Published in final edited form as:

Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2014 ; 21(2): 197–213. doi:

10.1080/13825585.2013.795513

Processing Speed in Normal Aging: Effects of White Matter Hyperintensities and Hippocampal Volume Loss

Kathryn V. Papp¹, Richard F. Kaplan¹, Beth Springate¹, Nicola Moscufo², Dorothy B. Wakefield³, Charles R.G. Guttman², and Leslie Wolfson³

¹Department of Psychiatry, University of Connecticut Health Center, Farmington, CT

²Department of Radiology, Brigham and Women's Hospital, Boston, MA

³Department of Neurology, University of Connecticut Health Center, Farmington, CT

Abstract

Changes in cognitive functioning are said to be part of normal aging. Quantitative MRI has made it possible to measure structural brain changes during aging which may underlie these decrements which include slowed information processing and memory loss. Much has been written on white matter hyperintensities (WMH), which are associated with cognitive deficits on tasks requiring processing speed and executive functioning, and hippocampal volume loss, which is associated with memory decline. Here we examine volumetric MRI measures of WMH and hippocampal volume loss together in relation to neuropsychological tests considered to be measures of executive functioning and processing speed in 81 non-demented elderly individuals, aged 75-90. Correlational analysis showed that when controlling for age, both greater WMH volume and smaller hippocampal volume were correlated with slower performances on most tests with the exception of a battery of continuous performance tests in which only WMH was correlated with slower reaction time (RT). We then performed a series of hierarchical multiple regression analyses to examine the independent contributions of greater WMH volume and reduced hippocampal volume to executive functioning and processing speed. The results showed that for the four measures requiring executive functioning and speed of processing, WMH volume and hippocampal volume combined predicted between 21.4 and 37% of the explained variance. These results suggest that WM integrity and hippocampal volume influence cognitive decline independently on tasks involving processing speed and executive function independent of age.

INTRODUCTION

Kral (1962) observed that declines in cognitive functioning occurred in normal aging and coined the term senescent forgetfulness to differentiate this from more malignant forms of cognitive decline due to neurological disease. However, even among the normal elderly there is considerable variability in cognitive aging. An examination of normative data tables comparing neuropsychological test scores by age for speed of processing, memory and executive function typically show decreasing levels of performance and increasing variability. Some of the increased variance can be attributed to health-related problems also associated with age, which can adversely affect cognitive functioning (Busch, Chelune and Suchy, 2006). Related to this are declines in brain volume (atrophy) in both the gray and white matter.

Historically, white matter changes in aging were attributed to vascular insufficiency secondary to small vessel disease and progressing to Binswanger's disease (BD) and vascular dementia (see Babikian and Roper for review, 1987). However, with the advent of neuroimaging it became clear that white matter abnormalities are ubiquitous in the elderly, and many patients with apparent white matter disease on imaging do not have dementia

(Bradley, Walluch, Brant-Zawadzki, Yardley, & Wyckoff, 1984). Hachinski and colleagues (1987) argued that the concept of BD evolved from an inaccurate and over-reaching description of white matter abnormalities to describe not only the pathology relating to vascular dementia, but also included more common and benign incidents of white matter changes that did not produce dementia. The term leukoaraiosis, meaning “rarified white matter,” was introduced to reflect a more neutral characterization of white matter abnormalities. Moreover, it has been estimated that about 10% of asymptomatic people aged 50-75 have confluent leukoaraiosis on MRI scans (O’Sullivan, 2008). Leukoaraiosis can be seen as bright foci (white matter hyperintensities) in the brain parenchyma on FLAIR (Fluid Attenuated Inversion Recovery) MRI scans, which are associated with increasing age, vascular risk factors and cerebrovascular disease (Breteler, van Swieten, Bots, Grobbee, & Claus et al. 1994; Liao, Myers, Hunt, Shahar, & Paton et al., 1997). They often begin as punctuate areas that expand forming larger confluent regions with disease progression. WMHs usually occur in the anterior and posterior periventricular regions and extend outward (Wakefield et al., 2010). WMHs may represent incomplete infarction due to hypoperfusion associated with underlying small vessel disease (Malloy et al., 2004) but other mechanisms are possible (Wolfson et al., 2005).

Although the precise relationship between WMH and vascular cognitive impairment remains unclear, numerous studies have shown that presence of WMH not only increases with age but is related to specific types of cognitive decline (Cook, Leuchter, Morgan, Dunkin, & Witte et al., 2004; Hentschel, Damian, Krumm, & Froelich, 2007), particularly tasks requiring speed and executive functioning (EF) (Rabbitt, Scott, Lunn, Thacker, & Lowe et al. 2007; Raz, Rodrigue, Kennedy, & Acker, 2007; van den Heuvel, den Dam, de Craen, Admiraal, Behloul & Olofsen et al., 2006).

