A Neuroimaging Approach to Capture Cognitive Reserve: Application to Alzheimer's Disease

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Abstract: Cognitive reserve (CR) explains interindividual differences in the ability to maintain cognitive function in the presence of neuropathology. We developed a neuroimaging approach including a measure of brain atrophy and cognition to capture this construct. In a group of 511 Alzheimer's disease (AD) biomarker-positive subjects in different stages across the disease spectrum, we performed 3T magnetic resonance imaging and predicted gray matter (GM) volume in each voxel based on cognitive performance (i.e. a global cognitive composite score), adjusted for age, sex, disease stage, premorbid brain size (i.e. intracranial volume) and scanner type. We used standardized individual differences between predicted and observed GM volume (i.e. *W*-scores) as an operational measure of CR. To validate this method, we showed that education correlated with mean *W*-scores in whole-brain ($r = -0.090$, $P < 0.05$) and temporoparietal ($r = -0.122$, $P < 0.01$) masks, indicating that higher education was associated with more CR (i.e. greater atrophy than predicted from cognitive performance). In a voxel-wise analysis, this effect was most prominent in the right inferior and middle temporal and right superior lateral occipital cortex ($P < 0.05$, corrected for multiple comparisons). Furthermore, survival analyses among subjects in the pre-dementia stage revealed that the *W*-scores predicted conversion to more advanced disease stages (whole-brain: hazard ratio [HR] = 0.464, $P < 0.05$; temporoparietal: HR = 0.397, $P < 0.001$). Our neuroimaging approach captures CR with high anatomical detail and at an individual level. This standardized method is applicable to various brain diseases or CR proxies and can flexibly

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incorporate different neuroimaging modalities and cognitive parameters, making it a promising tool for scientific and clinical purposes. *Hum Brain Mapp 00:000–000, 2017.*

Key words: cognitive reserve; Alzheimer's disease; magnetic resonance imaging (MRI); global cognition; education; voxel-based morphometry

INTRODUCTION

While neurodegeneration is generally accompanied by cognitive impairment, considerable differences between individuals exist in the degree to which brain pathology is clinically expressed. This heterogeneity was first described in postmortem studies, showing that in some individuals with advanced Alzheimer's disease (AD) pathology, typical cognitive symptoms had never emerged during life [Ince, 2001; Katzman et al., 1988]. To explain this phenomenon, both in the context of neurodegeneration and normal cognitive aging, the concept of cognitive reserve (CR) was introduced [Stern, 2002; see Fig. 1]. CR reflects the degree to which a person can maintain normal cognitive function despite neuropathological changes [Mitchell et al., 2012]. Possible mechanisms underlying CR include neural reserve, neural compensation, and generic "CR networks" [Steffener and Stern, 2012]. Among others, CR has been positively associated with education, occupation, IQ, premorbid brain size and cognitive and physical activity [Arenaza-Urquijo et al., 2015; Bennett et al., 2003; Groot et al., 2016; Rentz et al., 2007; Scarmeas et al., 2003, 2009; Stern, 2002; Valenzuela and Sachdev, 2006; Wilson et al., 2010, 2013].

The advent of neuroimaging techniques has provided in vivo support for the CR hypothesis by showing that individuals with presumably greater CR (e.g. higher educational or occupational levels) can tolerate more severe pathological burden at similar levels of cognitive function (see Fig. 2). In the field of AD, this effect has been shown in terms of greater amyloid beta (Aβ) accumulation [Kemppainen et al., 2008], increased tau deposition [Rentz et al., 2016], more gray matter (GM) atrophy [Liu et al., 2012; Querbes et al., 2009], increased white matter hyperintensities [Boots et al., 2016; Teipel et al., 2009], reduced cerebral perfusion [Liao et al., 2005; Stern et al., 1992] and decreased glucose metabolism [Ewers et al., 2013; Ossenkoppele et al., 2014]. The beneficial effect of CR also applies to brain diseases other than AD, such as frontotemporal dementia [Borroni et al., 2009], Parkinson disease [Hindle et al., 2015], Huntington's disease [Bonner-Jackson et al., 2013], traumatic brain injury [Kesler et al., 2003], vascular pathology [Dufouil et al., 2003; Elkins et al., 2006], and multiple sclerosis [Sumowski et al., 2009].

CR is a relative concept that cannot be measured directly [Jones et al., 2011]: it reflects a person's cognitive performance relative to pathology, in comparison with other individuals with similar pathology. Therefore, researchers often estimate CR based on measurable variables known to be related to the concept. Education, for example, is often used in studies as a surrogate marker (or "proxy") of CR. Despite its practical appeal, this approach introduces several conceptual problems, such as that it undermines the distinction between CR itself and the factors that contribute to it. To overcome these proxy-related issues, we present a novel neuroimaging approach to capture CR by directly quantifying individual differences in the relationship between pathology (i.e. brain atrophy, as measured with GM volume) and cognitive performance (i.e. a global cognitive composite score). Based on the premise that individuals with higher CR can tolerate more pathological burden at a similar level of cognitive function, we regard negative differences (i.e. less GM volume than predicted by cognition) as high CR, and positive differences (i.e. more GM volume than predicted by cognition) as low CR. We tested our method in a large group of biomarker-positive subjects in differences disease stages of AD. To validate our operationalization of CR, we hypothesized that it would correlate with education (i.e. a well-established CR proxy), and that this effect would be most prominent in AD specific temporoparietal brain regions [Frisoni et al., 2007; Karas et al., 2004; Ossenkoppele et al., 2015a; Ridgway et al., 2012]. Furthermore, we assessed whether our neuroimaging measure of CR could predict conversion of pre-dementia subjects to more advanced disease stages (i.e. mild cognitive impairment [MCI] or dementia).

