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Supporting performance in the face of age-related neural changes: testing mechanistic roles of cognitive reserve

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Abstract Age impacts multiple neural measures and these changes do not always directly translate into alterations in clinical and cognitive measures. This partial protection from the deleterious effects of age in some individuals is referred to as cognitive reserve (CR) and although linked to variations in intelligence and life experiences, its mechanism is still unclear. Within the framework of a theoretical model we tested two potential mechanistic roles of CR to maintain task performance, neural reserve and neural compensation, in young and older adults using functional and structural MRI. Neural reserve refers to increased efficiency and/or capacity of existing functional neural resources. Neural compensation refers to the increased ability to recruit new, additional functional resources. Using structural and functional measures and task performance, the roles of CR were tested using path analysis. Results supported both mechanistic theories of CR and the use of our general theoretical model.

Keywords Aging · Cognitive reserve · Multi-modal neuroimaging · Path analysis · Function · Structure

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Introduction

As we age it is essential that we understand the multi-faceted impact of aging on the brain and the subsequent consequences of those changes on behavior. Advancing age brings with it a variety of neural changes (e.g. in gray-matter volume (GMV), cortical thickness, white-matter integrity, cerebral blood flow, and functional activity). The relationships between such age-related neural changes and the clinical and cognitive expression of those changes are not entirely clear. Complicating the understanding of these relationships is the fact that some individuals show evidence of severe cognitive decline with advancing brain alterations, while others are seemingly able to cope with such changes without significant clinical or cognitive expression (Roe et al. 2008; Y. Stern et al. 1995). The concept of some individuals being partially protected from the deleterious effects of advancing age-related neural changes has been termed cognitive reserve (CR) (Y. Stern 2002, 2009). Cognitive reserve is a model suggesting that "individual differences in cognitive processes or neural networks underlying task performance allow some people to cope better than others with brain damage" (Y. Stern 2009).

Variability in CR may result from differences in innate intelligence or life events and experiences, such that current and past exposures have an impact on how the brain copes with progressive pathology. This suggests that through better understanding of the mechanisms of CR one may gain better insight into which behaviors have the largest positive neural impact. Such information will be necessary to guide behavioral interventions to maximize their neural impact and subsequently maintain cognitive and clinical outcomes with increasing age.

Two potential mechanisms of CR have been termed neural reserve and neural compensation (Y. Stern 2002, 2009; Y. Stern et al. 2005). Neural reserve is the concept that CR manifests itself as inter-individual variability in levels of efficiency, or capacity of existing functional brain networks. This enables individuals with high CR to be more capable of coping with brain pathology's negative effect. Neural compensation is the concept that CR manifests itself as the inter-individual variability in the brain's facility to withstand interruption of standard processing networks by employing alternate brain networks. This suggests that a potential mechanism of CR is a general network of brain activity that is independent of task demands and supports task performance in the face of age-related structural and/or functional brain changes (Y. Stern et al. 2008).

In a previous fMRI experiment conducted by our group, two functional brain networks were identified which were differentially utilized by young and older age groups during the information retention phase of a verbal delayed item recognition (DIR) cognitive task (Zarahn et al. 2007). Network 1 consisted of regions in the midline cerebellum, left insula/inferior frontal gyrus, left hippocampus, right middle/superior frontal gyri, left inferior/middle frontal gyri into the pre-central gyrus, left inferior/superior parietal lobule, right cingulate gyrus into medial/superior frontal gyri and left medial/superior gyri. Also included were regions with decreased signal in the midline cingulate, left medial/superior temporal gyri, right medial frontal gyrus and left cingulate gyrus. Network 2 included the right parahippocampal gyrus showing increased activity with increased working memory load.

While both age groups utilized the primary functional network (network 1), the elders used it to a greater extent. The second functional network (network 2) was differentially used by the two age groups. The older adults used (expressed) network 2, while the young adults, as a group, did not. As task demands increased, older adults had increased expression of network 1, resulting in increased expression of network 2 which was associated with slower task performance. This suggests that aging impacted functional activity, which in turn affected task performance. The differential expression of the functional networks was later shown to be related to their underlying brain anatomy (Steffener et al. 2009): increased utilization of network 2 was significantly related to the reduced GMV within the left pre-central gyral region of functional network 1. This provided support for the idea that utilization of network 2 was related to the structural integrity of network 1. These studies highlighted how age-related differences in task performance were related to functional activity and the underlying neural structure.