Decreases in hippocampal volume with age are well documented (Jernigan et al., 1991; Bartzokis et al., 2001; Chen, Chuah, Sim, & Chee, 2010; Pruessner, Collins, Pruessner, & Evans, 2001; Ystad et al., 2009) and a longitudinal study showed that the decline increases after age 70 (Scahill et al. 2003). Relationships between hippocampal volume loss and memory performance have also been demonstrated. In a cross-sectional study of nondemented elderly aged 60-90, those with a larger hippocampus scored significantly higher on memory tests (Hackert et al., 2002). In another cross-sectional study of middle-aged and elderly individuals, delayed recall of a list was also positively correlated with hippocampal volume (Ystad et al., 2009). Most longitudinal studies support a relationship between declining hippocampal volume and poorer memory. Mungas et al (2005) observed an annual 1.1% rate of decline in hippocampal volume over an average of 3.4 years in their study of nondemented adults aged 58-87; the rate of loss accelerated in individuals with cognitive complaints. Furthermore, atrophy of the hippocampus in a longitudinal study of 511 people aged 60-90 predicted dementia during a 6-year follow-up period (Heijer et al., 2006).

In summary, research shows that white matter abnormalities and decreases in medial temporal lobe gray matter in the hippocampus influence neuropsychological test performance in the normal elderly and are predictors of cognitive decline. WMH volume appears to be linked more closely to speed of information processing and executive functioning whereas hippocampal atrophy seems most directly related to learning and memory loss. However, to our knowledge few studies have examined WMH and hippocampal volume loss together in relation to cognitive decline in the normal elderly. In the present investigation several commonly used speed of processing measures whose executive functioning and motor requirements differ were examined in relation to WMH volume and total hippocampal volume. Speed of processing measures were defined as tests in which time to complete the task or the number of correct responses in a given time were

the dependent measures. Brain regions of interest included total WMH volume and WMH volume in the frontal lobe and corpus callosum, as well total gray matter volume of the hippocampus.

METHODS

Participants

Participants from greater Hartford CT aged 75 through 89 were recruited from senior centers, senior living facilities, physician referrals, and newspaper advertisements to take part in a study of mobility impairment. Three hundred and twelve individuals were screened by telephone, 164 were eligible, consenting individuals, and 117 presented for a physical examination. A total of 99 individuals participated at baseline. Exclusion criteria at baseline included neurologic disease compromising mobility (e.g., Parkinson's disease, stroke, ataxia), sensory deficit (e.g., vestibular impairment, corrected distance vision > 20/70), medication impairing motor function, cognitive impairment (Mini-Mental State Exam score < 24), unstable cardiovascular disease (e.g., myocardial infarct within 6 months, unstable angina), inability to walk 10 meters independently in 50 seconds or less, weight greater than 250 pounds, excessive alcohol intake, pacemaker or other metallic devices/implants which prohibit MRI, and expected lifespan < 4 years. Seventeen subjects were excluded because of arthritis, Parkinson's disease, and claustrophobia and one because of a clinically silent tentorial meningioma. Participants were given a detailed description of the study, after which they provided informed consent. Participants and assessors were blinded to clinical, mobility, and imaging outcomes. The protocol was approved by the University of Connecticut Health Center institutional review board.

The current analyses include data from 81 of the original 99 at the two year follow-up evaluation. All were Caucasian as attempts to recruit minority participants were not successful. This time point was chosen because it included measures not administered at baseline. Reasons for attrition include death (6), refused MRI (2), unable to locate (1), moved from the area (3), no longer interested (2) and health reasons (2). Demographic information for the final sample ($n=81$) is presented in Table 1.

Brain imaging

Brain MR images of the head were acquired on a 3-Tesla Siemens Allegra scanner (Erlangen, Germany) using the following three MR sequences: 1) T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE, 176 contiguous axial slices, slice thickness=1 millimeters (mm), TR=2500, TE=2.74 milliseconds (ms), TI=900 ms, field of view (FOV)=256×208 mm²); 2) 3D-Fast Spin Echo (T2, 176 contiguous sagittal slices, slice thickness=1 mm, TR=2500, TE=353 ms, FOV=256×220 mm²), and 3) Fluid Attenuated Inversion Recovery (FLAIR) (128 contiguous sagittal slices, slice thickness=1.3 mm, TR=6000, TE=353 ms, TI=2200 ms, FOV=256×208 mm²).

Image analysis

Image analysis was previously described (Moscufo et al., 2011). MPRAGE and FLAIR images were used for semi-automated expert-supervised segmentation of white matter hyperintensities (WMH) using the 3D-Slicer (version 2.6) (Pohl, Bouix, Kikinis, & Grimson, 2004) and Free Surfer (version 4.5) applications (Fischl, Salat, Busa, Albert & Dieterich et al. 2002). Free Surfer data output were reviewed visually for the presence of major errors, and if they were found, editing was performed. To account for differences in head size, the total WMH volumes were expressed as percent of the intracranial cavity volume (ICV), which included brain parenchyma and cerebrospinal fluid. The WMH burden in selected regions of interest (ROIs) was determined using a white matter parcellation atlas

