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Postmortem MRI: A Novel Window into the Neurobiology of Late Life Cognitive Decline

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Abstract

This study tested the hypothesis that indices of brain tissue integrity derived from postmortem MRI are associated with late life decline in cognitive function and dementia, over and above contributions from common age-related neuropathologies. Cerebral hemispheres were obtained from 425 deceased older adults who had undergone two or more annual cognitive assessments, which included clinical diagnosis of dementia. Specimens underwent MRI to produce maps of transverse relaxation rate, R_2 . Voxelwise regression revealed brain regions where R_2 was associated with cognitive decline. We then used random effects models to quantify the extent to which R_2 accounted for variation in decline, after adjustment for demographics and neuropathologic indices of the three most common causes of dementia: Alzheimer's disease, cerebrovascular disease, and Lewy body disease. We additionally tested whether R_2 was tied to greater likelihood of clinical diagnosis of Alzheimer's dementia using logistic regression models. During an average of 8.1 years, the mean rate of decline in global cognitive function was 0.13 unit

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All participants provided written informed consent. The study was approved by the Institutional Review Board of Rush University Medical Center.

All authors have reviewed the contents of the manuscript being submitted, approve of its contents and validate the accuracy of the data.

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per year ($p<0.0001$). The tissue alteration most commonly related to decline was R_2 slowing in white matter. Each unit decrease in R_2 was associated with an additional 0.053-unit per year steepening of the rate of global cognitive decline ($p<0.001$). Furthermore, R_2 accounted for 8.4% of the variance in rate of global cognitive decline, above and beyond the 26.5% accounted for by demographics and neuropathologic indices, and 7.1–11.2% of the variance of the decline rates in episodic, semantic, and working memory and perceptual speed. Alterations in R_2 were also related to an increased odds of clinical diagnosis of Alzheimer's dementia (OR=2.000, 95% confidence interval 1.600, 2.604). Therefore, postmortem MRI indices of brain tissue integrity, particularly in white matter, are useful for elucidating the basis of late life cognitive impairment in older adults and complement traditional indices of neuropathology derived using histopathologic methods.

Keywords

Postmortem MRI; transverse relaxation; white matter; Alzheimer's disease; voxelwise

1 INTRODUCTION

As life expectancies reach 80 years and beyond, late life decline in cognitive function is increasingly common (Brayne, 2007, Deary et al., 2009, Schonknecht et al., 2005, Ward et al., 2012). Prevention of cognitive decline remains a challenge, however, in part due to our incomplete view of the factors underlying the considerable heterogeneity in late life cognitive trajectories; whereas some individuals decline precipitously, others decline more gradually, and others maintain cognitive function until death (Lipnicki et al., 2013). Importantly, standard neuropathologic indices of the three most common causes of dementia – Alzheimer's disease (AD), cerebrovascular disease (CVD), and Lewy body disease (LBD) – are the major drivers of cognitive decline in old age but account for less than half of the variability in rates of decline (Boyle et al., 2013a). Thus, a majority of the variation in late life cognitive decline remains unexplained by current indices that are the primary focus of efforts to prevent loss of cognitive function in old age. This highlights the need to identify additional factors that are associated with cognitive decline, since such factors may reveal novel targets for preventive and therapeutic strategies.

Postmortem brain MRI can provide information on brain tissue condition that is complementary to that obtained via histopathologic techniques. The magnetic resonance transverse relaxation rate, R_2 , for example, captures information related to the integrity of neural tissue (Eriksson et al., 2007, MacKay et al., 2006, Melbourne et al., 2013, Wagner et al., 2015, Whittall et al., 1997). R_2 is simply the reciprocal of the transverse relaxation time constant, T_2 , and thus provides a similar view of the contrast mechanisms exploited in routine T_2 -weighted imaging, but through a quantitative lens that permits inter-subject comparisons. In recent work, we reported that this MRI metric of transverse relaxation accounted for a portion of the variation in level of cognitive function proximate to death, above and beyond that explained by standard neuropathologic indices alone (Dawe et al., 2014). The contribution of R_2 to longitudinal change in cognitive function based on repeated assessments prior to death, however, remains unknown.

In this study, we examined the association of postmortem R_2 with the rate of change in cognitive function over many years leading up to death, in analyses that controlled for common age-related neuropathologies (i.e., AD, CVD, and LBD), to determine the degree to which this MRI index contributes to cognitive decline in old age. We also investigated whether postmortem R_2 was associated with increased odds of clinical diagnosis of AD dementia. Participants ($n=425$) were autopsied individuals from two clinical pathologic cohort studies who had undergone annual assessment of cognition for up to 19 years, and whose brain tissue had undergone postmortem MRI and neuropathologic assessment. Postmortem MRI provided the relaxometric predictor variables for two sets of cognitive decline models: voxelwise linear regressions to delineate regions of strong association between R_2 and cognitive decline, and, subsequently, random effects models to quantify the extent to which R_2 accounts for variation in decline. These models were first carried out using an established composite measure of global cognitive function as the outcome. We repeated the analyses for each of five specific cognitive domains to obtain a more complete profile of the sensitivity of MRI to tissue abnormalities underlying late life cognitive decline. Logistic regression was then employed to evaluate the association of R_2 with clinical diagnosis of AD dementia.