Our previous work did not investigate whether CR influenced the relationships between task performance, functional activity and the underlying neural structure. It is possible that CR is related to increased efficiency of functional networks, supporting the idea of neural reserve. We could also seek support for the idea of neural compensation. Neural compensation suggests that people with higher CR might be able to better recruit some compensatory functional resources that help maintain performance when the standard functional resources are impaired by pathology. In this case CR might act via the recruitment of additional resources to moderate the effect that damage to the existing/standard networks has on task performance. That is, even when the networks are damaged by pathology and individuals are performing the task with a less than optimal network setup (high expression of both functional networks), people with higher CR may be able to recruit additional resources that allow them to maintain better performance than those with low CR.

Based on previous work in our laboratory and largely laid out in Stern (2009) we developed a conceptual path model, Fig. 1, which allows us to test the role of CR in our previous findings. This simplified model merges research into age-related changes in clinical and cognitive task performance, structural measures and measures of functional brain activity to better understand the relations between the brain and the potential role of CR. The path arrows represent some of relationships that may exist between the variables but

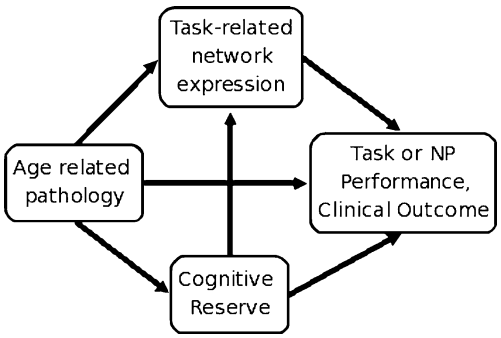

Fig. 1 A conceptual model of potential interactions between brain structure, functional activity, their relationship to cognitive outcome and the potential roles of cognitive reserve. This simplified model is not exhaustive in showing all of the potential relationships between the variables but includes paths based on our previous findings: 'pathology ➔ network expression' (Steffener, et al. 2009) and 'network expression ➔ task performance' (Zarahn, et al. 2007), the model includes 'CR ➔ network expression' supporting the idea that CR influences the expression of the functional networks; 'pathology ➔ CR' supporting the concept that at some point pathology must become too severe to support the processes that underlie CR (Y. Stern 2009). In addition, the path 'CR ➔ performance' supports the idea that CR may be operating via its own common network, which is unrelated to the expression of the task-related functional networks supporting task performance (Y. Stern, et al. 2008) and the path 'pathology ➔ performance' supports the idea that pathology may be affecting performance in a manner not captured by the other factors included in the model

is not exhaustive, e.g. this diagram does not include the potential moderating relationships.

Using the conceptual model as a guide, we used a specific instantiation to test the role of CR. First, a path analysis model was tested that encapsulated all of the relationships identified in our previous studies of healthy young and older adults, including the relationships of individual expression of the two functional MRI networks to both volumetric measures from structural MRI as well as a measure of cognitive performance (Steffener et al. 2009; Zarahn et al. 2007). Potential paths including CR were then included in the model. A significant relationship between the CR variable and the expression of the functional networks would provide support for the idea of neural reserve. A significant moderating effect of CR on the relationship between the expression of the functional networks and task performance would provide support for the idea of neural compensation. Based on previous findings suggesting that CR allows function to be maintained in the presence of age-related brain changes, we expected to find support for neural reserve.

Materials and methods

The current report extends previously published findings to investigate the role of CR (Steffener et al. 2009; Zarahn et al. 2007). Below is a review of the methods with greater detail found in the original two papers.