for the genu and splenium of the corpus callosum, anterior and posterior limbs of the internal capsule, anterior and posterior limbs of the corona radiata (Mori et al., 2008) and a cortical structures atlas for frontal WMH (Shattuck et al., 2008). These atlases were spatially normalized to each subject's brain at baseline (Moscufo et al. 2011). Regional WMH burden in specific white matter areas was expressed as percent of the ROI volume. Total and frontal WMH volume was expressed as a percent of the ICV. Volumes of deep GM structures such as the hippocampus were calculated from the FreeSurfer brain segmentation outputs and expressed as percent of subjects' ICV resulting in an intraclass correlation coefficient was 0.99 ($p=5\times 10^{-9}$, 95% CI: 97.7, 99.9). The mean overlap of WMH pixels between outputs and the gold standard maps was $82.9\% \pm 6.6$ (min-max: 71.3-92.2). Reproducibility was assessed on ten study subjects who agreed to participate in a test-retest experiment in which two MR images of the brain were taken the same day >1 hour apart. Anonymized scans were fully processed and the two WMH segmentation results for each subject compared. In this test the WMH intraclass correlation coefficient of 0.99 ($p=5\times 10^{-9}$). In overlap analysis the fraction of pixels reproducibly classified as WMH was $77.5\% \pm 12.3$ (95% CI: 68.7-86.3).

Neuropsychological Test Battery

The neuropsychological test battery included the following measures: 1) Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Form B (Randolph, 2003); 2) Trail Making Test, Parts A (TMT-A) and B (TMT-B) (Lezak, et. al., 2012); 3) Stroop Color and Word Test (Golden & Freshwater, 2002); 4) California Computerized Assessment Package, a continuous performance test (CalCAP; Miller, 2001) 5) the Grooved Pegboard Test, a measure of eye hand coordination and fine motor speed and control (GPT; Lafayette Instrument Company; Model 32025) and 6) the Controlled Oral Word Association Test (COWAT), a measure of semantic and phonemic verbal fluency. The Wechsler Test of Adult Reading Test (WTAR) was also included to provide an IQ estimate. All tests were administered by trained examiners using standardized procedures.

This report focuses on selected timed measures of speed of processing, executive functioning, fine motor control and reaction time chosen from the aforementioned battery. The Coding Subtest from the RBANS, the TMT Parts A and B, the Stroop Color and Word Test, and the COWAT were chosen as processing speed measures with an executive functioning component. The Grooved Pegboard test was used to assess fine motor control and three subtests from CalCAP were used to assess reaction time. These CalCAP subtests were simple reaction time (SRT), the time to respond to any digit, choice reaction time (CRT) which adds the element of memory component by having the participant only respond to the number '7' and sequential reaction time (SeqRT), which adds the element of working memory by having the participant respond only when the same digit is presented twice in succession. The means and standard deviations for these measures for the entire sample are presented in Table 1.

RESULTS

The relationships between these speed of processing measures and WMH volume and hippocampal volume were examined using a partial correlation coefficient to control for age. As shown in Table 2, total WMH volume was significantly related to slower speed of processing scores on most standard clinical measures, with the exception of fine motor control (Grooved Pegboard). To further examine executive functioning we attempted to control for psychomotor speed and attention using the ratio of raw time score for TMT-B divided by the raw time score for TMT-A (Oosterman et al, 2010), and calculated a similar formula for the Stroop, the Stroop Color Word score divided by the Stroop Color score (Stroop CW/C). The partial correlation coefficients for Trails B/A ratio were similar to those

using the raw Trails B score alone. However, Stroop CW/C ratio was only significantly correlated with hippocampal volume and not WMH.

These partial correlations using total WMH volume were almost identical to those calculated using only frontal lobe WMH volume. In the corpus callosum, greater WMH volume was also correlated with slower processing speeds on the same tests; however most of the significant correlations occurred within the splenium of the corpus callosum with the fewest in the genu. In comparison, lower hippocampal volume seemed to affect all the tasks which required speed of processing and executive functioning, with the exception of the CalCAP tests in which only WMH was correlated with RT. For the Grooved Pegboard test there was a significant relationship between increased WMH and performance, but only WMH in the splenium of the corpus callosum and the dominant, but not non dominant hand. Greater hippocampal volume was also significantly correlated to the time to complete the test, but again only for the dominant hand.

Greater WMH and smaller hippocampal volumes were both significantly correlated with slower processing speeds on Coding, COWAT, TMT- B and Stroop Color-Word tests. To further explore the independent contributions of WMH volume and hippocampal volume on these tasks, we used a hierarchical multiple regression analysis. When the Coding score was regressed on age alone an R value of .455 was obtained (Table 3). Adding total WMH volume to the model increased the proportion of explained variance from 20 to 27% and reduced the *beta* weight slightly from -.46 to -.45. The addition of hippocampal volume further improved prediction power to 36.1% of the variance indicating that all three variable independently influenced speed of processing on this measure.

A slightly different pattern emerged when we used the same hierarchical multiple regression analysis to predict COWAT scores (Table 4). Interestingly, age no longer was a significant predictor of better performance. When COWAT scores were regressed on total WMH an R value of .404 was obtained accounting for 16.4% of the variance, and the addition of hippocampal volume increased prediction to 21.4 % of explained variance.

The results for the TMT-B were similar to those of Coding (Table 5). When the TMT-B score was regressed on age alone we obtained a multiple R value of .295. The addition of total WMH volume increased the proportion of explained variance from 8 to 13%. When hippocampal volume was added to the model the amount of explained variance grew to 24%, but the final *beta* weight for age decreased from .29 to .20 and age was no longer significant suggesting that the greatest proportion of explained variance was by increased WMH volume and decreased hippocampal volume.

