The effects of white matter hyperintensities and amyloid deposition on Alzheimer dementia

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The effects of white matter hyperintensities and amyloid deposition on Alzheimer dementia

Brian A. Gordon a,b,c,* , Safa Najmi d, Phillip Hsu e , Catherine M. Roe c,f, John C. Morris c,f, Tammie L.S. Benzinger a,c,g

1. Introduction

Alzheimer disease (AD) is a rapidly expanding health crisis affecting over 26 million people, with the prevalence expected to rise dramatically (Brookmeyer et al., 2007). Research examining AD biomarkers suggests a rise in underlying pathology a decade or more before the onset of dementia, and continuing throughout the early stages of the disease (Bateman et al., 2012; Benzinger et al., 2013; Jack et al., 2010). Atrophy of cortical and subcortical gray matter has long been noted in AD (e.g. Fox et al., 1996; Gordon et al., 2013; Scheltens et al., 1992). Less attention has been paid to white matter damage and declines tied to AD disease progression. Early work with computed tomography (CT) images noted increased incidence of white matter leukoaraiosis in individuals with AD (Blennow et al., 1991; Rezek et al., 1987). Similar results were found with the introduction of magnetic resonance imaging (MRI) (Barber et al., 1999; Fazekas et al., 1987). In this initial work the most common way to characterize white matter damage was to use semi-quantitative scales (Fazekas et al., 1987; Kapeller et al., 2003; Scheltens et al., 1995) to grade the severity of white matter hyperintensities (WMHs) on T2-weighted or fluid-attenuated inversion recovery (FLAIR) scans. At a pathological level, the tissue suffering from WMHs demonstrates the loss of myelin and gliosis. Higher ratings on these scales are associated with both cognitive decline (Debette et al., 2007; Schmidt et al., 2005; van Straaten et al., 2008) and cortical atrophy (Capizzano, 2004; Schmidt et al., 2005). In general there is a rising interest on the clinical importance of WMH across diseases (Debette and Markus, 2010).

Background and purpose: Elevated levels of amyloid deposition as well as white matter damage are thought to be risk factors for Alzheimer Disease (AD). Here we examined whether qualitative ratings of white matter damage predicted cognitive impairment beyond measures of amyloid.

Materials and methods: The study examined 397 cognitively normal, 51 very mildly demented, and 11 mildly demented individuals aged 42–90 (mean 68.5). Participants obtained a T2-weighted scan as well as a positron emission tomography scan using 11C Pittsburgh Compound B. Periventricular white matter hyperintensities (PVWMHs) and deep white matter hyperintensities (DWMHs) were measured on each T2 scan using the Fazekas rating scale. The effects of amyloid deposition and white matter damage were assessed using logistic regressions.

Results: Levels of amyloid deposition (ps < 0.01), as well as ratings of PVWMH (p < 0.01) and DWMH (p < 0.05) discriminated between cognitively normal and demented individuals.

Conclusions: The amount of amyloid deposition and white matter damage independently predicts cognitive impairment. This suggests a diagnostic utility of qualitative white matter scales in addition to measuring amyloid levels.

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References:


The relationship between WMH and amyloid is complex and has not been fully evaluated, although there are suggestions that both contribute to cognitive impairment (Provenzano et al., 2013). White matter damage may be both a downstream result of elevated Aβ levels, as well as a marker of comorbid pathology (e.g. cardiovascular disease). Aβ leads to oxidative damage and the formation of free radicals (Hensley et al., 1994; Park et al., 2004; Thomas et al., 1996), and the administration of Aβ damages oligodendrocytes in vitro (Roth et al., 2005) and in vivo (Jantaratnotai et al., 2003). Conversely damage to myelin releases iron molecules that promote Aβ oligomerization (Bartzokis et al., 2007; Bartzokis, 2011). An initial rise in Aβ would damage white matter, which in turn would elevate Aβ levels, subsequently leading to more white matter damage in a continuing cyclical process. Alternatively, white matter lesions from a secondary process (e.g. head injury) may release iron, and initiate or accelerate the pathological influences of Aβ on white matter. Such results can be seen in the literature as circulating levels of Aβ are associated with WMH (Gurol et al., 2006), and baseline levels of white matter lesions predict an accelerated accumulation of amyloid over time (Grimmer et al., 2012).