Study participants

The current study used the same participants used in the previous study (Steffener et al. 2009), which is a subset of the original study (Zarahn et al. 2007). This study includes data from thirty-seven healthy, young participants (out of the original 40)(29 men and 8 women; mean (± s.d.) age=25.0±3.9; mean (± s.d.) years of education=15.6±1.4; all right handed), and 15 healthy, elderly participants (out of the original 18)(7 men and 8 women; mean (± s.d.) age=74.5±6.9; mean (± s.d.) years of education=15.5±2.4; all right handed). All participants in the original study did not have the T1-weighted anatomical scans required for the current investigations of measures of gray matter volume resulting in the current use of a subset of participants. All participants were screened with structured medical, neurological, psychiatric, and neuropsychological evaluations to ensure that they had no neurological or psychiatric disease or cognitive impairment. The screening procedure included a detailed interview that excluded individuals with a self-reported history of major or unstable medical illness, significant neurological history (e.g. epilepsy, brain tumor, stroke), history of head trauma with loss of consciousness for greater than 5 min, history of Axis I psychiatric disorder (American Psychiatric Association 1994). Individuals taking psychotropic medications were excluded. Global cognitive functioning was assessed with a modified version of the Folstein Mini Mental State Examination (mMMS: (Stern et al. 1987)), which has a maximum score of 57. All participants were classified as non-demented and without clinically significant cognitive impairment, although the elder group had lower scores than the young group (young mean (± s.d.) mMMS total=55.2±1.5; elder mean (± s.d.) mMMS total=53.3±2.6, t (18.1)=2.68, p=.015)). IQ was estimated with the American version of the New Adult Reading Test (NART: (Nelson and O'Connell 1978)). Although the group differences for mMMS were significant it was not clinically meaningful since these values are well above levels associated with MCI and dementia.

FMRI behavioral task

Working memory was examined in all participants using a delayed-item-recognition (DIR) task with 1, 3 or 6 (study) letters visually presented for 3 s followed by a 7 s unfilled delay period (Rypma and D'Esposito 1999; Sternberg 1966; Zarahn et al. 2007). Following the delay period, a single (probe) letter was presented and participants decided whether or not it was included in the initial set of letters. Participants engaged in three practice runs of this task outside the scanner and three runs within the scanner where each run comprised 30 trials, 10 trials per load level. Therefore, behavioral and fMRI results are based on 90 experimental trials, 30 at each load level. Based on previous findings, the cognitive performance measure of slope of reaction times with respect to memory load was used (sRT). The sRT is the variable indicating the speed with which the probe is compared to each member of the study set in a serial search (Sternberg 1966).

MRI data acquisition

During the performance of each block of the delayed item recognition task, 207 BOLD images, were acquired with an Intera 1.5 T Phillips MR scanner equipped with a standard quadrature head coil, using a gradient echo echo-planar (GE-EPI) pulse sequence (TE/TR=50 ms/3,000 ms; flip angle=90; 64×64 matrix, in-plane voxel size=3.124 mm×3.124 mm; slice thickness=8 mm (no gap); 17 trans-axial slices per volume). A high resolution T2-weighted, fast spin echo image was acquired from each participant for spatial normalization purposes (TE/TR=100 ms/2,000 ms; flip angle=90, 256×256 matrix; in-plane voxel size=0.781 mm×0.781 mm; slice thickness=8 mm (no gap); 17 trans-axial slices per volume). A T1-weighted spoiled gradient image was acquired for voxel-based morphometry (VBM)

analyses (107 slices; 256×256 grid; FOV=230 mm by 160.5 mm by 183.28 mm).

Individual-level time series analysis of the BOLD data

All functional image preprocessing and analyses were implemented using the SPM99 program (Wellcome Department of Cognitive Neurology) and in-house developed software written in MATLAB 5.3 (Mathworks, Natick, MA). The following preprocessing steps were applied to each participant's GE-EPI data set: data were temporally shifted to correct for the order of slice acquisition, realigned to the first volume of the first session, coregistered to the T2-weighted (structural) image using mutual information, transformed into standard space as defined by the Montreal Neurologic Institute template brain using the linear and non-linear transformation matrix determined from the structural image, resliced using sinc interpolation to 2×2×2 mm and finally spatially smoothed using a Gaussian kernel with FWHM of 8 mm.

The fMRI data analysis comprised two levels of voxel-wise GLMs (Friston et al. 1999). In the first-level GLM, the GE-EPI time series were modeled with regressors representing the expected BOLD fMRI response to the three DIR trial components of memory set presentation, retention delay, and probe presentation/response, separately for each crossing of the set size. The regressors were convolved with an assumed BOLD impulse response model (as represented by default in SPM99). The resulting 9 contrast images per participant after estimation of the model (3 trial components crossed with 3 load levels) were used as the dependent variables in a second-level GLM.

Functional image analysis

Group-level analysis of BOLD image data used multivariate linear modeling (MLM: (Worsley et al. 1997)) to identify significant load-dependent and load-independent networks, or covariance patterns, comprising latent spatial variables engaged by the young and older groups for each of the three task phases (stimulus presentation, information retention, probe). The MLM analyses of each of these six effects of interest was tested across the two age-groups and can identify, at most, two spatial patterns.