2 MATERIALS AND METHODS

2.1 Participants and specimens

Brain specimens were obtained from older participants from two longitudinal studies of aging, the Rush Memory and Aging Project (Bennett et al., 2012b) and the Religious Orders Study (Bennett et al., 2012a). In accordance with the Declaration of Helsinki, the Institutional Review Board of Rush University Medical Center approved these studies, and all participants signed an informed consent form and an anatomical gift act as a condition of enrollment. At the time of analyses, 2,995 individuals had been enrolled in these studies; of those, 1,343 were deceased, and 87.4% (1,174) of these had undergone autopsy. Postmortem brain MRI began in 2006. Since that time, 651 autopsied specimens have been imaged, and 454 of those had passed through our post-processing pipeline at the time of analyses. Of the 454 brain donors, 29 had less than two cognitive evaluations, leaving 425 participants for these analyses.

The study sample of the current work is a subgroup of the MAP and ROS studies from which specimens were obtained, owing to the later start of postmortem imaging within the studies. Thus, we examined potential differences in characteristics of the study sample relative to deceased individuals in MAP and ROS who did not have postmortem brain imaging. Imaged persons were more likely to be female (70.1% of total vs. 63.1%, $\chi^2_1=6.30$, $p=0.012$), older at death (89.8 vs. 88.1 years, $t_{1341}=4.30$, $p<0.0001$), and had fewer years of education (15.9 vs. 16.5, $t_{1341}=3.02$, $p=0.0025$). By contrast, imaged persons did not differ significantly from individuals without imaging in terms of rate of cognitive decline or AD, CVD, and LBD pathology. As we are now imaging nearly all autopsied brains, we anticipate that these differences will decrease over time.

2.2 Cognitive evaluation and clinical diagnosis

Participants underwent detailed annual cognitive evaluations, including MMSE testing, used for descriptive purposes only. Scores from 17 other cognitive tests common between the two studies (Bennett et al., 2012a, Bennett et al., 2012b) were standardized using the baseline mean and standard deviation of all participants. Then, these z-scores were combined to form composite scores representing global cognitive function (all 17 tests) and five specific cognitive domains, as previously described: episodic memory (word list recall, East Boston, and logical memory tests), semantic memory (Boston naming, category fluency, and reading tests), working memory (digit span and ordering tests), perceptual speed (number comparison, Symbol Digit Modalities, and Stroop tests), and visuospatial ability (line orientation and progressive matrices tests) (Boyle et al., 2013a, Boyle et al., 2013b, Wilson et al., 2015). Notably, since each composite is an average of z-scores, its standard deviation is not necessarily equal to 1.0. Therefore, the rates of decline are reported in units per year. Following a participant's death, a board-certified neurologist who was blinded to postmortem data reviewed all available clinical data and rendered an opinion on the most likely clinical diagnosis at the time of death, according to standard criteria (Bennett et al., 2012a, Bennett et al., 2012b, McKhann et al., 1984). Cases of possible AD and probable AD were classified as positive for clinical diagnosis of AD dementia in our analyses (Boyle et al., 2015).

2.3 Postmortem MRI

Upon death, the brain was extracted and hemisected during rapid autopsy (mean postmortem interval=8.5 hours, SD=5.9, range=1.5–21.2). One cerebral hemisphere was placed in 4% formaldehyde solution and refrigerated in preparation for histopathologic evaluation and postmortem MRI, as previously described (Dawe et al., 2011). MRI was carried out at approximately one month postmortem to allow for stabilization of R_2 values (Dawe et al., 2009). Cerebral hemispheres were imaged in a one-hour scan session in one of three 3-Tesla imagers employed during the ongoing study. The exam consisted of a 3D gradient echo sequence, a 2D fluid attenuation inversion recovery sequence, and, relevant to the current study, a 2D turbo spin echo sequence. Key features of the turbo spin echo sequence were maintained across scanners, including the following: multiple TEs, sagittal slice thickness of 1.5 mm, a field of view of 16 cm $\times$ 16 cm, approximately 256 $\times$ 256 acquisition matrix, yielding resolution of 0.625 mm $\times$ 0.625 mm and a scan time of approximately 30 minutes, as previously detailed (Dawe et al., 2014).