Using semi-quantitative scales, white matter lesions have often been seen in individuals with compromised cardiovascular systems (Breteler et al., 1994; Longstreth et al., 1996). Consistent with these results, there has been a suggestion that AD may have a larger vascular component than often recognized (Bartzokis, 2011; de la Torre, 2010; Launer, 2002). Indeed, in epidemiological studies, cardiovascular risk factors such as diabetes or stroke lead to increased risk of AD (Luchsinger et al., 2001). Damage to the cardiovascular system, such as a thickening and sclerosis of arteries, may lead to an impaired drainage of molecules such as Aβ (Huang et al., 2010). Due to their potentially related nature, it is of interest to know whether the incidence of WMHs provides any diagnostic value above and beyond levels of Aβ pathology in the brain.

White matter damage in the brain can be assessed using visual ratings of WMH, quantification of WMH volumes, and using diffusion tensor imaging (DTI). While there is a clear utility to quantifying damage using DTI and WMH volumetric measurement, visual rating scales are an easily obtained radiological measure available across both research and clinical settings. Here we examine the relationships between Aβ deposition, white matter damage, and dementia in a population of cognitively normal, very mildly demented, and mildly demented individuals. Based upon prior work in the literature, we hypothesize that more severe semi-quantitative ratings of white matter damage will be related to an impaired cognitive status.

2. Materials and methods

2.1. Study population

Middle aged and older adults were drawn from studies on aging and dementia conducted through the Knight Alzheimer’s Disease Research Center (ADRC) at Washington University in St. Louis. Based upon the Clinical Dementia Rating (CDR) Scale (Morris, 1993) participants were classified as cognitively normal (CDR = 0, n = 397, female = 256), very mildly demented (CDR = 0.5, n = 51, female = 20), or mildly demented (CDR = 1, n = 11, female = 1). Individuals with dementia are also given a primary diagnosis by the examining neurologist. Using these diagnoses individuals whose dementia was thought to be from a non-Alzheimer cause (e.g. Lewy bodies, vascular dementia, depression) were excluded from all analyses. The population ranged in age from 42 to 90, with a mean age of 68.5 years (Table 1). All participants underwent a structural imaging session as well as positron emission tomography (PET) to estimate amyloid deposition using 11C Pittsburgh Compound B (PiB) (Klunk et al., 2004). All procedures where approved by Washington University’s institutional review board and were conducted in accordance with the Declaration of Helsinki.

### Table 1

<table>
<thead>
<tr>
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<td>.61 male</td>
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<td>67–90</td>
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<tr>
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<td>26.7 (2.5) x</td>
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<tr>
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<td>16–30</td>
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<td>.91 (.69)</td>
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<td>PiB x</td>
<td>.32 (.43) +</td>
<td>.91 (.69)</td>
<td>1.32 (.66)</td>
</tr>
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2.2. T2 protocol

High-resolution T2-weighted images were acquired on a Siemens Trio 3 T scanner (Siemens Medical Systems, Iselin, NJ). Scan parameters were: repetition time (TR) of 3200 ms, echo time (TE) of 455, flip angle (FA) = 120°, with a 256 × 256 field of view, and a 1 mm isotropic resolution.

2.3. Clinical ratings

A trained neurologist (S.N.), blind to clinical diagnosis, examined the T2-weighted images. The presence and severities of WMH were rated using criteria outlined by Fazekas et al. (1987). Briefly, periventricular hyperintensities (PVWMHs) were rated as follows: 0 absence of WMH; 1 “caps” or pencil-thin linings; 2 “halos”; and 3 irregular PVH extending into deep white matter. Ratings of WMH in the deep white matter (DWMH) were rated as follows: 0 absence of WMH, 1 solitary foci; 2 the beginning aggregation of foci; and 3 large confluent areas of WMH. Examples are given in Fig. 1 and distributions of scores across the three clinical groups are presented in Fig. 2. A subset of 29 individuals was rated two times to establish reliability. The intraclass correlation was .91 for periventricular ratings and .98 for deep white matter ratings.