Abbreviations

Aβ	amyloid-beta
AD	Alzheimer's disease
CR	cognitive reserve
CSF	cerebrospinal fluid
GM	gray matter
ICV	intracranial volume
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
PET	positron emission tomography
SCD	subjective cognitive decline
VBM	voxel-based morphometry
VUMC	VU University Medical Center

MATERIALS AND METHODS

Participants

We selected a total of 511 AD biomarker-positive subjects in pre-dementia and dementia stages from the VU

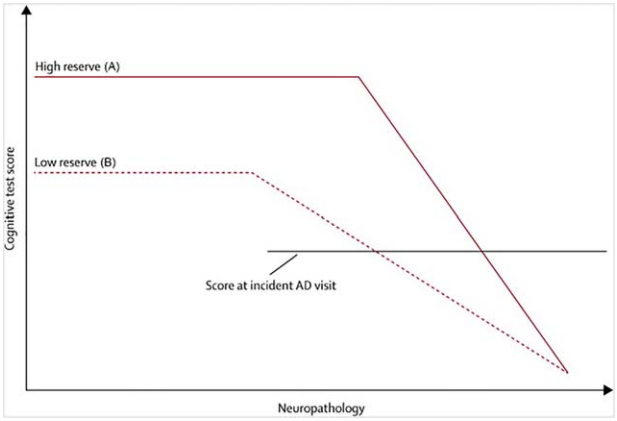

Figure 1.

Schematic representation of an individual with high cognitive reserve (**A**) and an individual with low cognitive reserve (**B**). Compared to individual B, individual A has a higher premorbid level of cognitive functioning, and is able to maintain this premorbid level at more advanced levels of neuropathology. When both subjects first present with significant cognitive impairment ("score at incident AD visit") individual A will have more underlying pathology than individual B. Reprinted with permission from Stern, Lancet Neurol, 2012, 11, 1006–1012, ©Elsevier. [Color figure can be viewed at wileyonlinelibrary.com]

University Medical Center (VUMC) Amsterdam Dementia Cohort [van der Flier et al., 2014, see Supporting Information Fig. 1 for a flow diagram of the selection procedure]. All underwent standard dementia screening between March 2008 and February 2015, including medical history and physical examination, a structured caregiver interview, lumbar puncture and/or positron emission tomography (PET) imaging, brain 3T magnetic resonance imaging (MRI) and neuropsychological testing. All subjects had positive AD biomarkers in cerebrospinal fluid (CSF) ($A\beta_{42} < 640$ ng/mL [Zwan et al., 2014] or tau/$A\beta_{42} > 0.52$ [Duits et al., 2014]) (n = 493) or PET (i.e. [^{11}C]Pittsburgh compound-B or [^{18}F]flutemetamol) [Ossenkoppele et al., 2013] (n = 18). Clinical diagnosis was established by consensus in a multidisciplinary team. Our group of subjects with AD dementia fulfilled National Institute on Aging-Alzheimer's Association criteria for probable AD [McKhann et al., 2011]. In the pre-dementia group, 108 subjects had MCI due to AD [Albert et al., 2011]. Among these subjects, 75% (81 of 108) had single domain MCI and 25% multiple domain MCI. Most MCI subjects had an amnestic clinical presentation (73%, 59 of 81) [Petersen et al., 1999]. The remaining 56 individuals without dementia presented with cognitive complaints but tested within normal limits at neuropsychological examination, and were classified as having subjective cognitive decline (SCD) [Jessen et al., 2014; Sperling et al., 2011]. Throughout this article, the SCD and MCI subjects are treated as one group (i.e. subjects without dementia). Exclusion criteria were: (1) severe dementia as indicated by a Mini-Mental State Exam (MMSE) [Folstein et al., 1975] score $\leq$10; (2) meeting core clinical criteria for another dementia or AD clinical variants such as posterior cortical atrophy or logopenic variant primary progressive aphasia (since these atypical AD presentations are associated with distinct atrophy patterns and cognitive profiles); (3) history of a neurological disorder; (4) presence of clinically significant cerebrovascular disease; (5) presence of a major psychiatric disorder; (6) a reported history of severe substance abuse; (7) substantial scanning or movement artefacts on MRI or (8) an interval >6 months between MRI and neuropsychological testing. The Ethics Committee of

Figure 2.

An example of two subjects in this study, who showed similar cognitive performance (global cognitive composite score-$= -2.65$) despite striking differences in the amount of atrophy. Subject **A** shows substantially greater AD-related atrophy in the temporoparietal cortex and medial temporal lobes compared to subject **B**. Using the neuroimaging method we present in this article, this resulted in lower *W*-scores for subject A, which indicates greater CR (i.e. comparable cognitive function under worse conditions of the brain). Importantly, subject A is highly educated (i.e. university degree), while subject B has a low education (i.e. a primary school diploma).

the VUMC approved the study and all subjects provided informed consent for their data to be used for research purposes.