2.4 R_2 image processing

While in a recent study we quantified each voxel's transverse relaxation with the transverse relaxation time constant (T_2), we have since observed its reciprocal, the transverse relaxation rate constant (R_2), to be more normally distributed (i.e., less skewed), indicating it may better satisfy the underlying assumptions of multivariate regression models. Therefore, we produced maps of R_2 (rather than T_2) from the spin echo images for further analysis. Specifically, we used a nonlinear algorithm to achieve a least squares fit of the monoexponential decay function $S = S_0 \cdot \exp(-R_2 \cdot TE)$ to the measured data at each voxel, where S is a voxel's intensity at a given echo time (TE) and S_0 is its theoretical signal at a

TE of zero. An empirically selected R_2 threshold of 6 s^{-1} was used to mask out fluid surrounding the specimen, as well as that contained within any lacunes, eliminating these voxels from all subsequent analysis. The images from the shortest TE were registered to a custom template (Dawe et al., 2014), first with linear and then with nonlinear registration methods, using FSL's FLIRT and the Automated Registration Toolbox, respectively. These transformations were applied to the R_2 maps, bringing them into a common space and facilitating voxelwise analyses. To reduce bias stemming from the use of three different scanners, we normalized the R_2 values in a voxelwise manner using the mean and standard deviation of each subgroup of hemispheres imaged on a given scanner.

2.5 Neuropathologic indices

Following postmortem MRI, neuropathologic indices for the three most common causes of dementia (AD, CVD, LBD) were derived via the following methods. *CVD*: After cutting the cerebral hemispheres into 1-cm thick coronal slabs, the size, location, and age (acute, subacute, chronic) of gross infarcts were recorded (Boyle et al., 2013a, Wilson et al., 2015). We previously observed that gross infarcts but not microinfarcts were related to faster rates of cognitive decline (Boyle et al., 2013a). Therefore, for these analyses, chronic gross infarcts were coded as present or absent, forming a binary variable for CVD. *AD*: Cortical blocks were excised, sectioned, stained, and examined microscopically. Using a modified Bielschowski silver stain on 6- μm sections, neuritic and diffuse plaques and neurofibrillary tangles were counted in four cortical regions (mid-frontal, superior temporal, inferior parietal, and entorhinal cortices) and the subiculum/CA1 region of the hippocampus. A continuous, composite measure of global AD pathology was computed as the mean of the plaque and tangle counts across the five regions, as previously described, constituting the AD index (Boyle et al., 2013a, Wilson et al., 2015). *LBD*: Lewy bodies were identified using a monoclonal antibody to alpha-synuclein (LB 509 1:150 or 1:100, Zymed Labs, Invitrogen Corp, Carlsbad, CA or pSyn#64 1:20,000, Wako Chemicals Inc., Richmond VA). Lewy bodies were rated as present if identified in any of seven brain regions (inferior parietal, superior or middle temporal, mid-frontal, entorhinal, and anterior cingulate cortices and the amygdala and substantia nigra) (Boyle et al., 2013a, Wilson et al., 2015).

2.6 Statistical Analyses

To identify regions in which the imaging metric, R_2 , was associated with cognitive decline, we first used in-house software developed in Matlab (The Mathworks, Inc.) to carry out voxelwise linear regressions with demographics (age, sex, education), neuropathologic indices (AD, CVD, LBD), and R_2 as explanatory variables, and the slope of cognitive decline estimated from all available cognitive exams as the outcome (Dawe et al., 2014). We controlled for multiple tests (approximately 400,000 tissue-containing voxels) by allowing a false discovery rate of 0.05 using the 'fdr' module of FSL (Genovese et al., 2002, Jenkinson et al., 2012) and retaining only those clusters of 100 or more contiguous voxels (100 mm^3) whose association of R_2 with the slope of decline met the adjusted p -value threshold. We then extracted the mean R_2 value of voxels within each of those clusters. Upon finding high correlation among most of the mean cluster values, we combined them via simple averaging to form a composite R_2 measure for global cognitive function as well as each cognitive

domain. A notable exception to this procedure occurred for the semantic memory domain, as detailed in the Section 3.

We next employed random coefficient models implemented in SAS 9.3 (SAS Institute, Inc.) to examine the extent to which the composite R_2 measures extracted from the voxelwise analysis might account for the variance in rate of decline in each cognitive domain. In these models, we examined the change in cognition using annual cognitive assessment as the longitudinal outcome. Notably, variance in the random slope of the models captures the person-specific deviation from the mean rate of cognitive decline (Laird and Ware, 1982). Our prior work suggests that part of this variation is explained by demographics and neuropathology (Boyle et al., 2013a). Here we sought to estimate the percentage of the variation accounted for by the composite R_2 measures, above and beyond demographics and standard neuropathologic indices. To do so, we started with the most parsimonious model with only a time term (defined as time in years before death), then sequentially added sets of explanatory variables and their interactions with time: first demographics (age, sex, education), then neuropathologic indices, and finally the domain-specific composite imaging metric R_2 . As more explanatory variables were included in the model at each step, the variance in the random slope decreased accordingly, allowing us to estimate the relative contribution of the most recently entered terms to the variance in cognitive decline, beyond the contributions of the previously entered terms.