Using same methods, we then tested the Stroop Color Word score. The findings were more similar to Coding, than TMT- B or the COWAT. When the Stroop Color Word score was regressed on age alone the resulting model yielded a multiple R of .466, similar to the Coding Test. The addition of total WMH to the model increased the percentage of explained variance from 21.7 to 26.7%, and when hippocampal volume was added to the model the total explained variance grew to 37.8%. Again, similar to Coding each variable added significantly to the model with the final *beta* weights for age (-.383), WMH volume hippocampal volume (-.206) and hippocampal volume (.342) all significant.

DISCUSSION

The present study looked at changes in cognitive aging by comparing several measures of processing speed and executive functioning in relation to two neurological changes associated with aging, the development of WMH and hippocampal volume loss. Commonly

used neuropsychological measures of speed of processing and executive functioning differ in what cognitive abilities are required even though time is the dependent metric. For example, the TMT-B test, a commonly used measure of divided attention and cognitive flexibility, involves motor speed, visual search and executive functioning, specifically working memory (Lezak et al., 2012). In contrast, the COWAT also considered a timed measure of executive functioning requires no visual search or motor speed. Nevertheless, a primary finding in these data was that the best model for predicting all four speed of processing and executive functioning measures, Coding, TMT-B, COWAT and Stroop Color Word, included both white matter integrity and hippocampal volume. The CalCAP tests, measures of visuomotor reaction time, were all strongly related to WMH, but not hippocampal volume, and the Grooved Pegboard, a measure of fine motor skills, was only related to WMH in the splenium in the dominant hand. It could be argued that the two tests which did not fit this pattern, the Grooved Pegboard and CalCAP, differ in that they require little executive functioning. However, two of the three CalCAP tests have a memory requirement, CRT and SeqRT, so it is unclear why there was no relation to hippocampal volume.

The relationship between processing speed and white matter abnormalities is well described (Bartzokis, Sultzer, Lu, Nuechterlein & Mintz, & et al. 2004; O'Sullivan, Jones, Summer, Morris & Williams et al. 2001). In their review of the literature, Gunning-Dixon and Raz (2000) found increased WMH volume in healthy elderly was most consistently related to declines in processing speed, executive functioning, and memory but not to crystallized or fluid intelligence and fine motor skills. Recent studies have attempted to more precisely define the relationship between white matter integrity and cognition by analyzing regional differences in WMH. Declines in processing speed in non-demented elderly have been linked to white matter integrity in the corpus callosum (Jokinen, Kalska, Mäntylä, Pohjasvaara, & Ylikoski et al. 2006; Bucur, Madden, Spaniol, Provenzale, & Cabeza et al. 2008), pericallosal frontal region (Bucur et al., 2008), anterior brain areas (Kennedy & Raz, 2009) and periventricular white matter (van den Heuvel et al. 2006). However, others argue that when white matter tracts are quantified using a principal components analysis, individual tracts show no associations beyond what the common integrity factor shows in explaining declines in processing speed (Penke, Maniega, Houlihan, Murray, & Gow et al. 2010). In a study from our group, an increase of 1% of total WMH volume resulted in a 1.5 to 2.4 fold increase in the likelihood of slowed performances on the Stroop Color and Word Test, the TMT-B test and the CalCAP (Wakefield et al. 2010). Although there is clearly a strong relationship between regional and total WMH (Wakefield et al. 2010), we also found that frontal, but not posterior WMH, affected speed of processing and executive functioning (Kaplan et al., 2009) suggesting some regional specificity. The correlations we report here further implicate WMH in some regions as more critical for certain speed of processing tasks when controlling for age. The frontal WMH and WMH in the splenium of the corpus callosum were both associated with decreases in performance on measures requiring RT, particularly on tasks requiring both speed and EF, whereas other white matter tracts were not. However, given that we generally obtained similar *r* values in our correlations between total WMH and regional WMH and the neuropsychological variables, we elected to use total WMH when comparing the contribution of WMH and hippocampal volume to cognitive functioning.

Although hippocampal volume loss has been linked to aging and memory loss and is a predictor of cognitive decline in the elderly (Heijer et al., 2006, Jack et al., 2010) less is known about its effect on other cognitive domains such as executive functioning. In a cross sectional study comparing hippocampal volume and cognitive functioning in younger (18-30 year old) and older (60-83 year old) adults, there was a significant positive relationship between hippocampal volume and a composite measure of fluid intelligence for older adults