Measures of Cognition and Education

We measured cognitive performance using a global cognitive composite score that combined 15 neuropsychological test scores across different cognitive domains. The memory domain included the total immediate and delayed recall of the Rey Auditory Verbal Learning Test [Rey, 1964] and total recall on condition A of the Visual Association Test [Lindeboom et al., 2002]. In the domain of executive functioning, we used Trail Making Test (TMT) part B [Reitan, 1955], color-word task of the Stroop test [Stroop, 1935], Digits Backwards [Wechsler, 1997], and Letter Fluency [Hughes, 1970]. The attention domain consisted of Digits Forward [Wechsler, 1997], TMT part A, and the Stroop word and color tasks. To measure language, we used the Category Fluency Test [Benton, 1968] and a short version of the Boston Naming Test [Lansing et al., 1999]. Finally, the visuospatial domain was assessed using Dot Counting and Number Location of the Visual Object and Space Perception battery [Warrington and James, 1991]. Since we had missing data for ~11% of our data (ranging from 2 to 29% per test), we used multiple imputation in SPSS 20.0 for Windows (SPSS, Chicago, IL) to obtain a complete dataset. We calculated *Z*-scores for each test score based on a cognitively healthy reference group (N = 533) and the average across all *Z*-scores represents a global cognitive composite score (note: we also created separate composite scores for memory, attention, executive function, visuospatial function, and language; *W*-scores and other results based on these data are described in Supporting Information Table I). Education was assessed using the Verhage system [Verhage, 1964], a standardized seven-item scale based on the Dutch educational system, in which higher scores represent more advanced levels of education (e.g. 1 = primary school not completed, 7 = academic degree). Some educational levels of the Verhage classification were represented by only few subjects, so we further categorized education into low (1 to 3; n = 52), intermediate (4 and 5; n = 244), and high (6 and 7; n = 215) for statistical analysis.

MRI Acquisition and Processing

Three-dimensional heavily T1-weighted scans were acquired on three different 3T scanners (Signa HDxt 3.0T, GE Healthcare, Milwaukee, WI, n = 417; Vantage Titan 3T, Toshiba Medical Systems, Otawara, Japan, n = 71; Ingenuity TF PET/MR, Philips Medical Systems, Best, Netherlands, n = 23). Acquisition parameters were as follows: Signa HDxt 3.0T: repetition time 7.8 ms, echo time 3.0 ms, flip angle 12°; field of view 240 mm; slice thickness 1 mm; voxel size 0.94 × 0.94 × 1 mm; Vantage Titan 3T: repetition time 9.5 ms, echo time 3.2 ms, flip angle 7°; field of view 256 mm; slice thickness 1 mm; voxel size 1 × 1 × 1 mm; Ingenuity TF PET/MR: repetition time 7.0 ms, echo time 3.0 ms, flip angle 12°; field of view 250 mm; slice thickness 1 mm; voxel size 0.87 × 0.87 × 1 mm. To account for differences in scanner type, all imaging statistical models included scanner type as a nuisance variable.

T1-images were segmented into GM, white matter and CSF using the "Segment" toolbox incorporated in Statistical Parametric Mapping (SPM) software version 12 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology at University College London). We created a Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) study-specific template by aligning the GM images nonlinearly to a common space. We then normalized native gray and white matter images to the DARTEL template using individual flow fields, and applied modulation to preserve the total amount of signal. Images were smoothed using an 8 mm full width at half maximum (FWHM) isotropic Gaussian kernel. We performed visual inspections of our images after each step of the processing pipeline to ensure data quality.

W-Score Neuroimaging Approach

Our neuroimaging approach to capture CR takes the association between GM volume (reflecting atrophy) and cognition as a starting point, and computes the difference between an individual's observed GM volume and the GM volume that would be expected based on his cognitive performance. First, we performed a FMRIB Software Library (FSL) voxel-wise regression in our total sample, with GM volume (i.e. smoothed-modulated-warped GM probability) as a dependent variable, the global cognitive composite score as an independent variable, and age, sex, disease stage (i.e. with or without dementia), premorbid brain size (i.e. intracranial volume [ICV]) and scanner type as nuisance variables (see Fig. 3A,B). The resulting beta values for each predictor in the model (see Supporting Information Fig. 2 for a T-map of the global cognitive composite score) were used to determine the expected GM volume at each voxel for each individual. Using an in-house developed automated script (https://github.com/amwink/bias/raw/master/scripts/bash/compute_w.sh), we then calculated *W*-scores (Jack et al., 1997; La Joie et al., 2012; Ossenkoppele et al., 2015b), which we consider an operational measure of CR. This calculation was based on the formula: *W*-score (CR) = (observed − predicted)/SD. Thus, "observed" is the actual GM volume for a given subject at a given voxel, "predicted" is the GM volume for that voxel as predicted based on the beta values from the regression, and SD is the standard deviation of all residuals (i.e. observed − predicted) in the total sample for that voxel (see Fig. 3C,D). In summary, *W*-scores (mean = 0, SD = 1, similar to *Z*-scores) represent the degree to which the observed GM volume in each voxel is higher (positive