Lastly, we used logistic regression to examine the relation of R_2 to clinical diagnosis of AD dementia. The composite R_2 derived from regions associated with decline in global cognitive function served as the predictor of interest, and we changed its sign in order to obtain a higher odds ratio under the assumption that smaller R_2 values would be related to a higher likelihood of AD dementia. We again controlled for age, sex, education, AD, CVD, and LBD pathology in this model in order to assess the independent association of R_2 with AD dementia diagnosis.

3 RESULTS

3.1 Descriptive data

Analyses included 425 participants, 298 (70.1%) of whom were female, who had an average of 8.1 annual cognitive exams ($SD=4.76$, range=2–19) and died at a mean age of 89.8 ($SD=6.29$, range=65.9–108.3), as shown in Table 1 with other descriptive data. At the time of death, 186 (43.8%) met the criteria for a clinical diagnosis of possible or probable AD dementia. Global cognitive function for the study sample at baseline was approximately normally distributed (mean=−0.12 unit, $SD=0.68$). Change in global cognition averaged −0.13 units per year ($SD=0.17$) and exhibited considerable variation, ranging from −1.07 to 0.31 units per year, with positive change corresponding to improvement in cognitive performance. This heterogeneity can be appreciated in Fig. 1, in which the cognitive trajectories for a random sample of 50 participants are plotted. Relationships among demographics and neuropathologic indices were assessed. Females were older than males at death (90.2 vs. 88.7 years, $t_{423}=2.23$, $p=0.026$) and had fewer years of education (15.4 vs. 16.9, $t_{423}=3.81$, $p=0.0002$). The summary index of AD pathology had a mean of 0.77 ($SD=0.63$) and was significantly higher in females (0.82 vs. 0.67 units, $t_{421}=2.27$, $p=0.024$).

Gross infarcts, the index of CVD pathology, were present in 148 (34.8%) of autopsied brains. Participants with gross infarcts were older at death (91.0 vs. 89.1 years, $t_{423}=2.96$, $p=0.0032$) and had fewer years of education (15.1 vs. 16.3 years, $t_{423}=3.15$, $p=0.0017$) than those who were free of gross infarcts. Lewy bodies were present in 102 (24.0%) of autopsied brains. Brains with Lewy bodies also tended to also have higher levels of AD pathology (0.91 vs. 0.73 units, $t_{421}=2.57$, $p=0.011$).

3.2 Brain regions exhibiting association of R_2 with cognitive decline

After FDR correction for multiple tests and clustering, voxelwise analyses controlling for demographics and neuropathologic indices revealed regions of association between the imaging metric R_2 and decline in global cognitive function as well as episodic, semantic, and working memory, and perceptual speed, which are visualized in Fig. 2. For global cognition, the associations were confined mainly to white matter regions and were positive in sign, meaning that a smaller value of R_2 (slower transverse relaxation) corresponded to a more negative rate of change in cognitive function (faster decline). Large portions of the frontal and temporal lobe white matter, including the parahippocampal region, were included. Decline in episodic memory performance was marked by a similar spatial pattern of R_2 association. Notably, the effect in the parahippocampal white matter, which likely impinged upon the CA1 subregion of the hippocampus itself, was more robust in the episodic memory domain than in any other. For semantic memory, in addition to positive R_2 associations in frontal and temporal white matter regions, a small but significant region near the caudal extent of the putamen exhibited a negative association with the rate of change in cognition. Thus, in this region, a larger value of R_2 (faster relaxation) corresponded to a more negative rate of change in cognitive function (faster decline). We created a second R_2 metric to accommodate this negative association, and included it in subsequent analyses of semantic memory. For working memory, the frontal lobe white matter exhibited a strong and widespread positive association of R_2 with rate of change in cognition. The temporal lobe R_2 failed to reach the adjusted significance threshold for this domain. Decline in perceptual speed shared a spatial pattern of R_2 association qualitatively similar to those of the memory domains, though the effect was generally smaller in magnitude and in fact did not reach the adjusted significance threshold in the parahippocampal region. The intercorrelations among the mean R_2 values for all significant regions are displayed graphically in Fig. 3. We did not observe any regional associations of R_2 with the rate of decline in visuospatial abilities.

3.3 Relation of R_2 to cognitive decline, controlling for pathologies

As presented in Table 2, demographics and neuropathologic indices accounted for 26.5% of the variance of global cognitive decline (i.e., the slope of global cognition), in random effects models. The composite R_2 metric accounted for an additional 8.4% of the variance (Table 2). The magnitudes of the R_2 associations with global cognitive decline are contextualized in Table 3 and graphically in Fig. 4. A composite R_2 value one standard deviation below the sample mean was associated with a steeper decline averaging 0.053 unit more per year ($p<0.0001$, Table 3), nearly equivalent to that of a one-unit increase in the AD pathology summary score (0.054-unit per year steeper decline, $p<0.0001$). Similarly, the composite R_2 values were significantly associated with rate of decline in four specific cognitive domains ($ps<0.0001$), explaining an additional 7.8%, 11.2%, 9.5%, and 7.1% of

the variance of decline in episodic memory, semantic memory, working memory, and perceptual speed domains, respectively, beyond that accounted for by demographics and neuropathologic indices (Table 2). Finally, because education is not purely a demographic variable and the inclusion of education could have affected our primary results, we repeated all analyses above without education in the models. In these secondary analyses, the variance in decline accounted for by pathology and R_2 changed by less than 0.7 percentage points in all cases (data not shown).