Sequential latent root testing, using a global F-test and an α level of 0.05, was used to determine the number of significant spatial patterns for each of the six effects of interest. Once calculated, the spatial patterns were multiplied voxel-wise by the participant specific load dependent contrast maps that were entered into the MLM analysis, then summed to calculate each participant's network expression (Zarahn et al. 2007). These network expression scores served as independent measures describing the degree to which each participant used, or expressed, a significant spatial pattern. The results of these analyses were such that all intercept comparisons resulted in identification of a single network used by both age groups. The slope contrasts for the stimulus and probe phases also identified a single network, while the slope effect during retention had two networks expressed. It is these two networks related to the slope effect during information retention, referred to as networks 1 and 2, which are the focus of this study.

Structural image analysis

Modulated, spatially normalized gray-matter probability maps, (gray-matter volume maps) as derived from the optimized segmentation protocol included with SPM5 (Good et al. 2001){Ashburner, 2005 #33}, were intensity thresholded at 10% (Busatto et al. 2003). The images were spatially smoothed and used for voxel based statistical parametric mapping using SPM5 (Wellcome Department of Cognitive Neurology). General linear modeling tested whether the expression of network 2 was associated with regional gray-matter volume within network 1 (see Steffener et al. 2009). It was found that only a region within the left pre-central gyrus demonstrated a significant relationship between expression of network 2 and GMV. The mean of the 91 significant voxels was used as the structural measure of regional gray-matter volume (rGMV). In addition, normalized whole brain volume (nWBV) was used as a structural measure and calculated from the image segments in native space as the summed volume of gray- and white-matter divided by the summed volume of gray-matter, white-matter and cerebrospinal fluid (Fotenos et al. 2005). This measure represents the percentage of the total intracranial volume occupied by gray and white matter.

Cognitive reserve factor

Cognitive reserve was represented as a factor score summarizing years of education and scores on two IQ indices, the NART (Nelson and O'Connell 1978) and WAIS-R vocabulary score (Wechsler 1987). Previous work from our laboratory has demonstrated the validity of this construct using these cognitive tests (Siedlecki et al. 2009). Using AMOS software (Arbuckle 2007) as implemented in SPSS release 18 (SPSS Inc. Chicago, Illinois) the factor weightings were determined from a set of 228 young and 104 elder participants from studies conducted in our laboratory. This large sample included the participants in the current study and the factor weights did not significantly differ between age groups based on between group tests of metric invariance.

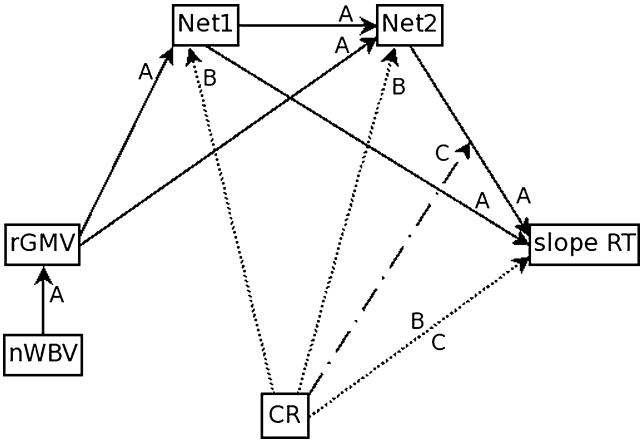

Fig. 2 Testing the mechanism of CR in the current instantiation of the theoretical model. Full path diagram showing the models tested. Solid lines (labeled A) are those paths tested in Model A and are used to confirm the relationships between the structural, functional and performance measures. The dashed line (labeled B) is the included path to test model B, which tests for the neural reserve mechanism of CR. Dash-dotted lines (labeled C) represent the testing of model C, which tests for the neural compensation mechanism of CR

Path models

All path models included two groups, young and elders; therefore, separate parameter estimates for each group were calculated and compared. Model reduction methods based on non-significant path weights included constraining path weight to be equal across groups or set to zero for both groups. Initially, a model of the relationships between the structural, functional and task performance measures without CR was tested, Model A in Fig. 2. After establishing the significant relationships in the absence of CR, two models of CR were tested. Model B tested whether CR took on the role of neural reserve by testing whether CR influenced the expression of the functional networks which led to changes in task performance; therefore, the indirect effect of CR on task performance via the functional networks was tested. Model C tested whether CR took the role of neural compensation by testing whether the previously identified relationship between functional network expression and task performance was moderated by an individual's level of CR. Both models B and C included the direct path between CR and task performance.