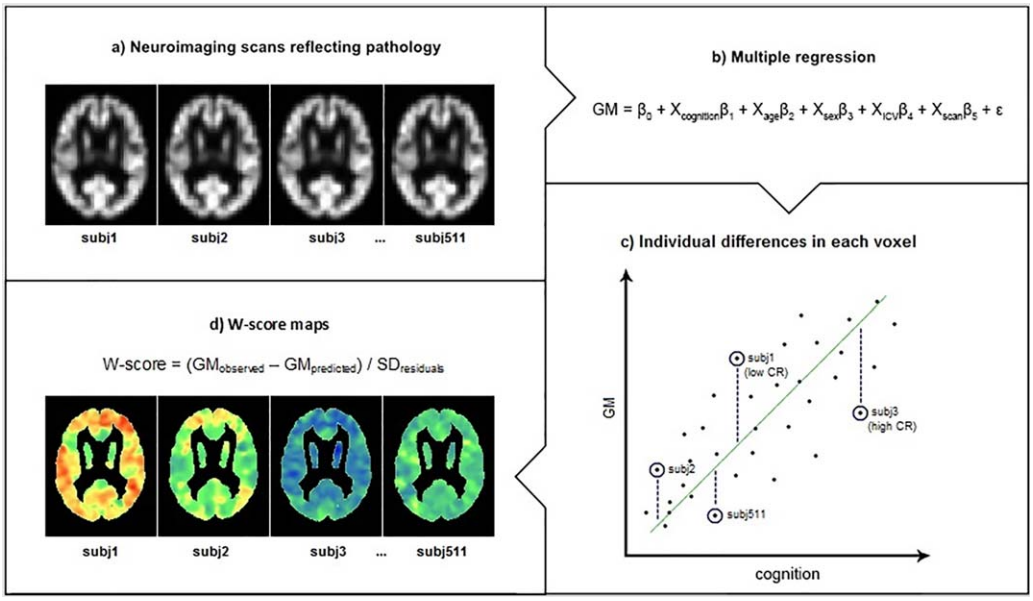

Figure 3.

Schematic representation of our neuroimaging approach. (**A**) For 511 subjects, a measure of pathology (i.e. brain atrophy) was collected. (**B**) This measure was then used as a dependent variable in a voxel-wise regression, with cognition (i.e. global cognitive composite score), age, sex, disease stage, intracranial volume and scanner type as independent variables. (**C**) Based on this regression, standardized differences between subjects' observed and predicted GM volume (residuals) were obtained in each voxel. (**D**) *W*-scores were calculated by dividing these residuals by their standard deviation, resulting in *W*-score maps for each subject. [Color figure can be viewed at wileyonlinelibrary.com]

W-score) or lower (negative *W*-score) than expected, based on an individuals' global cognitive composite score (adjusted for age, sex, disease stage, ICV and scanner type). Negative *W*-scores indicate high(er) CR (i.e. a relatively high degree of atrophy is being tolerated at a particular level of cognitive function), while positive *W*-scores reflect low(er) CR.

Statistical Analyses

Participants

Differences in *W*-scores and demographic and clinical characteristics between subjects in different disease stages (i.e. dementia, $n = 347$; without dementia, $n = 164$) were assessed using independent samples *t*-tests, Mann-Whitney *U* tests for ordinal data and χ^2 tests for dichotomous data.

Relationship between GM volume and cognition

The *W*-score approach is based on the assumption that GM volume and cognition are positively related. To replicate this in the current sample, we performed linear regression models in SPSS, with the global cognitive composite score as the independent variable, GM volume in either a whole-brain or temporoparietal mask [Ossenkoppele et al., 2015a] as the dependent variable, and age, sex, disease stage, ICV, and scanner type as covariates. The whole-brain mask included all GM voxels in our DARTEL template and the temporoparietal mask was based on previously identified common atrophy patterns across several AD clinical variants with mild-to-moderate dementia [Ossenkoppele et al., 2015a; see Supporting Information Fig. 3].

Relationship between W-scores and education

To examine the validity of our neuroimaging measure of CR, we correlated the *W*-scores (see previous section "*W*-Score Neuroimaging Approach") with education (an established proxy of CR). First, we performed two-tailed Spearman's rank order tests in SPSS with mean *W*-scores (in both the whole-brain and temporoparietal mask) and education (i.e. divided into low, intermediate and high) as variables. Second, we compared mean *W*-scores for subjects in the three education groups with an ANOVA and post hoc Bonferroni tests. Finally, we performed a non-parametric voxel-wise regression analysis using the Randomise toolbox in FSL [Winkler et al., 2014], with *W*-scores in each voxel as a dependent variable and education as an independent variable. Results were corrected for multiple comparisons using "threshold-free cluster

TABLE I. Demographic and clinical characteristics in the total sample and according to disease stage

	Total	Dementia	Without dementia	*P*
N	511	347	164	–
Diagnosis (*N*)		AD (347)	MCI (108), SCD (56)	–
Age	66.5 (7.3)	66.4 (7.3)	66.6 (7.3)	0.825
Sex (% male)	51.7	49.0	57.3	0.079
Education (Verhage scale: 1–7)[a]	5 (1–7)	5 (1–7)	6 (1–7)	<0.001
Global cognition (composite)	−1.84 (1.29)	−2.42 (1.12)	−0.61 (0.60)	<0.001
ICV	1.52 (0.17)	1.51 (0.17)	1.54 (0.16)	0.105
W-score (whole-brain)[b]	0.00 (0.46)	0.00 (0.50)	0.00 (0.52)	>0.999
W-score (temporoparietal)[c]	0.00 (0.61)	0.00 (0.61)	0.00 (0.63)	>0.999

Data are presented as mean (SD) unless indicated otherwise. Global cognition was measured with a composite score, which was based on 15 neuropsychological test scores. Differences between subjects in different disease stages were assessed using ANOVA with post hoc Bonferroni tests (age, global cognition, ICV, *W*-scores), Mann-Whitney *U* (education) and χ^2 tests (sex).
[a]Data represent median (range).
[b]Data represent mean *W*-scores in a whole-brain mask.
[c]Data represent mean *W*-scores in a temporoparietal mask.
AD, Alzheimer's dementia; MCI, mild cognitive impairment; SCD, subjective cognitive decline; ICV, intracranial volume in dm^3.

enhancement" (TFCE) at $P < 0.05$ [Smith and Nichols, 2009].