3.4 Relation of R_2 to clinical diagnosis of AD dementia

To contextualize the findings for cognitive decline, we examined the relation of R_2 with the clinical diagnosis of AD dementia. In a logistic regression model controlling for demographics and neuropathologic indices, the R_2 metric was independently associated with increased odds of clinical diagnosis of AD dementia (OR=2.000, 95% confidence interval 1.600, 2.604). Thus, lower R_2 values were associated with greater likelihood of AD dementia, even after accounting for the other common neuropathologies.

4 DISCUSSION

We investigated a potential radiologic marker of tissue integrity underlying cognitive decline, the transverse relaxation rate, R_2 , as measured in fixed, human cerebral hemispheres using 3-Tesla MRI. In analyses of more than 400 decedents with up to nearly 20 years of structured, annual cognitive assessments, R_2 accounted for nearly 10% of the variance in late life decline in global cognitive function, above and beyond neuropathologic indices representing the three most common causes of dementia – AD, CVD, and LBD. Similarly, R_2 accounted for a substantial portion of the variation in decline in episodic memory, semantic memory, working memory, and perceptual speed. Furthermore, R_2 was associated with increased odds of clinical AD dementia. The brain regions most highly associated with cognitive decline were chiefly localized in white matter, where slowing of R_2 corresponded to faster rates of decline. Thus, while indices of AD, CVD, and LBD are the major underlying determinants of cognitive decline in late life, measures of brain integrity derived from postmortem MRI are also associated with decline and AD dementia and may ultimately suggest additional targets for prevention and treatment.

As R_2 depends on the types of proton-containing substances contained within a voxel and their respective relaxation properties (Laule et al., 2006, Whittall et al., 1997), it is likely sensitive to certain tissue changes underlying cognitive decline. For example, a voxel in which the tissue has undergone rarefaction will exhibit slower decay of the MRI signal due to the relatively slow R_2 of the infiltrating free water (e.g., extracellular fluid). This translates to a smaller value of R_2 for the voxel as a whole, or equivalently, a prolonged (larger) value of T_2 . Conversely, paramagnetic compounds increase R_2 (i.e., accelerate transverse relaxation, shorten T_2) by disrupting the magnetic field's local homogeneity (House et al., 2007). Thus, the biophysical basis of R_2 informs us of potential brain regions likely to exhibit R_2 alterations, as well as the expected direction of their associations with cognition: slower R_2 associated with poorer cognitive function in regions susceptible to

increases in free water content due to tissue loss, and faster R_2 associated with poorer cognitive function in nuclei known to harbor paramagnetic metals.

Existing knowledge of the relationship between MRI measures of tissue integrity and late life cognitive decline and AD dementia stems from antemortem studies, in which histopathologic measures of neuropathology are not available. As such, it is not possible to directly compare the current study's findings with past work, though interesting similarities are noted. In particular, a recent longitudinal study of septuagenarians indicated that integrity of white matter, as reflected by a volumetric measure of hyperintensities, is highly associated with declines in fluid intelligence (encompassing working memory), perceptual speed, and episodic, verbal, and spatial memory (Ritchie et al., 2015b), parallel to the current study's findings of R_2 association with declines in perceptual speed and memory domains. There is also evidence of a predictive effect of hyperintensities on future cognitive decline (Brickman et al., 2008) and AD dementia (Brickman et al., 2012). The R_2 metric of the current work likely includes a contribution from white matter hyperintensities, since these are defined as high signal on T_2 -weighted images and $T_2=1/R_2$. Our R_2 analyses also share similarities with diffusion MRI studies investigating the association of cognitive decline with white matter FA (fractional anisotropy) and mean diffusivity, continuous measures reflecting the tissue's integrity, organization, and free water content. Specifically, tract-based FA values and whole-brain mean diffusivity histograms have been linked to declines in working memory (Charlton et al., 2010, Ritchie et al., 2015a), mirroring the domain's strong association with frontal lobe white matter R_2 revealed in the current study. At least one longitudinal diffusion MRI study highlighted decline in perceptual speed as being particularly vulnerable to altered diffusion indices (Lovden et al., 2014), but other studies did not replicate this finding (Charlton et al., 2010, Ritchie et al., 2015a). In the current work, we did find that perceptual speed was sensitive to white matter R_2 alterations, but not more so than other cognitive domains. Despite the apparent sensitivity of R_2 to myelin content (Laule et al., 2006, Moore et al., 2000) and paramagnetic materials (House et al., 2007), this metric has seldom been used to assess the integrity of brain tissue in studies of late life cognition. Though some studies have demonstrated correlations of R_2 (or T_2) values with cross-sectional levels of cognitive function (Dawe et al., 2014), with self-reported memory loss (House et al., 2006), or with clinical diagnosis of AD (Bartzokis et al., 2003, Raven et al., 2013), we are not aware of any studies investigating the association of R_2 with rate of change of cognition in late life. Taken together, these studies affirm white matter integrity as a prominent correlate of cognitive decline and AD dementia and demonstrate that imaging modalities including R_2 mapping can be used to quantify this and other components of brain tissue condition relevant to late life changes in cognitive function.