Significance of path weights was determined based on 95% confidence intervals determined using bias-corrected percentile method with 1000 bootstrap estimates (MacKinnon et al. 2004). Several statistics determined the fit of the path models: chi-square (X^2), root mean square error of approximation (RSMEA) and the comparative fit index (CFI) (Hu and Bentler 1998; MacCallum et al. 1996). Model comparisons were made using the Browne-Cudeck Criteria (BCC) (Browne and Cudeck 1989) and the Akaike Information Criteria (AIC) (Akaike 1987). Path analyses were performed using AMOS software.

Results

Summaries of means, standard deviations and bivariate correlations for all variables used in this analysis are in Tables 1 and 2. The older adults had decreased regional and whole brain gray matter volume. Older adults also had slightly lower mean NART and vocabulary scores, but these IQ measures were above average in both age groups and the difference posed no clinical significance. Expression of both functional networks differed significantly between the two age groups, with increased expression in the older group. Task performance was significantly poorer in the older group.

Model A: The relationships between structure, function and performance

The first path model tested (model A), included structural MRI measures, expression of both functional MRI networks and the task performance variable, see Fig. 3A. As determined from previous work, this model constrained the relationship between rGMV and Network 1 at zero and the relationship between rGMV and Network 2 to be equal across age groups (Steffener et al. 2009). The path from network 1 to the performance measure was non-significant and constrained to zero. This model significantly fit the data and resulted in no non-significant paths (X^2=13.087 (df=18), p=.786; RMSEA=.000; CFI=1.000; AIC=37.087; BCC=48.952). The reduced model is summarized as follows: nWBV had a positive direct effect on rGMV for

Table 1 Descriptive data for variables used in path model

	Mean (S.D.)	
	(n=37) Y	(n=15) E
Age	25.0(3.93)^{**a}	74.5(6.95)
rGMV	0.46(0.052)**	0.33(0.068)
nWBV	0.80(0.040)**	0.64(0.041)
CR	0.088(0.35)^{b}	−0.10(0.50)
NART	120.38(6.14)*	116.13(6.79)
Vocab.	14.51(2.78)^{**c}	12.27(1.94)
Edu.	15.62(1.42)^{d}	15.53(2.44)
Net1	0.10(0.081)*	0.17(0.080)
Net2	−0.050(0.12)**	0.16(0.13)
s RT	56.6(29.5)**	90.0(35.6)

*p<0.05; **p<0.01; df=50 except for [a]: df=17.8,[b]:df=19.64 [c]:df=36.89 [d]:df=17.96

Table 2 Correlations between variables used in path model; Young: Above midline, Elders: Below midline

Y➔↓E	Age	rGMV	nWBV	CR	NART	Vocab.	Edu.	Net1	Net2	s RT
Age		.04	−.26	.39*	.20	.32	.36*	−.05	.03	−.01
rGMV	−.69**		.27	.07	.12	.31	−.02	−.13	−.34*	.07
nWBV	−.05	.19		−.28	−.19	−.16	−.29	.06	−.08	.20
CR	−.15	.27	−.31		.79**	.80**	.83**	−.26	−.04	−.20
NART	−.16	.22	−.04	.84**		.72**	.44**	−.36*	−.16	−.10
Vocab.	−.25	.025	.01	.56*	.71**		.35*	−.28	−.16	−.09
Edu.	.11	.15	−.32	.94**	.67**	.28		−.11	.10	−.25
Net1	−.29	−.28	−.11	−.36	−.44	−.16	−.30		.43**	.22
Net2	.07	−.58*	.03	−.18	−.27	−.07	−.11	.77**		−.02
s RT	.26	−.40	−.12	−.50	−.63*	−.60*	−.32	.49	.58*	

*$p < .05$; **$p < .01$

the young adults but not the elders (higher nWBV was associated with higher rGMV); rGMV had a significant negative direct effect on network 2 in both age groups (more rGMV was related to lower expression of network 2); network 1 had a significant positive direct effect on network 2 for both age groups (greater expression of network 1 was associated with greater expression network 2); network 2 had a significant positive direct effect on slope RT in the elders but not the young adults (greater expression of network 2 resulted in longer RT with increasing memory load).

