073	**-0.466**	0.154
ECOG			

Coefficients higher than .40 are bolded to indicate the most important measures contributing to each factor. (RAVLT: Rey Auditory Verbal Learning Test; MMSE: Mini Mental State Exam; MoCA: Montreal Cognitive Assessment; ADAS-Cog: Alzheimer's Disease Assessment Scale, Cognition; FAQ: Functional Activities Questionnaire; ECOG: Everyday Cognition)

Table 4 *Models of cross sectional associations between neuroimaging Factor 1 and Factor 2, and ADAS-Cog at both time points.*

Parameters	**ADAS-Cog (baseline) (β; *p*-value)**	**ADAS-Cog (time point 2) (β; *p*-value)**
n = 127 (MCI)		
Gender	-0.19; 0.7351	-0.55; 0.4784
Education	0.11; 0.8383	-0.52; 0.4893
Translation motion	1.53; 0.3529	3.03; 0.1943
Rotation motion	-2.09; 0.2018	-3.42; 0.1374
Age at baseline	-0.73; 0.2922	-1.70; 0.0840
Factor 1 (baseline)	**-2.57; 0.0001**	-
Factor 2 (baseline)	**-2.56; <0.0001**	-
Factor 1 (tp2)	-	**-4.45; <0.0001**
Factor 2 (tp2)	-	**-3.94; <0.0001**

Corrected parameter estimates (β) and p-values are presented and significant associations with $p < 0.05$

are bolded. All continuous variables, with the exception of ADAS-Cog baseline and time point 2 scores, were standardized prior to running models to compare parameter estimates. Non-parametric associations are presented in related figures. (MCI: mild cognitive impairment; ADAS-Cog: Alzheimer's Disease Assessment Scale, Cognition; tp2: time point 2)

Table 5 *Models of longitudinal associations between ADAS-Cog and Factors 1 and 2. Comparing changes in both neuroimaging factors and change in ADAS scores, as well as the change in ADAS related to baseline neuroimaging factor measures.*

Parameters	**Change in ADAS-Cog (β; *p*-value)**
n= 124 MCI	
Gender	-0.73; 0.0895
Education	-0.81; 0.0512
Translation motion	1.57; 0.2157
Rotation motion	-0.63; 0.6137
Age at baseline	-0.40; 0.4586
Factor 1 (baseline)	0.02; 0.9732
Factor 2 (baseline)	-0.31; 0.4946
Change in Factor 1	**-2.37; <0.0001**
Change in Factor 2	**-1.89; <0.0001**
ADAS-Cog (baseline)	0.26; 0.6361

Corrected parameter estimates (β) and p-values are presented and significant associations with $p < 0.05$ are bolded. All continuous variables, with the exception of Change in ADAS-Cog scores, were standardized prior to running models to compare parameter estimates. Uncorrected associations are presented in related figures. (MCI: mild cognitive impairment; ADAS-Cog: Alzheimer's Disease Assessment Scale, Cognition)

Table 6 *Models of cross sectional associations (at two time points) between neuroimaging factor 1 and 2 scores and neuropsychological factor scores.*

Parameters	**General Cognition Factor (β; *p*-value)**	**Clinical Factor (β; *p*-value)**	**Executive Function Factor (β; *p*-value)**	**General Cognition Factor (β; *p*-value)**	**Clinical Factor (β; *p*-value)**	**Executive Function Factor (β; *p*-value)**
		BASELINE			**TIME POINT2**	
n = 104 MCI						
Gender	0.11; 0.2484	0.03; 0.6197	**0.24; 0.0326**	0.15; 0.1355	0.03; 0.7912	**0.33; 0.0102**
Education	0.09; 0.3263	0.04; 0.4262	-0.05; 0.6551	**0.22; 0.0212**	0.14; 0.2081	0.11; 0.3651
Translation motion	-0.15; 0.5536	0.05; 0.7593	0.19; 0.5370	-0.42; 0.1250	-0.11; 0.7208	-0.08; 0.8291
Rotation motion	0.35; 0.1943	0.00; 0.9979	-0.19; 0.5561	**0.61; 0.0363**	0.22; 0.4942	0.09; 0.8022
Age at baseline	0.09; 0.4578	0.11; 0.1409	0.13; 0.3445	0.12; 0.3632	**0.31; 0.0328**	-0.02; 0.8899
Factor 1 (baseline)	**0.27; 0.0157**	**0.20; 0.0040**	**-0.28; 0.0398**	-	-	-