but no relationship with composite scores for memory or processing speed (Rueban et. al, 2010). However, one of the composite tests comprising the fluid intelligence score was the letter number sequencing test, a measure requiring working memory and executive functioning, suggesting a relationship between hippocampal volume and executive functioning. Oosterman et al. (2010) attempted to isolate the executive function component of the TMT-B test using a ratio of TMT-B/TMT-A. When analyzed in a step-wise multiple regression the TMT-B raw score was predicted by medial temporal lobe atrophy and WMH, whereas the TMT-B/TMT-A ratio was primarily related to medial temporal lobe atrophy. Our data showed that both total WMH and hippocampal volume loss were significant predictors of TMT-B and TMT-B/TMT-A performance, although like Oosterman et al. (2010) hippocampal volume seems to have a stronger relationship to the TMT-B. Although both studies were conducted in normal elderly samples, our sample was considerably older, more educated and had better TMT scores overall. As such one or all of these differences could explain differences in our findings. Interestingly, when we attempted to isolate the executive component of the Stroop Color Word score by calculating a similar ratio with Stroop Color naming, the results were similar to what Oosterman et al. (2010) reported for TMT-B/TMT-A, in that only hippocampal volume loss significantly predicated poorer performance. The implications of this, as Oosterman et al. (2010) suggested, is that the hippocampus may have a role beyond memory and be directly involved in executive functioning. For the Stroop Color Word Raw Score, Coding and COWAT, the results were similar to TMT-B with both WMH and hippocampal volume predicting slower performances or fewer responses. However, for the COWAT and TMT-B, age did not add to the prediction.

Although the Grooved Pegboard test is a timed test, i.e., the instruction is to complete the task as quickly as possible, it is a relatively pure measure of fine motor skill without an executive functioning component. As in previous studies (Gunning-Dixon & Raz, 2000), we did not find a strong relationship between Grooved Pegboard performance and WMH. Fazekas and colleagues (2005) also did not find a relationship between frontal WMH and a similar task, the Purdue Pegboard, but did find a relationship between fine motor control and white matter abnormalities using another technique, magnetization transfer ratio (MTR). They proposed that MTR was more sensitive in quantifying WMH associated with tissue damage. Interestingly, in our study greater hippocampal volume was significantly correlated with better fine motor performance, but only in the dominant hand. Others (Kluger et al., 1997) have shown a decline in fine motor skills in mild cognitive impairment and early Alzheimer's disease, where the primary site of pathology is the hippocampus. However, our finding involved only one hand, suggesting the relationship between hippocampal atrophy and fine motor control requires further study.

These data also suggest that cognitive decline attributed to normal aging, such as slowed information processing and declines in executive functioning and working memory, are in part due to increased WMH and decreases in hippocampal volume which, while associated with age, vary independently. This has implications for what is considered normal aging because recent research has shown the role of elevated blood pressure in the progression of WMH volume and cognitive impairment, suggesting that intervention can reduce vascular disease in the brain and associated cognitive declines (Soderlund et al., 2003, White et al., 2011). Other lines of research have shown that the 1-2% annual hippocampal volume loss and associated memory loss in older adults can be mitigated by systematic aerobic exercise training (Erickson et al., 2010, Ahlskog et al., 2011). Taken together it is clear that the boundary between the declines in cognitive functioning occurred in normal aging and cognitive decline due to neurological disease as proposed by Kral (1962) may be shifting.

Lastly, certain characteristics of our sample need mentioning as they may limit the extent to which these findings can be generalized to a broader aging population. Our sample was exclusively Caucasian as attempts to recruit minority participants were unsuccessful. The age range of the sample was relatively narrow, 77-91, compared to other studies. Our sample was highly educated with 90% having graduated high school, and 70% having gone beyond high school. Our sample was also relatively healthy. The mean 24-average systolic blood pressure (SBP) was 130 (12.8) and mean 24-average diastolic 66.7 (7.2) with only 17 of 73 having Stage 1 hypertension (SBP >140), and no one with Stage 2 hypertension (SBP >160). As such, this cohort was not entirely representative of the elderly population at large, and future studies should attempt to include a more representative sample. Nevertheless differences in WMH and hippocampal volume can help explain the increasing variability in cognitive function with increasing age even in a relatively homogeneous normal elderly sample.

Acknowledgments

This work was made possible through the support of the National Institute of Health Grant RO1 AG022092 (LW) and the University of Connecticut Health Center General Clinical Research Center (MO1 RR06192).

References

- Ahlskog JE, Geda YE, Graff-Radford NR, Peterson RC. Physical exercise as a preventive or disease modifying treatment of dementia and brain aging. *Mayo Clin Proc.* 2011; 86(9):876–884. [PubMed: 21878600]
- Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, et al. Disruption of large-scale brain systems in advanced aging. *Neuron.* 2007; 56(5):924–935. [PubMed: 18054866]
- Babikian V, Roper AH. Binswanger's disease: A review. *Stroke.* 1987; 18:2–12. [PubMed: 3544352]
- Bartzokis G, Sultzer D, Lu PH, Nuechterlein KH, Mintz J, Cummings JL. Heterogeneous age-related breakdown of white matter structural integrity: Implications for cortical “disconnection” in aging and Alzheimer's disease. *Neurobiology of Aging.* 2004; 25(7):843–851. [PubMed: 15212838]
- Bradley WG, Walluch V, Brant-Zawadzki M, Yardley RA, Wycoff RR. Patchy, periventricular white matter lesions in the elderly: A common observation during NMR imaging. *Noninvasive Medical Imaging.* 1984; 1:35–41.
- Breteler MMB, van Swieten JC, Bots ML, Grobbee DE, Claus JJ, van den Hout JHW, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study. *Neurology.* 1994; 44:1246. [PubMed: 8035924]
- Bucur B, Madden DJ, Spaniol J, Provenzale JM, Cabeza R, White LE, et al. Age-related slowing of memory retrieval: Contributions of perceptual speed and cerebral white matter integrity. *Neurobiology of Aging.* 2008; 29(7):1070–1079. [PubMed: 17383774]
- Busch, RM.; Chelune, GJ.; Suchy, Y. Norms in the neuropsychological assessment of the elderly. In: Attix, DK.; Welsh-Bohmer, KA., editors. *Geriatric neuropsychology: Assessment and Intervention.* New York: Guilford Press; 2006. p. 133-140.
- Chen KHM, Chuah LYM, Sim SKY, Chee MWL. Hippocampal region-specific contributions to memory performance in normal elderly. *Brain and Cognition.* 2010; 72(3):400–407. [PubMed: 20044193]
- Chiaravalloti ND, Christodoulou C, Demaree HA, DeLuca J. Differentiating simple versus complex processing speed: Influence on new learning and memory performance. *Journal of Clinical and Experimental Psychology.* 2003; 25(4):489–501.
- Cook IA, Leuchter AF, Morgan ML, Dunkin JJ, Witte E, David S, et al. Longitudinal progression of subclinical structural brain disease in normal aging. *American Journal of Geriatric Psychiatry.* 2004; 12(2):190–200. [PubMed: 15010348]
- den Heijer T, Geerlings MI, Hoebeek FE, Hofman A, Koudstaal PJ, Monique MBB. Use of hippocampal and amygdala volumes on magnetic resonance imaging to predict dementia in