Predictive value of the W*-scores*

Finally, we tested whether *W*-scores can be used to predict conversion to more advanced disease stages. We performed Cox proportional hazards analyses in predementia subjects who had a follow-up diagnosis available with a minimum interval of 6 months (n = 116, mean follow-up time [months)]: 27, SD: 14). For subjects with MCI, conversion was operationalized as a follow-up diagnosis of AD dementia, while in the SCD group a change of diagnosis to MCI or AD dementia during the follow-up period was considered conversion. We used mean *W*-scores in the whole-brain and temporoparietal masks as predictors in separate analyses. For both masks, we performed an uncorrected model (i.e. mean *W*-score as a single predictor) and a model in which age, sex, and medial temporal lobe atrophy (MTA) score [Scheltens et al., 1992] were added. While age and sex were already accounted for in the calculation of the *W*-scores, we wanted to ensure that age and sex had no confounding effects on the relationship between *W*-scores and disease progression. MTA score was included because greater GM atrophy is known to result in faster progression, and we aimed to assess the predictive ability of the *W*-scores independent of this effect. Finally, we replaced the *W*-scores with education (using dummy variables) in the same Cox proportional hazards models, to compare our neuroimaging method with the use of a proxy as a measure of CR in terms of their predictive value.

Stratification for scanner type

Since we used three different 3T MRI scanners to measure GM volume (i.e. Signa HDxt, n = 417; Vantage Titan, n = 71; Ingenuity TF, n = 23), we repeated the calculation of the *W*-scores (and subsequent statistical analyses) separately for each scanner subgroup. Note that in our original method to obtain *W*-scores, we adjusted for the potential bias of scanner type by including it as a nuisance variable in our analyses. In these additional analyses, we instead performed three separate voxel-wise regressions (i.e. one for each scanner subgroup) in which GM volume was predicted based on age, sex, disease stage, and premorbid brain size. We correlated the *W*-scores that resulted from these regressions to the original *W*-scores, and used these new values in repeated Spearman's rank order correlations with education and Cox proportional hazards analyses to predict progression. The purpose of these analyses was to ensure that the use of different scanner types did not influence our results. We report findings for mean *W*-scores in the whole-brain mask in the Result section, while more elaborate results (i.e. from the temporoparietal mask) are included in Supporting Information Tables II and III.

RESULTS

Participants

Demographic and clinical characteristics are presented in Table I. Subjects were relatively young at time of diagnosis (mean age: 66.5 ± 7.3) and had a median Verhage education score of 5, which is indicative of ~10/11 years of schooling [Hochstenbach et al., 2003]. Education was lower in subjects with dementia (median education: 5, range 1–7) than in subjects without dementia (median education: 6, range 1–6). As expected, subjects with dementia had lower global cognitive composite scores (mean score: -2.42 ± 1.12) than subjects without dementia (mean score: -0.61 ± 0.60). Since we corrected for disease stage in the calculation of *W*-scores, both groups showed similar mean

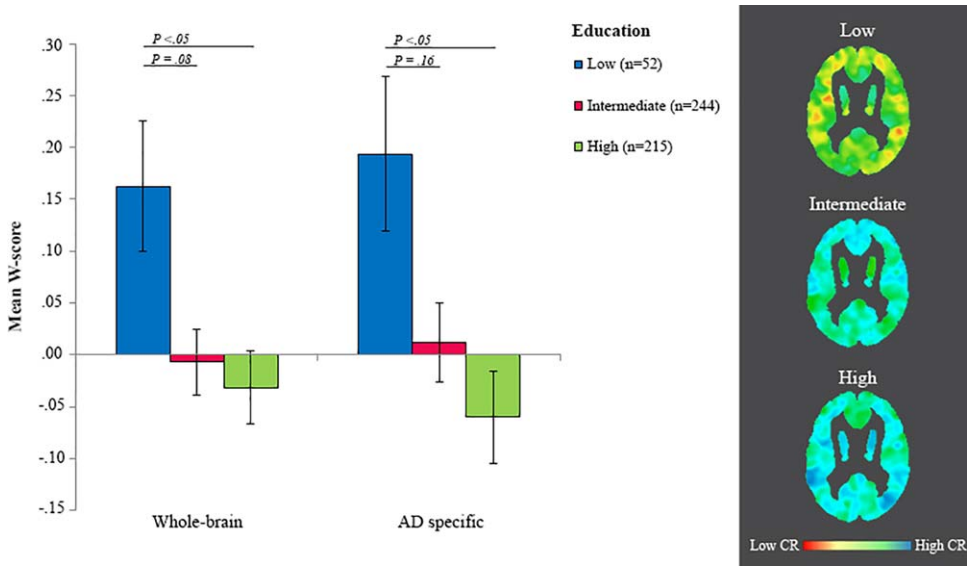

Figure 4.