The origins of the white matter changes underlying R_2 associations with cognitive decline are not obvious and are potentially multifactorial. In one plausible scenario, the R_2 alterations may reflect axonal loss secondary to neurodegenerative pathology, such as AD (Agosta et al., 2011, Alves et al., 2015, Bozzali et al., 2002). This dovetails with our observations in that the single compartment estimate of R_2 would be expected to decrease, either due to additional infiltration of the tissue by cerebrospinal fluid, reduction in myelin content (Dyakin et al., 2010), or both. The current study's most compelling evidence in support of this Wallerian viewpoint is the sharply defined parahippocampal region of R_2

depression, whose shape, location, and preferential association with decline of episodic memory are suggestive of tract-specific damage to fibers serving the hippocampal formation (Salat et al., 2010). Further, previous work indicated that R_2 in this region was marginally associated with pathology of AD (Dawe et al., 2014). Based on this information, it is reasonable to speculate that AD pathology or other damage to the hippocampus precipitated the adjacent white matter degeneration.

There are several reasons why R_2 accounts for variance in cognitive decline above and beyond indices of the common age-related neuropathologies from which it may in part stem. For example, MRI provides spatial coverage of the entire cerebral hemisphere, whereas the pathologic indices of AD and LBD are derived from a necessarily limited number of brain regions. In addition, AD, CVD, and LBD are complex disease processes, and even the most robust indices are unlikely to capture all facets of these pathologies. Thus, the R_2 metric may capture neural changes that are independent of the common neuropathologies, as well as additional dimensions of common neuropathologies that are not captured by standard pathologic indices, and in doing so can serve as a valuable adjunct to neuropathologic evaluation.

Another possibility is that the observed slowing of the transverse relaxation rate R_2 represents a white matter pathology unto itself (Alves et al., 2015, Brun and Englund, 1986, Stricker et al., 2015). For example, hypoxia-induced demyelination is possible in the absence of gross infarcts (the CVD index of the current study), though they share vascular risk factors (Kovari et al., 2007). The loss of myelin leaves axons less effective in conducting precisely timed action potentials (Felts et al., 1997, Waxman, 1977), thereby disrupting cognition. An accompanying shift toward slower transverse relaxation would be expected in this situation, as myelin-trapped protons have inherently fast R_2 (Galisova et al., 2014, Laule et al., 2006, Moore et al., 2000). In the current study, the spatial pattern of frontal lobe R_2 alterations provides qualitative support for this model of hypoxia-driven demyelination leading to cognitive decline. These R_2 alterations, which were most evidently associated with global cognitive function and working memory, appeared diffuse and therefore resembled a perfusion territory rather than tract-specific damage.

A third plausible scenario is that the observed R_2 values in white matter are an indicator of one component of brain reserve protecting against cognitive decline. In short, individuals with more intact, myelinated, or simply a greater number of axons at baseline might be more able to withstand accumulating neurodegenerative pathology, due to something of a redundancy in the quantity or quality of connections between nodes of widely distributed neural networks (Brickman et al., 2011). Myelination, for example, is now thought to be a dynamically regulated process underlying brain plasticity (Long and Corfas, 2014). The implication is that engagement in skill development and other experiences literally shapes the brain (Benes et al., 1994), with enhanced development potentially serving as a buffer against future neurodegeneration. The interplay among starting level of cognitive function, rate of decline, and brain reserve is complex, and further investigation will be required to affirm the sensitivity of R_2 to the neurobiologic substrates of reserve.

Voxelwise analyses of the current study also detected a single region of R_2 quickening (rather than slowing) associated with decline in semantic memory and located principally in the caudal portion of the putamen. R_2 values from this region were entirely uncorrelated with those of the larger white matter regions, suggesting that the two may not share a common root neuropathologic basis. Specifically, faster R_2 hints at an overabundance of paramagnetic compound, such as iron in the form of ferritin, which has previously been identified as a possible risk factor for AD (Bartzokis G, Sultzer D, Cummings J, et al, 2000). Because the voxelwise approach of the current study was not tailored for detection of R_2 alterations in cortical gray matter, future studies employing manual or automatic parcellation methods may prove more statistically powerful in identifying associations between cognition and R_2 in these regions.