- cognitively intact elderly people. *Archives of General Psychiatry*. 2006; 63:57–62. [PubMed: 16389197]
- Erikson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. *Proceeding of the National Academy of Sciences*. 2011; 108:3017–3022.
- Fazekas F, Ropele S, Enzinger C, Gorani F, Seewann A, Petrovic K, et al. MTI of white matter hyperintensities. *Brain*. 2005; 128:2926–2932. [PubMed: 15958507]
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; 33:341–355. [PubMed: 11832223]
- Golden, CJ.; Freshwater, SM. The stroop color and word test: A manual for clinical and experimental uses. Wood Dale, IL: Soelting; 2002.
- Gunning-Dixon FM, Raz N. The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. *Neuropsychology*. 2000; 14(2):224–232. [PubMed: 10791862]
- Hachinski VC, Potter P, Merskey H. Leuko-araiosis. *Archives of Neurology*. 1987; 44(1):21–23. [PubMed: 3800716]
- Hackert VH, den Heijer T, Oudkerk M, Koudstaal PJ, Hofman A, Breteler MMB. Hippocampal head size associated with verbal memory performance in nondemented elderly. *NeuroImage*. 2002; 17(3):1365–1372. [PubMed: 12414276]
- Hentschel F, Damian M, Krumm B, Froelich L. White matter lesions – age-adjusted values for cognitively healthy and demented subjects. *Acta Neurologica Scandinavica*. 2007; 115:174–180.
- Jack CR, Peterson RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, et al. Rates of hippocampal atrophy correlate with the change in clinical status in aging and AD. *Neurology*. 2000; 55:484–489. [PubMed: 10953178]
- Jernigan TL, Archibald SL, Berhow MT, Sowell ER, Foster DS, Hesselink JR. Cerebral structure on MRI, Part 1: Localization of age-related changes. *Biological Psychiatry*. 1991; 29:55–67. [PubMed: 2001446]
- Jokinen H, Kalska H, Mäntylä R, Pohjasvaara T, Ylikoski R, Hietanen M, et al. Cognitive profile of subcortical ischaemic vascular disease. *Journal of Neurology, Neuropsychiatry, and Psychiatry*. 2006; 77:28–33.
- Kennedy KM, Raz N. Aging white matter and cognition: Differential effects of regional variations in diffusion properties on memory, executive functions, and speed. *Neuropsychologia*. 2009; 47(3): 916–927.
- Kluger A, Gianutsos JG, Golomb J, Ferris SH, George AJ, Franssen E. Patterns of motor control in normal aging, mild cognitive decline, and early Alzheimer's disease. *Journal of Gerontology: PSYCHOLOGICAL SCIENCES*. 1997; 52B:P28–P39.
- Kral VA. Senescent forgetfulness: Benign and malignant. *Journal of the Canadian Medical Association*. 1962; 86:257–260.
- Lezak, MD.; Howieson, DB.; Bigler, ED.; Tranel, D. Neuropsychological assessment. 5. New York: Oxford University Press; 2012.
- Liao D, Myers R, Hunt S, Shahar E, Paton C, Burke G, et al. Familial history of stroke and stroke risk: The family heart study. *Stroke*. 1997; 28:1908–1912. [PubMed: 9341694]
- Malloy P, Correia S, Stebbins G, Laidlaw DH. Neuroimaging of white matter in aging and dementia. *The Clinical Neuropsychologist*. 2007; 21:73–109. [PubMed: 17366279]
- Miller, EN. California computerized assessment package. Los Angeles: Norland Software; 2001.
- Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage*. 2008; 40:570–582. [PubMed: 18255316]
- Moscufo N, Guttmann C, Meier D, Csapo I, Hildenbrand P, Healy B, et al. Brain regional lesion burden and impaired mobility in the elderly. *Neurobiology of Aging*. 2011; 32:646–654. [PubMed: 19428145]
- Mungas D, Harvey D, Reed BR, Jagust WJ, DeCarli C, Beckett L, Mack WJ, et al. Longitudinal volumetric MRI change and rate of cognitive decline. *Neurology*. 2005; 65(4):565–571. [PubMed: 16116117]