Left, mean *W*-scores in the whole-brain and temporoparietal mask for the total sample, across three levels of education (i.e. low [Verhage 1 to 3, $n = 52$]; intermediate [Verhage 4 and 5, $n = 244$]; high [Verhage 6 and 7, $n = 215$]). Right, *W*-scores in each GM voxel averaged across subjects with low (top), intermediate (middle), and high (bottom) educational levels. Low CR is reflected by positive *W*-scores, and high CR by negative *W*-scores. [Color figure can be viewed at wileyonlinelibrary.com]

W-scores in the whole-brain (with dementia: 0.00 ± 0.50; without dementia: 0.00 ± 0.52) and temporoparietal (with dementia: 0.00 ± 0.61; without dementia: 0.00 ± 0.63) mask.

Relationship Between GM Volume and Cognition

Linear regression models showed a positive relationship between the global cognitive composite score and GM volume in the whole-brain ($\beta = 0.322$, $P < 0.001$) and temporoparietal ($\beta = 0.379$, $P < 0.001$) mask. This confirms the basic assumption of the *W*-score approach that more severe cognitive impairment was associated with greater atrophy (see Supporting Information Fig. 2 for a *t*-map of the voxel-wise relationship between GM volume and cognition).

Relationship Between W-scores and Education

Education correlated with mean *W*-scores in the whole-brain ($r = -0.090$, $P < 0.05$) and temporoparietal ($r = -0.122$, $P < 0.01$) mask, indicating that individuals with higher education had more CR (i.e. greater atrophy relative to the global cognitive composite score) than lower educated subjects. Moreover, the ANOVA confirmed that in both masks, low educated individuals had less CR (whole-brain mean *W*-score: 0.16 ± 0.46; temporoparietal mean *W*-score: 0.19 ± 0.54) compared to those with high education (whole-brain mean *W*-score: -0.03 ± 0.52, $P < 0.05$; temporoparietal mean *W*-score: -0.06 ± 0.65, $P < 0.05$), while mean *W*-scores for subjects with low and intermediate education (whole-brain mean *W*-score: -0.01 ± 0.50; temporoparietal mean *W*-score: 0.01 ± 0.59) only showed a trend-significant difference in the whole-brain mask ($P = 0.08$; temporoparietal mask: $P = 0.16$). There were no differences between the intermediate and high education group (see Fig. 4). The voxel-wise regression analysis in the total sample revealed associations between higher education and negative *W*-scores (i.e. higher CR) in the right inferior

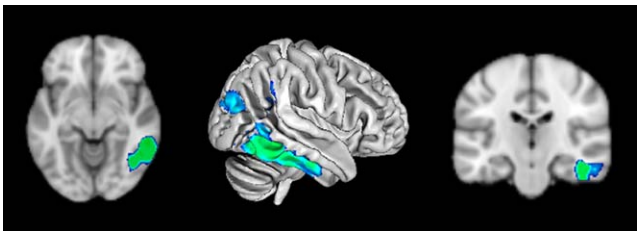

Figure 5.

Brain regions showing a negative relationship between *W*-scores and education (mean *t*-statistic = 4.35, $P < 0.05$, TFCE-corrected; displayed in neurological convention). This indicates that highly educated subjects could tolerate more atrophy (i.e. lower GM volume) while maintaining cognitive function, compared to subjects with lower education. *W*-scores were generated based on a voxel-wise linear regression with global cognitive composite score as a predictor for GM volume, adjusted for age, sex, disease stage, ICV, and scanner type. [Color figure can be viewed at wileyonlinelibrary.com]

and middle temporal and right superior lateral occipital cortex ($P < 0.05$, TFCE-corrected, see Fig. 5). For an overview of the correlations between education and *W*-scores based on separate cognitive domains, see Supporting Information Table I.

Predictive Value of the *W*-Scores

In a subgroup of 116 subjects, 55 cases converted to more advanced stages of AD (i.e. from MCI to AD dementia: $n = 43$; from SCD to MCI: $n = 11$; from SCD to AD dementia: $n = 1$). In the uncorrected models, mean *W*-scores in both masks were significant predictors of conversion (whole-brain: hazard ratio [HR] = 0.552, $P < 0.05$; temporoparietal: HR = 0.530, $P < 0.01$). More specifically, lower *W*-scores (i.e. higher CR) were associated with higher hazard rates for conversion. These effects survived when age, sex and MTA score were included as confounding variables (whole-brain: HR = 0.464, $P < 0.05$; temporoparietal: HR = 0.397, $P < 0.001$). In contrast, educational level was not associated with clinical progression in both the uncorrected ($HR_{intermediate\_education} = 1.831$, $P = 0.23$, $HR_{high\_education} = 1.247$, $P = 0.65$) and corrected model ($HR_{intermediate\_education} = 1.716$, $P = 0.30$, $HR_{high\_education} = 1.362$, $P = 0.54$).