Factor 2 (baseline)	**0.26; 0.0035**	**0.14; 0.0122**	-0.12; 0.2512	-	-	-
Factor 1 (tp2)	-	-	-	**0.39; 0.0012**	**0.44; 0.0010**	**-0.31; 0.0364**
Factor 2 (tp2)	-	-	-	**0.30; 0.0024**	**0.41; 0.0002**	**-0.40; 0.0011**

Corrected parameter estimates (β) and p-values are presented and significant associations with $p < 0.05$ are bolded. All continuous variables, with the exception of General Cognition Factor, Clinical Factor, and Executive Function Factor scores, were standardized prior to running models to compare parameter estimates. Uncorrected associations are presented in related figures. (MCI: mild cognitive impairment; tp2: time point 2)

Table 7 *Models of longitudinal associations between all neuropsychological factors and neuroimaging Factor 1 and Factor 2.*

Parameters	**Change in General Cognition Factor (β; *p*-value)**	**Change in Clinical Factor (β; *p*-value)**	**Change in Executive Function Factor (β; *p*-value)**
n = 104 (MCI)			
Gender	0.10; 0.1335	0.06; 0.5535	0.18; 0.1371
Education	**0.17; 0.0089**	0.13; 0.1943	0.10; 0.3891
Translation motion	-0.33; 0.0733	-0.19; 0.5092	-0.13; 0.6857
Rotation motion	0.29; 0.1374	0.15; 0.6027	0.21; 0.5272
Age at baseline	0.01; 0.8711	0.21; 0.1259	-0.03; 0.8683
Factor 1	0.02; 0.8167	0.11; 0.4342	-0.05; 0.7485
Factor 2	0.02; 0.8195	0.20; 0.0528	-0.22; 0.0597
Change in Factor 1	**0.20; 0.0030**	**0.30; 0.0035**	**-0.23; 0.0457**
Change in Factor 2	0.11; 0.0809	0.18; 0.0695	**-0.30; 0.0101**
General Cognition Factor (baseline)	**-0.22; 0.0014**	-	-
Clinical Factor (baseline)	-	-0.20; 0.1796	-
Executive Function Factor (baseline)	-	-	**-0.62; <0.0001**

Corrected parameter estimates (β) and p-values are presented and significant associations with $p < 0.05$ are bolded. All continuous variables, with the exception of General Cognition Factor, Clinical Factor, and Executive Function Factor scores, were standardized prior to running models to compare parameter estimates. Uncorrected associations are presented in related figures. (MCI: mild cognitive impairment)

Table 8 *Models of longitudinal associations between changes in the highest loadings from all neuropsychological factors and Factor 1 and 2 changes or baseline values.*

Parameters	**Change in recognition memory (β; *p*-value)**	**Change in MMSE (β; *p*-value)**	**Change in Trails executive function (β; *p*-value)**
n = 104 (MCI)			
Gender	0.28; 0.2406	0.22; 0.3345	5.00; 0.3150
Education	**0.66; 0.0052**	**-0.43; 0.0452**	1.24; 0.7899
Translation motion	**-1.37; 0.0401**	0.98; 0.1137	-1.74; 0.8969
Rotation motion	1.08; 0.1168	-0.98; 0.1292	5.74; 0.6812
Age at baseline	0.27; 0.3877	-0.27; 0.3427	-5.03; 0.4200
Factor 1	0.05; 0.8634	-0.38; 0.1806	-3.38; 0.5921
Factor 2	0.01; 0.9786	**-0.53; 0.0195**	**-12.80; 0.0081**

Change in Factor 1	**0.89; 0.0003**	**-1.00; <0.0001**	**-16.06; 0.0008**
Change in Factor 2	0.39; 0.0939	**-0.63; 0.0051**	**-17.45; 0.0003**
Recognition memory (baseline)	**-0.99; <0.0001**	-	-
MMSE (baseline)	-	**0.69; 0.0133**	-
Trails Executive function (baseline)	-	-	**-24.80; <0.0001**