- O'Brien, AR.; Tulskey, DS. The history of processing speed and its relationship to intelligence. In: DeLuca, J.; Kalmar, JH., editors. Information processing in clinical populations. New York: Psychology Press; 2007. p. 1-28.
- Oosterman JM, Raymond L, Vogels C, van Harten B, Gouw AA, Poggesi A, Scheltens P, et al. Assessing mental flexibility: Neuroanatomical and neuropsychological correlates of the Trail Making Test in elderly people. *The Clinical Neuropsychologist*. 2010; 24:203–219. [PubMed: 20162494]
- O'Sullivan M. Leukoaraiosis. *Practical Neurology*. 2008; 8:26–38. [PubMed: 18230707]
- O'Sullivan M, Jones D, Summer P, Morris R, Williams S, Markus H. Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology*. 2001; 57:632–638. [PubMed: 11524471]
- Park, DC.; Schwarz, N. Cognitive aging: A primer. Philadelphia, PA: Psychology Press; 2000.
- Penke L, Maniega SM, Houlihan LM, Murray C, Gow AJ, Clayden JD, et al. White matter integrity in the splenium of the corpus callosum is related to successful cognitive aging and partly mediates the protective effect of an ancestral polymorphism in ADRB2. *Behavior Genetics*. 2010; 40(2): 146–156. [PubMed: 20087642]
- Pohl, KM.; Bouix, S.; Kikinis, R.; Grimson, WEL. IEEE International Symposium on Biomedical Imaging: From Nano to Macro. Arlington, VA, USA: 2004. Anatomical guided segmentation with non-stationary tissue class distributions in an expectation-maximization framework; p. 81-84.
- Pruessner JC, Collins DL, Pruessner M, Evans AC. Age and Gender Predict Volume Decline in the Anterior and Posterior Hippocampus in Early Adulthood. *Journal of Neuroscience*. 2001; 21(1): 194–200. [PubMed: 11150336]
- Rabbitt P, Scott M, Lunn M, Thacker N, Lowe C, Pendleton N, et al. White matter lesions account for all age-related declines in speed but not in intelligence. *Neuropsychology*. 2007; 21(3):363–370. [PubMed: 17484599]
- Randolph, C. RBANS manual: Repeatable Battery for the assessment of neuropsychological status. San Antonio, TX: Psychological Corporation; 1998.
- Raz N, Rodrigue KM, Kennedy KM, Acker JD. Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology*. 2007; 21(2):149–157. [PubMed: 17402815]
- Reitan RM. Validity of the TMT as an indicator of organic brain damage. *Perceptual and Motor Skills*. 1958; 8:271–276.
- Scahill RI, Frost C, Jenkins R, Whitwell JL, Rosser MN, Fox N. A longitudinal study of brain volume changes in normal aging using serial magnetic resonance imaging. *Archives of Neurology*. 2003; 60:989–994. [PubMed: 12873856]
- Shattuck DW, Mirza M, Adisetiyo V, Hojatkashani C, Salamon G, Narr KL, et al. Construction of a 3D probabilistic atlas of human cortical structures. *Neuroimage*. 2008; 39:1064–1080. [PubMed: 18037310]
- Soderlund H, Nyberg L, Adolfsson R, Nilsson L-G, Launer LJ. High prevalence of white matter hyperintensities in normal aging: Relation to blood pressure and cognition. *Cortex*. 2003; 39:1093–1105. [PubMed: 14584568]
- Stroop JR. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*. 1935; 18:643–662.
- van den Heuvel DMJ, ten Dam VH, de Craen AJM, Admiraal Behloul F, Olofsen H, Bollen ELEM, et al. Increase in periventricular white matter hyperintensities parallels decline in mental processing speed in a non demented elderly population. *Journal of Neurology, Neuropsychiatry, and Psychiatry*. 2006; 77(2):149–153.
- Wakefield DB, Moscufo N, Guttmann CR, Kuchel GA, Kaplan RF, Pearlson G, et al. White matter hyperintensities predict functional decline in voiding, mobility and cognition in older persons. *Journal of the American Geriatric Society*. 2010; 58(2):275–281.
- White WB, Wolfson L, Wakefield DB, Hall CB, Cambell P, Moscufo N, et al. Average daily blood pressure, not office blood pressure, is associated with progression of cerebrovascular disease and cognitive decline in older people. *Circulation*. 2011; 124:2312–2319. [PubMed: 22105196]

- Wolfson L, Wei X, Hall CB, Panzer V, Wakefield D, Benson RR, et al. Accrual of MRI white matter abnormalities in elderly with normal and impaired mobility. *Journal of the Neurological Sciences*. 2005; 232:23–27. [PubMed: 15850578]
- Ystad MA, Lundervold AJ, Wehling E, Espeseth T, Rootwelt H, Westlye LT, Andersson M, et al. Hippocampal volumes are important predictors for memory function in elderly women. *BMC Medical Imaging*. 2009; 9:17. [PubMed: 19698138]