Model B: The neural reserve model of cognitive reserve

Starting with the reduced model A path diagram, the neural reserve model of CR was tested within the same path diagram. This tested whether there was an indirect effect of CR on task performance via the functional networks. The path between CR and network 2 was non-significant for both age groups and constrained to zero. The path from CR to network 1 was in the same direction and significant for both age groups and therefore constrained to be equal across age groups resulting in a significant model fit, see Fig. 3B (X^2=41.101 (df=32), p=.130; RMSEA=.075; CFI=.872; AIC=89.101; BCC=129.288). To summarize, higher CR resulted in decreased expression of network 1 (i.e. greater efficiency) in both age groups; decreased expression of network 1 led to decreased expression of network 2 in both age groups; decreased expression of network 2 led to improved task performance (i.e. less increase in RT as memory load increased) in the older adults. That is, cognitive reserve had a significant indirect effect in the older adults on task performance due to it lowering the expressions of networks 1 and 2 which resulted in a lower negative impact on task performance.

In addition, the previously reported negative indirect effect of rGMV on task performance in the older adults (greater rGMV was related to a smaller impact of memory load on RT via network 2) was still significant in this model, although its indirect effect on sRT is now shown to be influenced by CR. Thus, at any level of local atrophy, individuals with higher CR can sustain reduced expression of network 2 and therefore preserve task performance.

Model C: The neural compensation model of cognitive reserve

Model C tested whether the relationship between functional network expression and task performance was moderated by an individual's levels of CR. The path between CR and performance was non-significant for both age groups and constrained to be equal between the groups. Cognitive reserve significantly moderated the effect of network 2 on task performance in the elder group but not the young and resulted in a significant model fit, see Fig. 3C (X^2=38.438 (df=31), p=.168; RMSEA=.069; CFI=.896; AIC=88.438; BCC=130.300). Thus, increased CR led to a decreased impact of expression of network 2 on task performance. To summarize, higher CR led to a decreased negative impact of increased expression of the functional networks on task performance in the older adults. Once this CR moderating effect was included in the model there was no longer any direct effects of CR on task performance in either age group. Therefore, older adults with high CR were better able to maintain task performance even when increased local atrophy is decreasing the efficiency of their functional networks.

Model D: Combined neural reserve and neural compensation as a model of cognitive reserve

In order to determine if CR could be playing a role of maintaining efficiency of functional networks and moderating the effects of functional network expression on task performance, Models B and C were combined to form Model D. In this combined model no additional constraints were required. The indirect effect of CR on task performance via the functional networks and the moderating effect of CR on the relationship between