R_2 mapping is one of several MRI techniques that may be appropriate for investigation of tissue changes underlying cognitive decline and AD dementia. Among these are fluid-attenuated inversion recovery (FLAIR) imaging, which is typically used to create a binary lesion map for each specimen, and diffusion imaging, which is promising in its sensitivity to white matter damage, but holds certain challenges in acquisition and processing for postmortem brain specimens. In addition, since R_2 alterations possibly stem from gray matter pathologies, MRI-based volumetry of cortical and subcortical gray matter regions may provide additional predictors of cognitive decline. Notably, however, at least one study found greater association of AD diagnosis with white matter integrity than with hippocampal volume when the two predictors were considered simultaneously (Brickman et al., 2012). Because of the potential for increased sensitivity and specificity, multimodal postmortem brain imaging remains a developing area of research.

This study has strengths and limitations. First, because brain imaging data were collected postmortem, causality cannot be inferred. Second, the relation between ante- and postmortem imaging findings is not entirely clear. We have previously found strong correlations between transverse relaxation parameters in a single cerebral hemisphere imaged both antemortem and postmortem (Dawe et al., 2014), but a more thorough validation awaits accrual of antemortem and postmortem imaging data from several more specimens. Establishing correspondence between antemortem and postmortem R_2 values would extend the findings of the current work to living persons, enhancing the study's clinical relevance by providing a potential MRI biomarker of cognitive decline and dementia. Even in the absence of an extensively validated association between antemortem and postmortem R_2 , however, the ability to account for the common neuropathologic causes of dementia allows for a better understanding of the independent relation imaging measures may have with cognitive decline and dementia, and thus has clinical implications. Finally, the R_2 metric remains at present a nonspecific marker of tissue damage or condition. A more rigorous analysis of R_2 correlations with specific types of histopathology, ideally in spatially matched brain regions, will shed light on the mechanisms underlying R_2 alterations related to cognitive decline, which is a future direction of this line of research.

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Abbreviations

MMSE	mini-mental state examination
AD	Alzheimer's disease
CVD	cerebrovascular disease
LBD	Lewy body disease

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Highlights

- MRI transverse relaxation (R_2) is associated with rate of cognitive decline in late life.
- Association of R_2 with decline persists after accounting for neuropathologic indices.
- R_2 slowing in white matter is the most commonly observed correlate of decline.
- Postmortem R_2 accounts for 8.4% of variation in rate of global cognitive decline.
- Spatial patterns of R_2 alterations vary among cognitive systems.

Figure 1. Longitudinally measured global cognition (left) and the estimated trajectories from random effects models (right) in the years leading up to death for 50 participants selected at random. The bold line in the right panel represents the estimated trajectory from the random effects models for a typical participant (female, age 90 at death, 16 years of education).
[GRAYSCALE FIGURE]

Figure 2.

Select axial slices showing regions in which the imaging metric R_2 was significantly associated with rate of change in global cognition and each of four cognitive domains, after accounting for demographics and neuropathologic indices of Alzheimer's disease, cerebrovascular disease, and Lewy body disease. All regions exhibited lower (slower) R_2 values corresponding to more rapid cognitive decline, except for the small region in the putamen for semantic memory (white arrow), which exhibited elevated (faster) R_2 values corresponding to faster cognitive decline. Colors indicate the portion of variance in cognitive decline accounted for by the R_2 value of a given voxel, beyond that accounted for by neuropathologic indices. The grayscale underlay is the R_2 -weighted study specific template. GL = global cognition, EP = episodic memory, SE = semantic memory, WO = working memory, PS = perceptual speed. [COLOR FIGURE]

Figure 3.

Intercorrelations of mean R_2 values from regions identified as having significant associations with cognitive decline, for global cognition and each of four domains. The asterisk denotes the region detected as having a negative association of R_2 with semantic memory decline (elevated R_2 corresponding to a more negative, or faster, rate of change in cognition). Within each domain, Pearson correlation coefficients typically exceeded 0.4 and the correlations were significant ($p < 0.0001$ among all except the region with asterisk). GL = global cognition, EP = episodic memory, SE = semantic memory, WO = working memory, PS = perceptual speed. [COLOR FIGURE]

Figure 4.

Theoretical trajectories of global cognitive decline for a female participant having 16 years of education and dying at age 90, according to the type(s) of pathology and R_2 alterations present. The “No Pathology” line follows the trajectory for an individual with summary Alzheimer’s disease pathology at only the 10th percentile (0.078 unit), and no chronic gross infarcts or Lewy bodies. “AD” refers to the summary measure of Alzheimer’s disease pathology being at the mean level (0.78 unit). “CVD” refers to the index of cerebrovascular disease, the presence of chronic gross infarcts. “LBD” refers to the presence of Lewy bodies. “Low R_2 ” refers to the composite measure of R_2 being 1.0 standard deviation lower than the mean. [GRAYSCALE FIGURE]