2.4. PiB imaging

Participants underwent a 60-minute dynamic scan with PiB. Binding potentials were calculated for multiple regions of interest (ROIs) derived from Freesurfer using a cerebellar reference for regions-of-interest. The raw time–activity curve for each region was adjusted by a CSF dilution factor in a given voxel to yield partial volume corrected data. An average across both left and right lateral orbitofrontal, interior parietal, precuneus, rostral middle frontal, superior frontal, superior temporal, and middle temporal ROIs yielded the mean cortical binding potential (MCBP). All analyses used MCBP as a continuous variable. As supplementary analyses, individuals were also codified as PiB positive or negative using a previously published value from our center of unadjusted MCBP of 0.18 (Vlaskenko et al., 2011). A second supplementary analysis defined the cutoff on partial-volume corrected MCBP data derived from a ROC analysis comparing 212 cognitively normal individuals to 59 CDR = 0.5 with an AD diagnosis. Using this approach the partial-volume adjusted MCBP cutoff was determined to be .23, which was the point that maximized the Youden Index (sensitivity + specificity – 1). Distributions of partial-volume adjusted MCBP scores are presented in
Fig. 3 and distributions of unadjusted values are presented in Supplemental Fig. 1.

2.5. Measures of vascular health

We assessed the presence (1) or absence (0) of a history of hypertension, heart attack, atrial fibrillation, angioplasty, bypass surgery, congestive heart failure, stroke, transient ischemic attack, and diabetes. Height information and weight information were used to calculate BMI, and coded for the presence or absence of obesity (BMI $\geq$ 30). An aggregate vascular risk factor was created by summing the scores of all variables (possible range of 0–10) (actual range 0–6, mean 1.14, median 0). Across the entire sample there was a modest bivariate correlation between a history of hypertension and PVWMH ($r = .21, p < .0001$) and DWMH ($r = .19, p < .0001$) scores. Similarly the summary vascular risk score significantly correlated with both PVWMH ($r = .17, p < .001$) and DWMH ($r = .16, p < .001$). Unsurprisingly, a history of hypertension and the vascular risk were highly correlated ($r = .65, p < .00001$).

2.6. Effects of WMH and MCBP on cognition

Initial stepwise logistic regressions examined the effects of age, gender, MCBP and a measure of white matter damage (either DWMH or PVWMH). Models additionally allowed for an interaction between white matter damage and MCBP to enter the model. Models tested whether each predictor discriminated between cognitively normal individuals and demented individuals (combined CDR = 0.5 and 1). For the gender variable women were coded as 0 and males as 1.

For each predictor the exponentiation of the beta coefficient (Exp(B)) indicates the odds ratio, or the change in relative log odds of being in the tested group (e.g. CDR $\neq 0$) relative to the reference group (e.g. CDR = 0) with a one unit change in the predictor. If the odds
ratio for a given predictor (e.g., age) is $>1$, then an increase in the predictor indicates a greater likelihood to be in the test group (e.g., $CDR > 0$). If the odds ratio is $<1$, then the outcome is more likely to be in the reference group (e.g., $CDR = 0$). For all analyses an increase in the $Exp(B)$ indicated greater cognitive impairment.

An additional way to examine the data was presented by calculating the area under the curve (AUC) values from receiver operating characteristics (ROC) curves separating cognitively normal individuals from demented individuals. The first model looked at the AUC using the initial covariates of age and gender. A second set of models examined the AUC using the covariates and then one predictor of interest (i.e., MCBP, PVWMH, or DWMH). A final set of models examined the AUC when using covariates, MCBP, and either of the WMH measures. Significant changes in the AUC in the initial analyses were assessed using DeLong’s test for correlated ROC curves (DeLong et al., 1988) using a package implemented in R (Robin et al., 2011).

Exploratory multinomial logistic regressions compared predictors across all three groups. These analyses test whether each predictor of interest (e.g., WMH, MCBP, age) significantly differs between each level of the dependent variable ($CDR 0, 0.5$, and $1$). The structure of these models was set to be identical to that revealed by the stepwise logistic regression comparing cognitively normal to all demented individuals.