Stratification for Scanner Type

Mean whole-brain *W*-scores separately calculated for each scanner subgroup were highly correlated with the original *W*-scores, both when combined into a single variable ($N = 511$, $r = 0.988$, $P < 0.001$) and as separate variables (Signa HDxt: $r = 0.998$, $P < 0.001$; Vantage Titan: $r = 0.972$, $P < 0.001$, Ingenuity TF: $r = 0.808$, $P < 0.001$). Spearman's rank order correlations consistently showed negative correlations between education and the new *W*-scores (total group: $r = -0.092$, $P < 0.05$), although these effects did not reach significance in the subgroups (Signa HDxt: $r = -0.074$, $P = 0.13$; Vantage Titan: $r = -0.168$, $P = 0.16$; Ingenuity TF: $r = -0.201$, $P = 0.36$). The Cox proportional hazards models revealed similar predictive effects in the total group (uncorrected: HR = 0.548, $P < 0.05$; corrected: HR = 0.471, $P < 0.05$) and the Signa HDxt subgroup (uncorrected: HR = 0.551, $P < 0.05$; corrected: HR = 0.465, $P < 0.05$). Since 113 of the original 116 pre-dementia subjects (97%) had a Signa HDxt scan, this latter analysis was not repeated in the other two scanner subgroups. All stratified analyses were also performed for mean *W*-scores in the temporoparietal mask, revealing similar results (see Supporting Information Table II and III).

DISCUSSION

In the current study we present a novel neuroimaging approach to capture CR. We used structural MRI and a global cognitive composite score as a model to demonstrate the validity of our approach in a group of subjects with AD pathology. The method starts by estimating the expected GM volume based on cognitive performance (adjusted for variables such as age, sex and disease stage) in the whole group, and uses standardized individual differences between the observed and expected GM volume (expressed as *W*-scores) as a measure of CR. GM volume that is lower than expected indicates greater CR as, compared to other subjects, more atrophy is tolerated at a similar level of cognitive function. Our method correlated with education (all $P < 0.05$), especially in temporoparietal and lateral occipital areas, which is in line with previous studies [e.g. Arenaza-Urquijo et al., 2013; Ewers et al., 2013; Liu et al., 2012; Querbes et al., 2009; Teipel et al., 2009]. This association indicates a certain overlap and similar directionality between both measures, but also unshared variability. These findings suggest that our neuroimaging approach does capture CR, but in a conceptually different (and arguably more accurate) way compared to the use of proxies. This is further supported by the finding that the neuroimaging measure of CR was associated with conversion to more advanced disease stages of AD in pre-dementia subjects, while education was not.

Advantages of our Neuroimaging Measure of CR

Our neuroimaging method has several potential advantages over current approaches to estimate CR. First, it is based on parameters that constitute the core of the concept (i.e. pathology and cognition), which should yield a more "pure" measure of CR. Unlike methods based on CR proxies, our approach treats CR as an independent concept that is influenced by, but does not equate, factors such as education, IQ, premorbid brain size, and cognitive and physical activity. Measuring CR without the use of proxies also allows better differentiation between CR and parallel concepts, such as brain maintenance. Brain maintenance has been defined as the ability to prevent the occurrence of neuropathology [Almeida et al., 2015; Landau et al., 2012; Nyberg et al., 2012; Valenzuela et al., 2008], and is directly related to various proxies of CR. Education, for example, has a great impact on an individual's (cardiovascular) health and risk to develop neuropathology through factors such as lifestyle, income and access to healthcare [Kaplan and Keil, 1993]. Therefore, education is not only related to the ability to cope with pathology (i.e. CR), but also to the degree to which pathology will occur (i.e. brain maintenance). Our neuroimaging approach accounts for the extent to which pathology is present, and thus measures the unique effect of CR, independent of brain maintenance.

Second, compared to existing methods, our neuroimaging approach provides a more precise and detailed measure of CR. Since the *W*-scores were created on a voxel level, it allowed studying the regional manifestation of CR in AD. In addition, our method enables computation of

voxel-wise CR values on an individual level (in comparison with a reference group), which is in contrast with previous neuroimaging approaches studying CR at a group-level. This individual and tailor-made approach has great potential for both scientific application (e.g. a better understanding of individual differences in CR) and clinical application (e.g. more accurate diagnosis or prognosis for individual patients).

Third, proxies such as education and IQ yield static estimations of CR (i.e. these proxies will not change as the disease progresses), while our values reflect the current status of CR, which is likely to change within a person over time. This is a critical feature, considering that the ability to maintain cognitive function gradually becomes depleted as severity of neuropathology increases [Stern, 2012]. The value of measuring "current CR" is also supported by the survival analysis, showing that our *W*-scores were predictive for conversion to more advanced disease stages in subjects without dementia. Importantly, when we used education as a substitute measure of "static" CR, we did not find an association with disease progression. The finding that subjects with the lowest *W*-score (i.e. highest CR) showed a higher risk for conversion is in line with the CR model, which dictates that individuals with higher CR can delay the onset of cognitive impairment, but once cognitive deterioration has started, they subsequently decline in a faster rate [Stern et al., 1995; Stern, 2012; Wilson et al., 2010]. Previous studies have reported inverse relationships between current CR and conversion to more advanced disease stages [Reed et al., 2010; Zahodne et al., 2015]. This difference could be related to the fact that the follow-up time in our study was relatively short (mean of ~2 years) and our subsample predominantly consisted of MCI subjects. The converters were thus in more advanced stages of AD at baseline (i.e. mostly in a prodromal stage, around 2 years before dementia onset) compared to the group of largely cognitively normal, preclinical converters in these previous studies. While in preclinical stages, high CR may be mainly related to the ability to delay the onset of cognitive symptoms (i.e. resulting in less "overall" decline), high CR in prodromal subjects is most likely associated with the faster rate of decline that occurs after onset of cognitive symptoms.