Corrected parameter estimates (β) and p-values are presented and significant associations with $p < 0.05$ are bolded. All continuous variables, with the exception of Change in recognition memory, Change in MMSE, and Change in Trails executive function scores, were standardized prior to running models to compare parameter estimates. Uncorrected associations are presented in related figures. (MCI: mild cognitive impairment; MMSE: Mini Mental State Exam)

Table 9 *Model of longitudinal associations between changes in all neuropsychological factors and the sum of both neuroimaging Factor scores at baseline.*

Parameters	**Change in General Cognition Factor (β; *p*-value)**	**Change in Clinical Factor (β; *p*-value)**	**Change in Executive Function Factor (β; *p*-value)**
n = 104 (MCI)			
Gender	0.05; 0.4765	-0.01; 0.9550	0.24; 0.7196
Education	**0.14; 0.0372**	0.09; 0.3736	0.13; 0.0578
Translation motion	-0.29; 0.1288	-0.13; 0.6509	-0.17; 0.2767
Rotation motion	0.30; 0.1446	0.21; 0.4945	0.17; 0.6075
Age at baseline	0.00; 0.9782	0.23; 0.0725	-0.12; 0.6302
Factor 1 + Factor 2 (baseline)	0.08; 0.3193	**0.32; 0.0134**	**-0.32; 0.0271**
General Cognition Factor (baseline)	**-0.16; 0.0183**	-	-
Clinical Factor (baseline)	-	-0.13; 0.4158	-
Executive Function Factor (baseline)	-	-	**-0.63; <0.0001**

Corrected parameter estimates (β) and p-values are presented and significant associations with $p < 0.05$ are bolded. All continuous variables, with the exception of Change in General Cognition Factor, Change in Clinical Factor, and Change in Executive Function Factor scores, were standardized prior to running models to compare parameter estimates. Uncorrected associations are presented in related figures. (MCI: mild cognitive impairment)

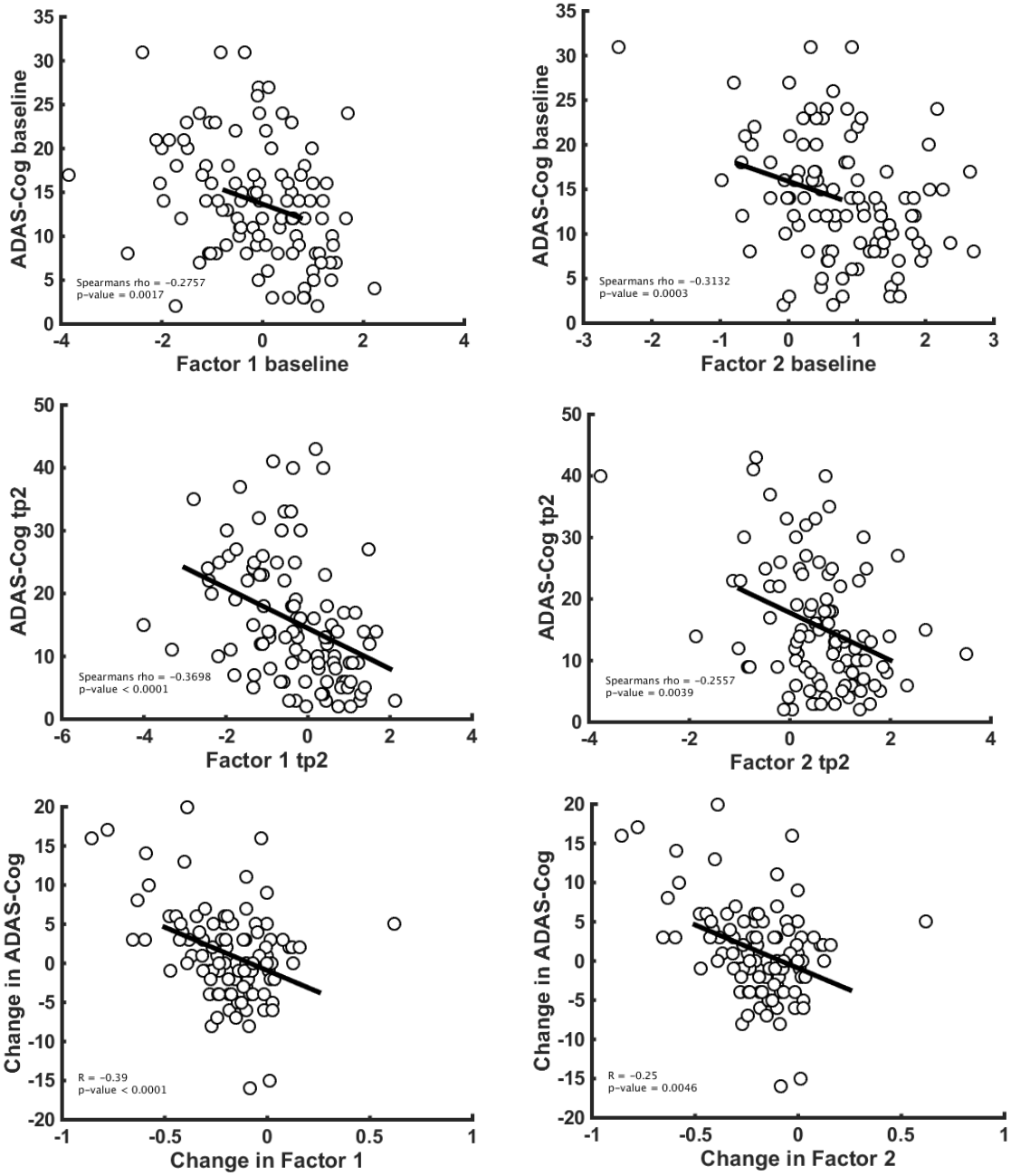
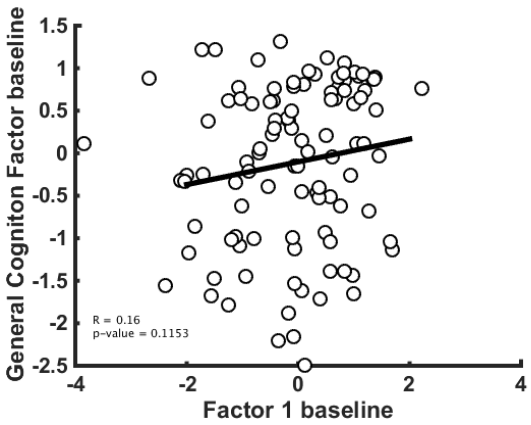