### 3. Results

#### 3.1. Demographics

Demographics are presented in Table 1. There were baseline demographic differences between groups. There were more males in the $CDR 0.5$ ($X^2 = 12.2, p < .0005$) and $CDR 1$ ($X^2 = 14.1, p < .0005$) groups relative to CDR 0. Compared to CDR 0 individuals, CDR 0.5 individuals were older ($t = 7.0, p < .000001$), had lower MMSE ($-13.2, p < .000001$), greater MCBP ($t = 8.3, p < .000001$), and a greater proportion of PiB+ individuals ($X^2 = 45.2, p < .000001$). Similarly relative to CDR 0 individuals those with a $CDR = 1$ were older ($t = 3.81, p < .001$), had lower MMSE ($-18.9, p < .000001$), greater MCBP ($t = 7.4, p < .000001$), and a greater proportion of PiB+ individuals ($X^2 = 22.7, p < .0000005$). CDR 1 individuals had lower MMSE than CDR 0.5 individuals but did not significantly differ in any other way. As age and gender differed across groups, they were considered as covariates when examining the effects of WMH and amyloid on cognition.

#### 3.2. Effects of WMH and MCBP on cognition

The full results from the initial logistic regressions are presented in Table 2. For all significant effects, an increase in the odds ratio for the measure of interest (e.g., age) indicated a greater likelihood of being cognitively impaired. When examining MCBP alongside PVWMH there was a significant effect of age ($Exp(B) = 1.08, p < .0001$), gender ($Exp(B) = 3.50, p < .0001$), MCBP ($Exp(B) = 3.68, p < .0001$), and PVWMH ($Exp(B) = 2.03, p < .01$). When examining MCBP alongside DWMH there was a significant effect of age ($Exp(B) = 1.10, p < .0001$), gender ($Exp(B) = 3.60, p < .0001$), MCBP ($Exp(B) = 3.63, p < .00001$), and DWMH ($Exp(B) = 1.52, p < .05$). The interaction terms between MCBP and WMH were non-significant and not entered into either model. The significant effect of WMH on cognition can clearly be seen in Fig. 2, which depicts the distribution of the Fazekas scores for periventricular white matter hyperintensities (PVWMHs) and deep white matter hyperintensities (DWMHs) across the three groups. Treating amyloid deposition as a dichotomous PiB+/− variable did not substantively change the models (Supplementary Tables 1 and 2).

It is possible to gain a bit more understanding of the size of these effects by calculating the ROC AUC. When predicting dementia status solely from the covariates (age and gender) the AUC is .831. When adding MCBP to the model the AUC significantly increased to .875 ($z = -2.41, p < .05$). There were non-significant increases in the AUC when adding only the PVWMH ($AUC = .849, z = -1.34, p = .18$) or DWMH ($AUC = .836, z = -.5242, p = .60$) to the covariate only

#### Table 2

<table>
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<tr>
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<th>Std. error</th>
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<td>.001</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
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<tr>
<td></td>
<td>DWMH</td>
<td>$.42$</td>
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<td>.036</td>
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MCBP = mean cortical binding potential; PVWMH = periventricular white matter hyperintensity; DWMH = deep white matter hyperintensity.
model. Including both MCBP and PVWMH led to an AUC of .886 (z = −2.63, p < .01) and AUC of .876 when using MCBP DWMH (z = −2.26, p = .05). While significant relative to the covariate only models, the increase in AUC in the models combining MCBP and WMH was not significantly different from models considering MCBP alone. Combined with the results from the logistic regressions, this suggests only modest effects of WMH above amyloid deposition.

The full results from the multinomial logistic regressions are presented in Tables 3 and 4. These results are quite similar to the logistic regressions above when comparing cognitively normal individuals to either group of demented individuals. When contrasting those with very mild dementia (CDR 0.5) to those with mild dementia (CDR 1) there were no significant differences. However, both amyloid burden, estimated by PiB MCBP, as well as vascular risk, or an aggregate vascular risk factor in the model. A history of hypertension or a history of vascular risk demonstrated modest trends.

As WMH are thought to be vascular in nature (Breteler et al., 1994), we additionally examined the initial models predicting dementia status with MCBP and measures of WMH while including a history of hypertension, or an aggregate vascular risk factor in the model. A history of hypertension was not significant in either model (PVWMH or DWMH, see Table 5) and only slightly lowered the contributions of WMH to the model, but such effects were also significant. The aggregate vascular risk factor was significant in both models, but again the effects on the WMH scores were minor (Table 6).