Table 1

Demographic, Cognitive, and Pathologic Characteristics of Participants

Variable	Mean (SD) or N (%)
Total Participants	425 (100%)
Demographic	
Age at Death (years)	89.8 (6.29)
Female	298 (70.1%)
Education (years)	15.9 (3.60)
White, Non-Hispanic	409 (96.5%)
Cognitive	
Baseline MMSE	27.2 (4.00)
Proximate to Death MMSE	19.9 (9.52)
Global Cognition, Baseline	−0.12 (0.68)
Global Cognition, Proximate to Death	−1.04 (1.21)
Global Cognition, Rate of Change (per year)	−0.13 (0.17)
Met Criteria for AD Dementia at Death	186 (43.8%)
Pathologic	
Global Alzheimer's disease Pathology	0.78 (0.63)
Gross Infarcts (present)	148 (34.8%)
Lewy Bodies (present)	102 (24.0%)

Table 2

Contributions to Between-Subject Variance in Cognitive Decline from Demographics, Neuropathologic Indices, and R_2

Model Outcome (Cognitive Domain)	Predictors	Variance of Cognitive Decline	Reduction in Variance Relative to Previous Model	% of Variance Accounted for by Boldface Predictor
Global Cognition	Reference Model	0.00898	-	-
	Ref + Demo	0.00879	0.00020	2.2
	Ref + Demo + Path	0.00661	0.00218	24.3
	Ref + Demo + Path + R_2	0.00585	0.00076	8.4
Episodic Memory	Reference Model	0.01134	-	-
	Ref + Demo	0.01124	0.00010	0.9
	Ref + Demo + Path	0.00862	0.00262	23.1
	Ref + Demo + Path + R_2	0.00773	0.00089	7.8
Semantic Memory	Reference Model	0.01064	-	-
	Ref + Demo	0.01051	0.00013	1.2
	Ref + Demo + Path	0.00777	0.00274	25.7
	Ref + Demo + Path + R_2	0.00658	0.00119	11.2
Working Memory	Reference Model	0.00521	-	-
	Ref + Demo	0.00512	0.00009	1.7
	Ref + Demo + Path	0.00418	0.00095	18.2
	Ref + Demo + Path + R_2	0.00368	0.00049	9.5
Perceptual Speed	Reference Model	0.00811	-	-
	Ref + Demo	0.00785	0.00026	3.2
	Ref + Demo + Path	0.00654	0.00131	16.2
	Ref + Demo + Path + R_2	0.00597	0.00057	7.1

Reference models include only an intercept and a time term. Demo includes age, sex, education, and their interactions with time. Path includes Alzheimer's, cerebrovascular, and Lewy body indices, and their interactions with time. R_2 represents the composite R_2 value and its interaction with time. For semantic memory only, two separate R_2 composites were included: one derived from regions having a positive association of R_2 with cognitive decline, and the other derived from the single region having a negative

association of R_2 with decline.

Table 3Associations of Pathologic Indices and R_2 with Rate of Cognitive Decline

Model Outcome (Cognitive Domain)	Variable	Slope Estimate	SE	<i>p</i>
Global Cognition	Time (reference)	−0.0527	0.0095	0.0009
	Alzheimer's Pathology	−0.0544	0.0077	<0.0001
	Gross Infarcts	−0.0258	0.0100	0.0099
	Lewy Bodies	−0.0268	0.0108	0.013
	Composite R_2	0.053	0.0084	<0.0001
Episodic Memory	Time (reference)	−0.0450	0.0112	<0.0001
	Alzheimer's Pathology	−0.0636	0.0091	<0.0001
	Gross Infarcts	−0.0299	0.0117	0.011
	Lewy Bodies	−0.0106	0.0127	0.40
	Composite R_2	0.054	0.0092	<0.0001
Semantic Memory	Time (reference)	−0.0390	0.0106	0.0012
	Alzheimer's Pathology	−0.0629	0.0086	<0.0001
	Gross Infarcts	−0.0199	0.0110	0.069
	Lewy Bodies	−0.0117	0.0117	0.32
	Composite $R_2(+)$	0.060	0.0087	<0.0001
	Composite $R_2(-)$	−0.020	0.0061	<0.0001
Working Memory	Time (reference)	−0.0538	0.0837	<0.0001
	Alzheimer's Pathology	−0.0338	0.0073	<0.0001
	Gross Infarcts	−0.0258	0.0097	0.0079
	Lewy Bodies	−0.0145	0.0103	0.16
	Composite R_2	0.038	0.0069	<0.0001
Perceptual Speed	Time (reference)	−0.0979	0.0110	<0.0001
	Alzheimer's Pathology	−0.0375	0.0087	<0.0001
	Gross Infarcts	−0.0149	0.0114	0.19
	Lewy Bodies	−0.0391	0.0121	0.0013
	Composite R_2	0.038	0.0079	<0.0001

For each cognitive domain, a random effects model included terms for time before death, demographic measures, all pathologic indices, and R_2 variables, as well as slope terms (interactions with time). Estimated coefficients for these slope (rate-of-change) terms are shown in the table. The positive slope estimates for the R_2 variables indicate that smaller values of R_2 (slower transverse relaxation) are associated with more negative (faster) rates of cognitive decline, the exception being the second $R_2(-)$ variable for semantic memory. SE = standard error.