Figure 1 Neuroimaging Factors in relation to ADAS-Cog. Both cross-sectional and longitudinal associations shown. Cross sectional correlation coefficients and significance from Spearman's rho. Longitudinal correlation coefficients and significance from Pearson's R. (tp2: time point 2; ADAS-Cog: Alzheimer's Disease Assessment Scale, Cognition)


General Cogniton Factor baseline
Factor 1 baseline
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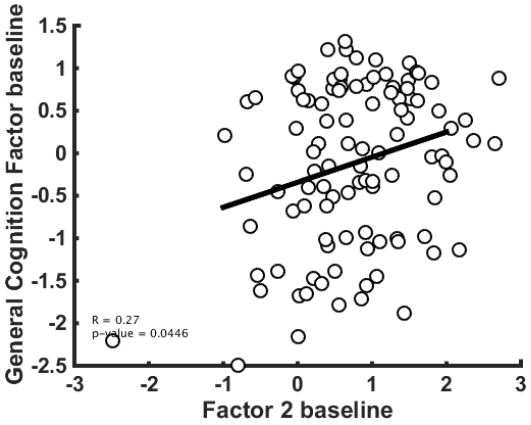
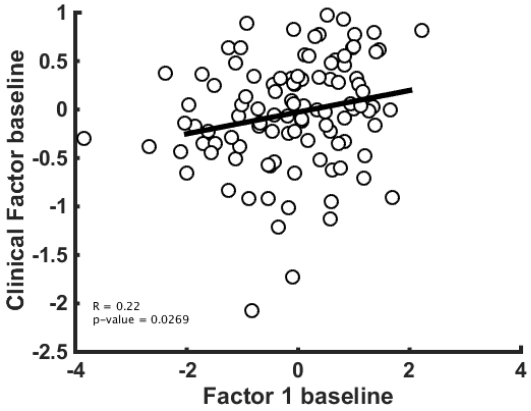
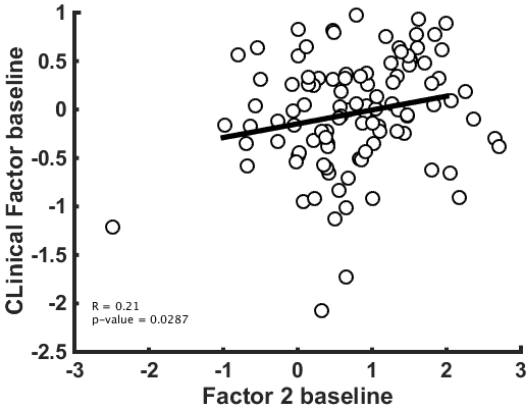
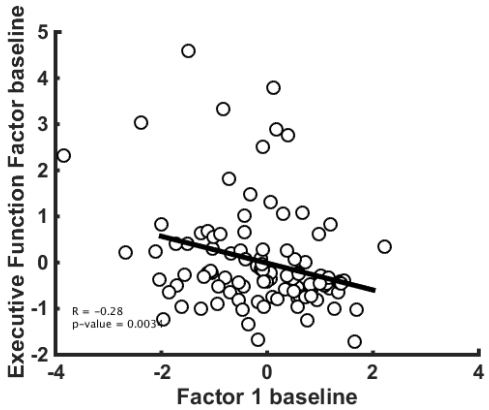
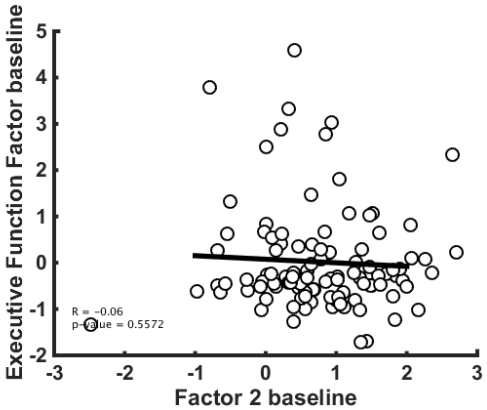
p-value = 0.1153