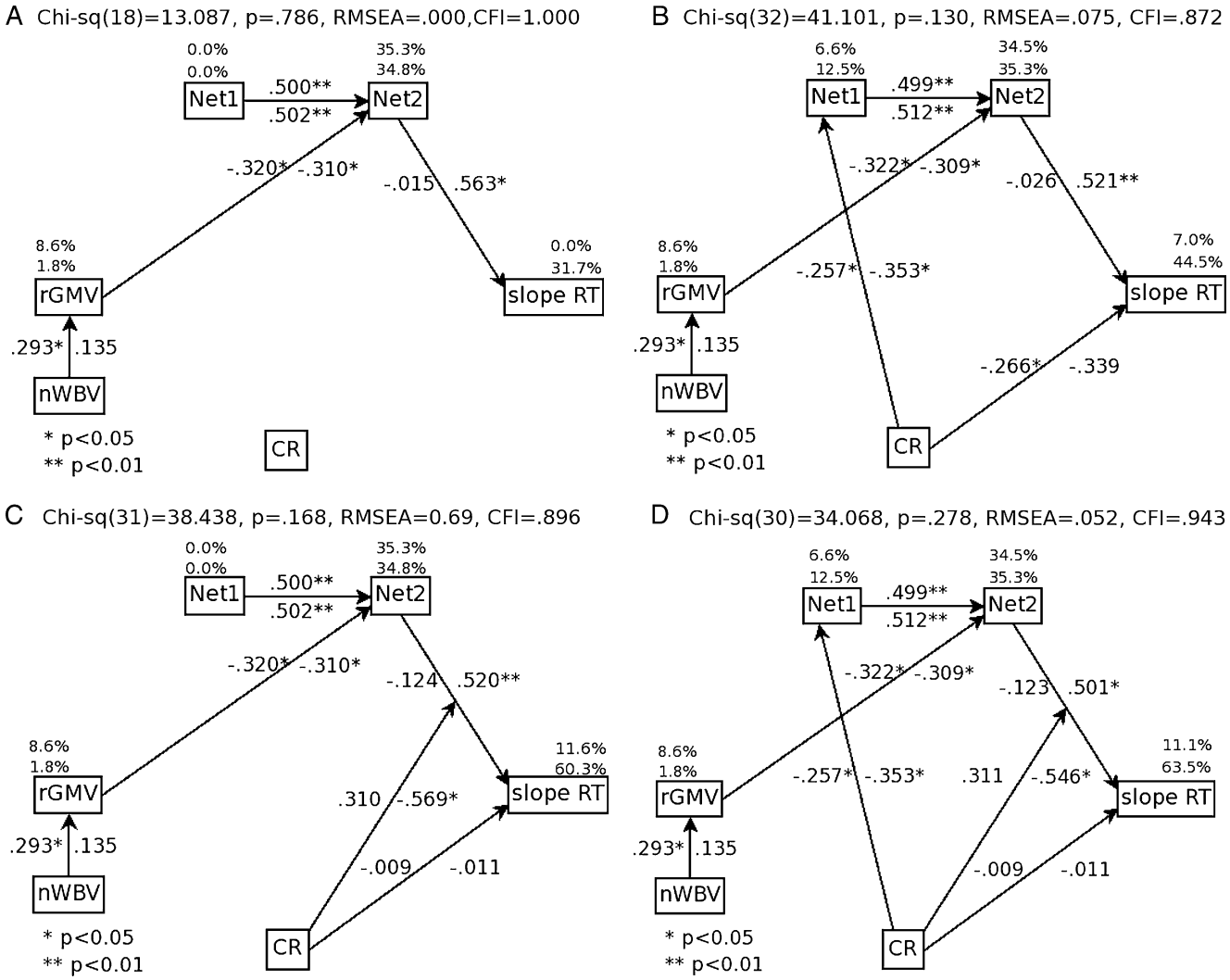

Fig. 3 Path model results for cognitive reserve. **a** Confirmatory model of the relationships between the structural, functional and performance measures. **b** Model results for testing of neural reserve as a mechanism of CR. **c** Model results for testing of neural compensation as a mechanism of CR. **d** Combination of neural reserve and neural compensation as joint models of CR. Values on path arrows are standardized regression coefficients of direct relationships. Percentage values above variable boxes are the variance accounted for. In all cases the left or upper number is for the young age group and the right/lower for the older age group. Solid lines represent paths in the final model, light, dotted lines represent paths that were initially included in the models but dropped in the final model due to non-significant path weights. Abbreviations: Net1 and Net2: individual expression of the two functional networks; RT: reaction times; slope: increase in measure with increasing memory load demands; inter: intercept of measure across memory load demands; CR: cognitive reserve; rGMV: regional gray-matter volume within the left pre-central gyrus. nWBV: normalized whole brain volume

functional network expression and task performance both remained significant in the older adults resulting in a significant model fit, see Fig. 3D (X^2=34.068 (df=30), p=.278; RMSEA=.052; CFI=.943; AIC=86.068; BCC=129.603). Standardized indirect effect sizes and significance for both age groups are in Table 3. To summarize, increased CR in the older adults maintained task performance due to it lowering the expressions of networks 1 and 2 which resulted in a lower negative impact of local atrophy on task performance. CR additionally allowed older adults to better maintain task performance even

Table 3 Standardized indirect effects for model D

		E	Y
Net1	sRT	0.257**	−.062
CR	sRT	−0.091**	.016
rGMV	sRT	−0.155*	.040
nWMV	sRT	−0.021	.012
CR	Net2	−0.181**	−.128**
nWBV	Net2	−0.042	−.094*

*p < .05; **p < .01

when increased local atrophy is decreasing the efficiency of their functional networks.

Discussion

Cognitive reserve was operationalized as a construct derived from measures of verbal intelligence and education. Previous studies have demonstrated that these measures have convergent validity such that they are highly correlated amongst themselves and with the latent construct CR. More importantly these measures have demonstrated discriminant validity in that this construct represents a unique aspect of individual variability (Siedlecki et al. 2009). In the current work CR had significant effects on memory load-related speeded task performance (sRT) and the two proposed mechanisms of CR (neural reserve and neural compensation) were supported in the older adults and only the neural reserve mechanism in the young adults.