Finally, our method is flexible and can incorporate a wide variety of variables measuring neuropathology (e.g. PET) and cognition (e.g. specific domains such as memory, executive functioning, or behaviour). In addition, since CR plausibly is a generic, non-task specific phenomenon reflecting the ability to cope with many different types of pathology and associated cognitive problems [Stern et al., 2008], our method can be applied to any patient group of interest (e.g. non-AD dementias, Parkinson's disease, multiple sclerosis) and in relation to different proxies (e.g. physical activity, IQ). Importantly, our *W*-scores are standardized values, allowing direct comparisons between CR estimates derived from different parameters.

Limitations

We acknowledge that CR is operationalized in a rather simplified manner in this study, as not all residual variation between individuals in neuropathology (after subtracting the effect of cognitive function and other predictors) can be attributed to CR. This is illustrated by a large-scale study that investigated the effect of brain volumetrics on cognitive function (adjusted for age, sex, education, and ethnicity), showing that only 33% of the variance in cognition could be explained by the model [Gupta et al., 2015]. It is unlikely that all remaining variance could be attributed to CR, as multiple neurobiological factors might affect cognitive function independently of these measures of brain volume (e.g. white matter microstructure, vascular injury, neurotransmitter function, network connectivity) [Hedden and Growdon, 2015]. In the context of the current study, this indicates that differences in GM volume between two subjects with similar global cognitive composite scores may not be fully explained by CR alone, but also by the presence and degree of alternative pathogenic processes. For example, subjects with significant vascular burden or strategic lesions may tolerate less additional GM atrophy and thus show earlier cognitive decline relative to others despite similar levels of CR. Moreover, other sources of error variance in our model unrelated to CR are introduced by the inherent noise of brain imaging and neuropsychological measurements.

The aim of the present study, however, was not to present a method that captures CR in its full complexity, but rather to introduce an operational measure of CR that improves the empirical study of this phenomenon. Our method resembles that of the "residual memory variance" approach, in which a latent variable model was used to define CR as variance in episodic memory that was not explained by brain variables (i.e. total brain matter, hippocampus volume and white matter hyperintensities) or demographics [Reed et al., 2010]. Recently, other methods based on the same principle were reported, such as the "residual cognition" measure that was used to identify (epi)genetic underpinnings of CR [White et al., 2017], the "biological versus chronological age" model to study brain maintenance [Habeck et al., 2016; Steffener et al., 2016] and the calculation of hippocampal volume residuals to quantify resilience to AD pathology [Hohman et al., 2016]. Compared to the residual memory variance method to study CR [Reed et al., 2010], we took an opposite approach. Instead of using measures of pathology as a predictor for cognition, we used a measure of pathology (i.e. GM volume) as the outcome variable, predicted by cognition, age and other covariates. An advantage of this approach is that it yields multiple residual values (i.e. *W*-scores on a voxel level) for each subject, while the residual memory variance approach results in a single CR score per individual (i.e. an age or cognitive residual). The calculation of *W*-scores in each voxel of the brain therefore

provides more spatial detail, and allows the visualization of within-subject variability in the manifestation of CR across the brain. Also, it enables the selection of specific regions of interest (e.g. areas in which CR has the most prominent effect) to study CR with greater anatomical specificity. An advantage of the residual memory approach, compared to our method, is that it includes measures of white matter pathology in addition to GM pathology. As will be discussed in the following paragraphs, we intend to follow this example and expand our model by including multiple imaging modalities.

Future Directions

The present study represents the first step into validating a neuroimaging measure of CR, by showing that it correlates with a well-established proxy (i.e. education). In addition, the potential usefulness of the *W*-score method was demonstrated by its predictive value for disease progression in subjects without dementia. In future studies, we intend to expand our understanding of contributing factors to CR by correlating our neuroimaging measure to other proxies (e.g. cognitive/physical activity, premorbid IQ). In addition, we plan to utilize longitudinal data to further examine the predictive effect of our CR measure on cognitive decline across different cognitive domains (e.g. memory, executive function, attention). Finally, quantification of CR based on this neuroimaging approach could serve as a starting point from which underlying mechanisms can be studied. For example, functional neuroimaging techniques (e.g. functional MRI) could be used to determine whether the ability to maintain cognition in the presence of pathology is associated with functional compensation in relatively preserved regions of the brain or more effective pre-existing networks. Studies using other measures of CR have provided evidence for the existence of such functional mechanisms [Franzmeier et al., 2017; Marques et al., 2016].

We also intend to refine this neuroimaging method by including multiple measures of pathology (e.g. cortical thickness, white matter lesions, amyloid, and/or tau burden) in our model, to optimize the estimation of the unique contribution of CR in the relationship between pathology and cognition. Eventually, we aim to validate a more comprehensive version of our method using a large and independent sample as a reference group, to create a standard formula that can be used to instantly calculate CR on an individual level. Apart from an improved measurement of CR for research purposes, this could also have implications in a clinical setting. Our method has the potential of becoming a useful tool to estimate CR in a standardized and feasible manner for any given patient, which could improve clinical prognosis and allows tracking of intra-individual changes in CR over time (e.g. to examine effects of interventions targeted at increasing CR).

CONCLUSION

We presented a novel neuroimaging approach to capture CR in a more direct and specific manner. The method can easily be applied (we provide an automated script), flexibly incorporates different measures of neuropathology and cognition, and can be used to study various patient groups and CR proxies. Our method results in a standardized outcome measure (voxel-wise *W*-scores) that can be used to visualize and quantify CR with high neuroanatomical detail, and uniquely yields estimations of CR at an individual level.

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