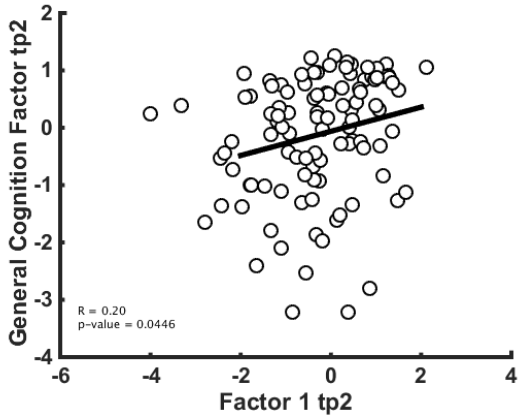

General Cognition Factor baseline
Factor 2 baseline
R = 0.27
p-value = 0.0446

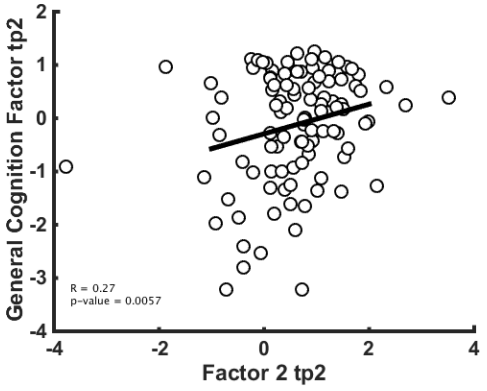

Clinical Factor baseline
Factor 1 baseline
R = 0.22
p-value = 0.0269


CLinical Factor baseline
Factor 2 baseline
R = 0.21
p-value = 0.0287


Executive Function Factor baseline
Factor 1 baseline
R = -0.28
p-value = 0.003


Executive Function Factor baseline
Factor 2 baseline
R = -0.06
p-value = 0.5572


General Cognition Factor tp2
Factor 1 tp2
R = 0.20
p-value = 0.0446


General Cognition Factor tp2
Factor 2 tp2
R = 0.27
p-value = 0.0057

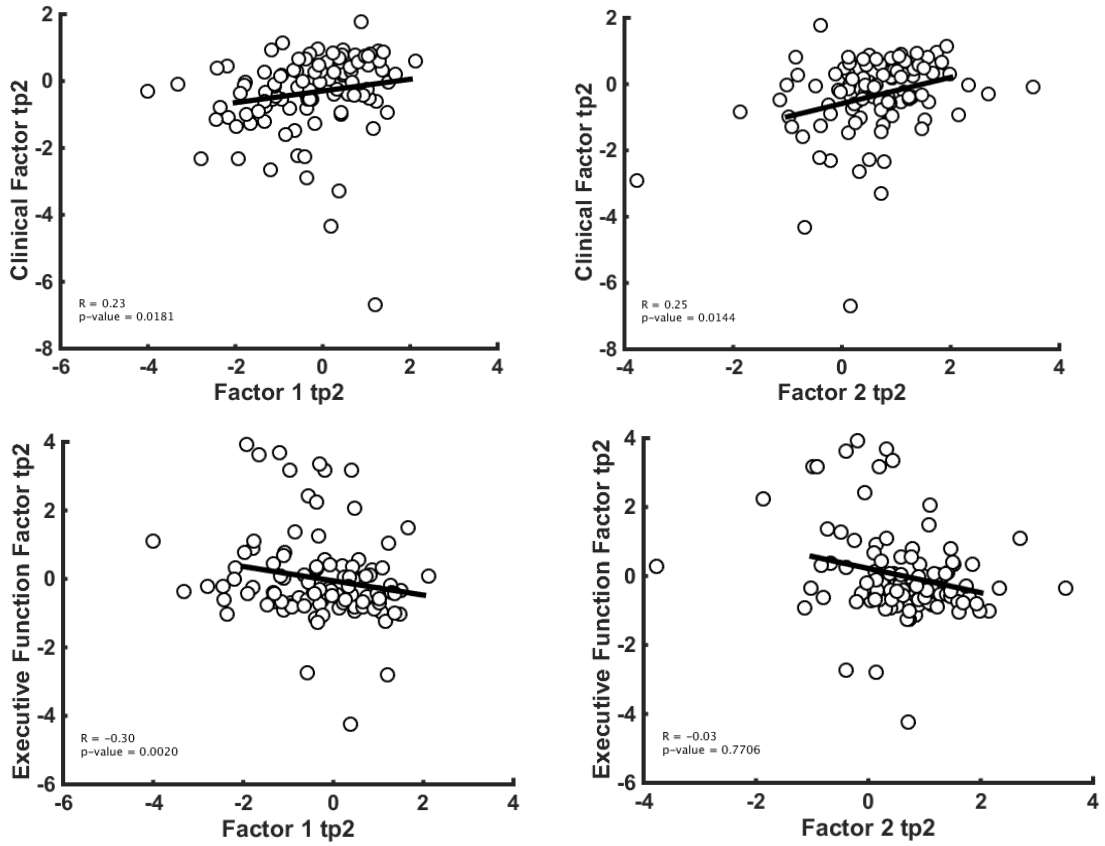


Figure 2 Neuroimaging Factors in relation to all neuropsychological factors. Cross-sectional associations at both baseline and time point 2 shown. Cross sectional correlation coefficients and significance from Pearson's R. (tp2: time point 2)

