Neurobiology of Aging 45 (2016) 169–177

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Postmortem MRI: a novel window into the neurobiology of late life cognitive decline

Robert J. Dawe [a,b], Lei Yu [a,c], Sue E. Leurgans [a,c], Julie A. Schneider [a,c,d], Aron S. Buchman [a,c], Konstantinos Arfanakis [a,b,e], David A. Bennett [a,c], Patricia A. Boyle [a,f,*]

[a] Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA
[b] Department of Diagnostic Radiology and Nuclear Medicine, Rush University Medical Center, Chicago, IL, USA
[c] Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA
[d] Department of Pathology, Rush University Medical Center, Chicago, IL, USA
[e] Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL, USA
[f] Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL, USA

ARTICLE INFO

Article history:
Received 22 December 2015
Received in revised form 2 May 2016
Accepted 30 May 2016
Available online 6 June 2016

Keywords:
Postmortem MRI
Transverse relaxation
White matter
Alzheimer's disease
Voxelwise

ABSTRACT

This study tested the hypothesis that indices of brain tissue integrity derived from postmortem magnetic resonance imaging (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 2 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 3 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 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 (odds ratio = 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.

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 3 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

* Corresponding author at: Rush Alzheimer's Disease Center, 600 S. Paulina, Suite 1020B, Chicago, IL 60612, USA. Tel.: 312-942-8749; fax: 312-942-2297.
E-mail address: Patricia_Boyle@rush.edu (P.A. Boyle).

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http://dx.doi.org/10.1016/j.neurobiolaging.2016.05.023

highlights the need to identify additional factors that are associated with cognitive decline because such factors may reveal novel targets for preventive and therapeutic strategies.

Postmortem brain magnetic resonance imaging (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 intersubject 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 before 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 2 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 2 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 5 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 used 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 2 longitudinal studies of aging, the Rush Memory and Aging Project (MAP) (Bennett et al., 2012b) and the Religious Orders Study (ROS) (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 the participants signed an informed consent form and an anatomical gift act as a condition of enrollment. At the time of analyses, 2995 individuals had been enrolled in these studies; of those, 1343 were deceased, and 87.4% (1174) 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 postprocessing pipeline at the time of analyses. Of the 454 brain donors, 29 had less than 2 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 2 studies (Bennett et al., 2012a,b) 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 5 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,b; Wilson et al., 2015). Notably, because 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. After 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,b; 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

On death, the brain was extracted and hemisected during rapid autopsy (mean postmortem interval = 8.5 hours, standard deviation [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 1 month postmortem to allow for stabilization of R_2 values (Dawe et al., 2009). Cerebral hemispheres were imaged in a 1-hour scan session in 1 of three 3-Tesla imagers used during the ongoing study. The examination consisted of a 3D gradient echo sequence, a 2D fluid attenuation inversion recovery sequence, and, relevant to the present 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 × 16 cm, approximately 256 × 256 acquisition matrix, yielding resolution of 0.625 mm × 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