### Table 5
Logistic regression examining the effects of white matter hyperintensities on cognition controlling for hypertension.

<table>
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<td></td>
<td>DWMH</td>
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4. Discussion

In the current analyses we examined whether measures of amyloid deposition and white matter damage predict cognitive impairment. We found that both amyloid burden, estimated by PiB MCBP, as well as measures of WMH independently discriminate between cognitively normal individuals and those with very mild or mild dementia. The effects varied when considering either periventricular or deep white matter lesions. This is unsurprising as the correlation between ratings of DWMH and PVWMH lesions was .58 (p < .000001).

The Fazekas visual rating of white matter disease was associated with a greater risk of AD. This can clearly been seen in how the distribution of the Fazekas scores shifts across groups in Fig. 2. Individuals who are cognitively normal have highly right skewed distributions, with the vast majority of individuals having no observable white matter damage. As dementia severity increases, the scores become more and more left skewed as higher proportions of the population accrue white matter damage. Although the graphs in Fig. 2 suggest differences between CDR = 0.5 and 1 individuals the effects were not statistically significant. This is most likely due to the modest sample size of mildly demented subjects (CDR = 1, n = 11). Alternatively these markers may possess nonlinear trajectories that do not significantly differ across graded levels of dementia severity.

In our cohort all of the individuals with a CDR = 1 had a primary clinical diagnosis of dementia of the Alzheimer’s type at baseline. Of the 51 individuals with a CDR rating of 0.5, 21 had a DAT diagnosis at baseline and 14 received a diagnosis at a later clinical point. Overall 75% of individuals in the study received a clinical diagnosis of DAT. Along with the high levels of amyloid deposition, this would suggest that the majority of the impaired cohort are representative of an AD trajectory. There were no significant differences in age, gender composition, or severity of white matter damage between those with and without an AD diagnosis. This suggests that the white matter effects...
are not being driven by a small subsample of individuals who are de-
mented but are not on an AD trajectory.

Many healthy older adults show elevated levels of amyloid without significant cognitive impairment (Arriagada et al., 1992). Additionally there are numerous risk factors for a clinical diagnosis of AD including a family history of AD (Breitner et al., 1988), the APOE ε4 genotype (Corder et al., 1993), head trauma (Mortimer et al., 1985), and diabetes (Luchsinger et al., 2001). The additive effects in our study of WHM and PiB deposition are consistent with a broader view of AD that suggests that multiple factors can influence substantial cognitive decline and dem-

The results of our analyses are consistent with a large body of prior work linking white matter damage with impaired cognition (Bozzali et al., 2002; Debette et al., 2010; Prins et al., 2004). An increased prevalence of white matter damage is thought to be mainly vascular in nature, as hypertension, stroke, and di-
abetes all lead to increases in white matter lesions (Debette and Markus, 2010; Pico et al., 2002). In the current work there were modest correla-
tions (r < .2) between measures of vascular health and WMH. Further an aggregate measure of vascular risk was itself predictive of dementia status above the effects of amyloid deposition and WMH. However measures of WMH were still predictive of dementia status after includ-
ing vascular risk as a covariate. This may be due to the fact that our mea-
sures of vascular health are imperfect as they are derived from self-
report and do not account for medication usage.

Although the examinations presented here indicated unique statisti-
cal effects of age, MCBP, and WMH this does not necessarily mean that the biological processes these values represent are truly orthogonal pro-
cesses. One of the greatest challenges facing ongoing studies of AD is how to tease apart the contributions of comorbid pathologies. Large co-
hort studies are just now reaching the point to investigate modifiers (e.g. cardiovascular health, stroke, diabetes, head trauma) of longitudi-

5. Conclusions

The work presented here demonstrated the detrimental influences of advancing age, amyloid deposition in the brain, and white matter damage. These factors independently discriminated healthy controls from very mildly and mildly demented individuals. From a clinical standpoint, this suggests that easily available radiological measures of white matter health could be an asset in disease diagnosis in addition to psychometric testing and AD biomarkers such as amyloid imaging.

Supplementary data to this article can be found online at http://dx.
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