Table 1**Subject Characteristics**

Demographics	Mean (SD)	Range
Age	83.8 (3.9)	77-91
Sex (Males/Females)	31/50	
Education	15.0 (2.7)	9-20
WTAR	114.0 (12.3)	78-128
Tests	Mean (SD)	Range
RBANS Coding	34.9 (8.7)	10-62
TMT-A	48.8 (15.9)	25-95
TMT-B	130.0 (75.6)	45-488
COWAT	36.9 (11.5)	12-69
Stroop Word	85.0 (15.0)	53-121
Stroop Color	56.0 (11.3)	22-87
Stroop Color-Word	26.2 (9.3)	2-49
CalCAP SRT	429.5 (181.5)	228-1332
CalCAP CRT	475.25 (87.4)	344-853
CalCAP Seq RT	602.5 (118.4)	366-854
GP Dominant	117.5 (40.1)	65-251
GP Nondominant	134.6 (56.6)	64-500

Note. WTAR = Wechsler Test of Adult Reading; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; TMT=Trail Making Test; COWAT = Controlled Oral Word Association Test; CalCAP = California Computerized Assessment Package; SRT=simple reaction time; CRT= complex reaction time; SeqRT= sequential reaction time; GP = Grooved Pegboard

Partial Correlations Controlling for Age

Note. WMH = white matter hyperintensity; CC= corpus callosum
COWAT = Controlled Oral Word Association Test; CalCAP = California Computerized Assessment Package; SRT=simple reaction time; SeqRT= sequential reaction time

$$** = p < .01$$

Table 3

Multiple Regression Analysis Predicting RBANS Coding

(Step) Predictor	Beta [§]	Multiple R	R ²	R ² Change	F Change	F Model
Analysis 1 (1) Age	-.455**	.455	.207	.207	F(1,74)=19.28***	F(1,74) = 19.28***
Analysis 2 (1) Age	-.445**					
(2) WMH	-.251	.519	.270	.063	F(1,73) = 6.29*	F(2,73) = 13.47***
Analysis 3 (1) Age	-.378**					
(2) WMH	-.236*					
(3) Hipp Volume	.310****	.601	.361	.091	F(1,72) = 10.30**	F(3,72) = 13.56***

Note. WMH = white matter hyperintensities; Hipp = hippocampal; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status

[§] Refers to Beta weight at final step in each analysis

* = $p < .05$;

** = $p < .01$;

*** = $p < .001$,

ns = non significant

Table 4

Multiple Regression Analysis Predicting COWAT

(Step) Predictor	Beta [§]	Multiple R	R ²	R ² Change	F Change	F Model
<i>Analysis 1</i>						
(1) Age	-.041ns	.041	.002	.002	F(1,72) = .120ns	F(1,74) = .120ns
<i>Analysis 2</i>						
(1) Age	-.025ns					
(2) WMH	-.403***	.404	.164	.162	F(1,71) = 13.7***	F(2,73) = 6.94**
<i>Analysis 3</i>						
(1) Age	.025ns					
(2) WMH	-.392***					
(3) Hipp Volume	.231*	.463	.214	.051	F(1,70) = 4.51*	F(3,70) = 6.35**

Note. WMH = white matter hyperintensities; Hipp = hippocampal; COWAT = Controlled Oral Word Association Test

[§] Refers to Beta weight at final step in each analysis

* = $p < .05$;

** = $p < .01$;

*** = $p < .001$;

ns = not significant

Table 5

Multiple Regression Analysis Predicting TMT-B

(Step) Predictor	Beta§	Multiple R	R²	R² Change	F Change	F Model
Analysis 1						
(1) Age	.295**	.295	.0874	.087	F(1,73)=6.94**	F(1,74) =6.94**
Analysis 2						
(1) Age	.286*					
(2) WMH	.224*	.370	.137	.050	F(1,72) =4.19*	F(2,72) = 5.72**
Analysis 3						
(1) Age	.203ns					
(2) WMH	.206*					
(3) Hipp Volume	-.383***	.526	.277	.139	F(1,71) = 13.6***	F(3,71) = 9.04***

Note. WMH = white matter hyperintensities; Hipp = hippocampal; TMT = Trail Making Test

§ Refers to Beta weight at final step in each analysis;

* = $p < .05$;

** = $p < .01$;

*** = $p < .001$,

ns = non significant

Table 6

Multiple Regression Analysis Predicting Stroop Color Word

(Step) Predictor	Beta [§]	Multiple R	R ²	R ² Change	F Change	F Model
Analysis 1 (1) Age	-.466***	.466	.217	.217	F(1,74)=20.5***	F(1,74)=20.5***
Analysis 2 (1) Age	-.457***					
(2) WMH	-.222*	.516	.267	.049	F(1,73)=4.91*	F(2,73)=13.28***
Analysis 3 (1) Age	-.383***					
(2) WMH	-.206*					
(3) Hipp Volume	.342**	.615	.378	.111	F(1,72)=12.8***	F(3,72)=14.57***

Note. WMH = white matter hyperintensities; Hipp = hippocampal

[§] Refers to Beta weight at final step in each analysis;

* = $p < .05$;

** = $p < .01$;

*** = $p < .001$,

ns = non significant