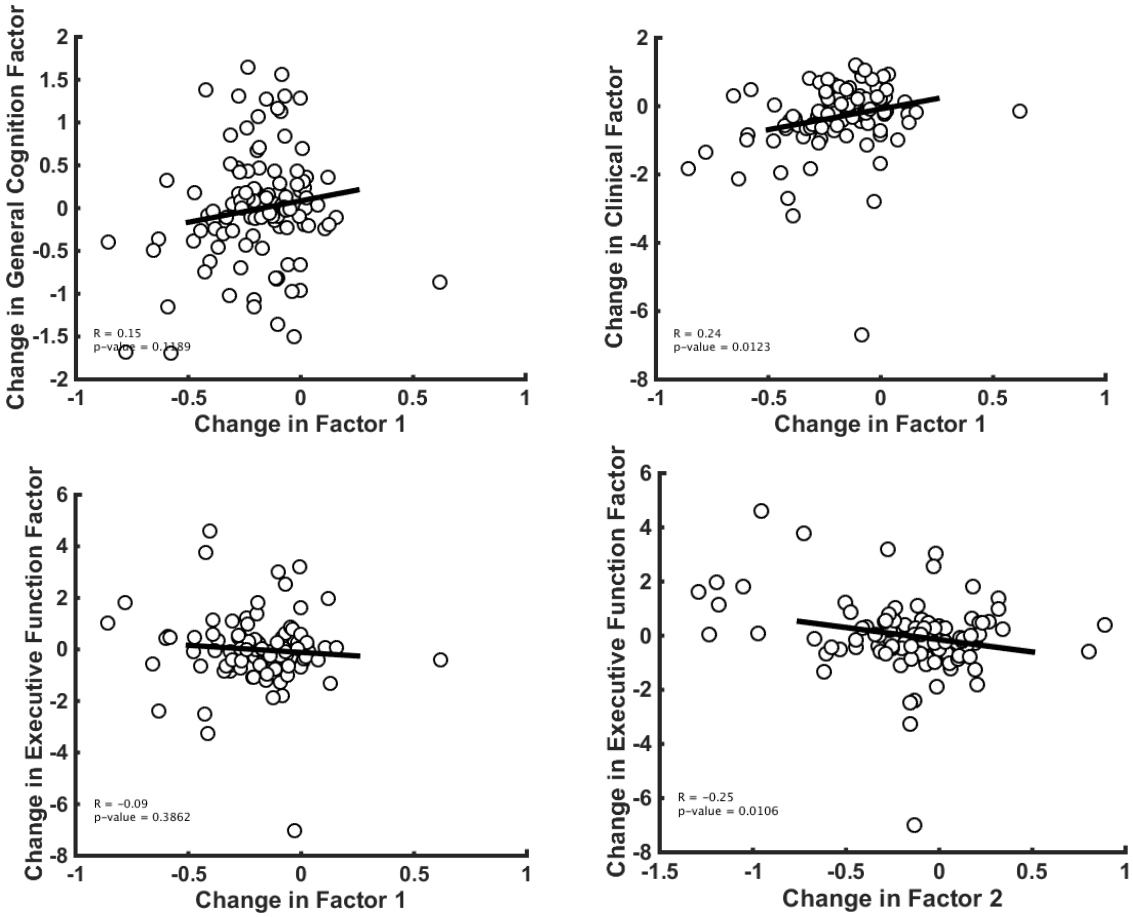


Figure 3 Longitudinal associations between both neuroimaging factors and neuropsychological factors. Longitudinal correlation coefficients and significance from Pearson's R.

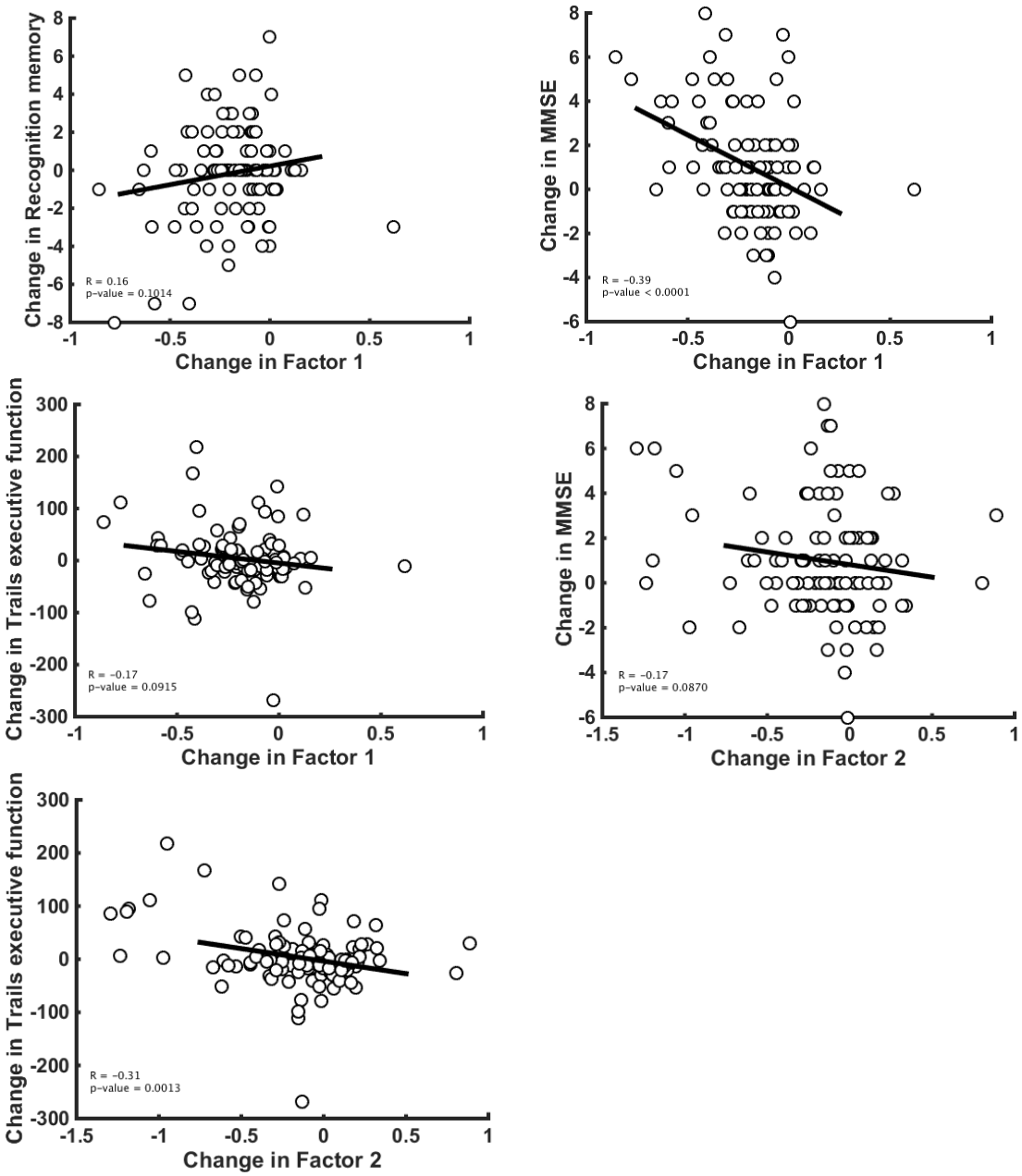


Figure 4 Longitudinal associations between both neuroimaging factors and neuropsychological measures representing the highest loadings from each neuropsychological factor. Longitudinal correlation coefficients and significance from Pearson's R. (MMSE: Mini Mental State Exam)

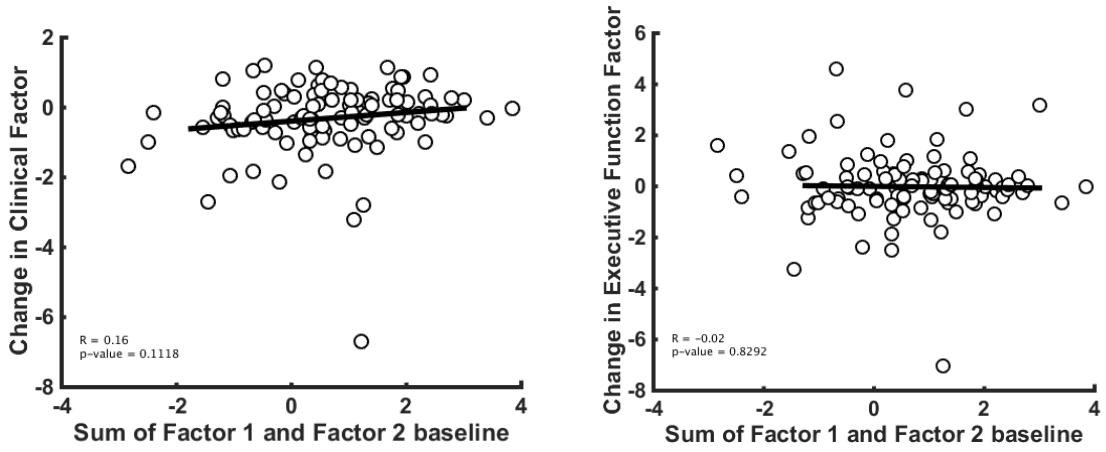


Figure 5 Associations between all neuroimaging measures at baseline and the change in Clinical and Executive Function Factors. Correlation coefficients and significance from Pearson's R.