In model D, the measure of age-related atrophy (rGMV) in network 1 was related to the expression of network 2 similarly for both age groups. We have posited that smaller gray matter volume within the primary functional network (network 1) resulted in the reliance on less-efficient functional resources to maintain task performance (network 2 (Steffener et al. 2009)). As reported, expression of network 2 increased as network 1 became more inefficient due to less gray matter volume. In the current study CR acted as a mechanism to maintain the efficiency of network 1 in the presence of the smaller volume: those with low CR used their functional resources to a greater extent (higher expression of the networks) for equal performance as compared to those with high CR, whose functional networks maintained efficiency and were expressed to a lower degree. Thus CR acted to maintain efficiency of the functional networks in the presence of smaller gray matter volume. Therefore, in the older adults CR had an indirect effect on task performance by altering the efficiency of the functional networks. This finding is concordant with the concept of neural reserve, which posits that CR could maintain performance in the face of brain changes via the differential efficiency or capacity of existing networks.

Interestingly, in the young adults there was also a significant relationship between gray matter volume in network 1 and expression of network 2 suggestive of neural reserve. While we report that as a group the young adults do not express the secondary pattern, the individual variation in the expression of this network is related to the gray matter volume within the pre-central cortex, a region functionally involved in performance of the current task. Work by Sakai et al. (2002) suggests that in the face of interference during the information retention phase of a DIR task, young adults demonstrated increased signal in their parahippocampal gyri, the primary region comprising our network 2 (Sakai et al. 2002). This suggests that the use of the parahippocampus is a viable option for the young adults to reactivate information stored off-line; however, this method of information retention may be less efficient than alternative mechanisms, such as continued on-line maintenance (Sakai 2003). Furthermore, as in the older adults, increased CR in the young adults resulted in decreased use of network 1. Therefore, this suggests that neural reserve, the increased ability to use efficient functional processing, may be formulated early in life as a result of higher verbal intelligence and education, whose measures form our CR variable.

We also found that, within the older adults, the relationship between functional network expression and task performance was moderated by an individual's level of CR. Those older adults with greater CR demonstrated less of a negative impact of the expression of network 2 on task performance then those with lower CR but an equal expression of network 2. This is suggestive that those with higher IQ and educational attainment may efficiently utilize the functional resources identified by network 2 for maintaining task performance. The neural underpinnings of the ability to efficiently incorporate, or recruit, the additional functional resources are currently unknown. This finding is consistent with the concept of neural compensation (Y. Stern 2009) in that CR may be associated with the activation of a new network that allows performance to be maintained in the face of alterations to the networks that typically support performance (in this case networks 1 and 2). Such a CR related compensatory network could be particular to performance of the current task or CR might be acting through a more generalized network that supports performance of many different tasks. In the current case, the results suggest that the compensatory network is not captured by the 2 identified task-related networks so it is interesting to hypothesize that neural compensation here is mediated via a separate non-task-related CR network.

Returning to our initial conceptual model, our data support the notion that in the current case CR had indirect effects on task performance through the expression of functional networks and minimal direct effects on task performance. This conceptual model, and the presented results, incorporate three diverse modalities of aging research: cognitive testing, structural neuroimaging and functional neuroimaging. This incorporation presents one unified conceptual framework, garnering a more complete view of the aging process. With more complete understanding of the aging mechanisms and the role of CR, targets of intervention for forestalling cognitive decline may be developed, such as cognitive exercise (Erickson et al. 2010; Valenzuela and Sachdev 2009). While we previously postulated that neural reserve and

compensation may be mechanisms of CR(Y. Stern 2009; Y. Stern et al. 2005), the current study provides evidence to support their presence. Although there is evidence for differential neural efficiency and capacity with advancing age (Schneider-Garces et al. 2009) the current work integrates structural and cognitive reserve measures into explaining the role that age-related differences in efficiency and capacity play in maintaining task performance.

A limitation in this study is the small number of participants. The main findings of this work are related to the elder age group and it is important to emphasize that these results are from a sample of 15 participants. As one means to minimize the impact this has on our findings, path significance was assessed using the bias-corrected percentile method with 1000 bootstrap estimates (MacKinnon et al. 2004). The variables in the model were also exhaustively permuted and the models re-estimated. None of the model estimations for the 5040 permutations resulted in a better fit between the model and the data. While replication with larger sample sizes is certainly warranted to address issues of robustness and replicability, the boot-strap and permutation tests provide support for our confidence in these findings.

While the age groups significantly differed in their measures of rGMV, nWBV, NART, Vocab, sRT and expression of the two functional networks, the variances in age, Vocab, education and CR also significantly differed. Therefore, the older adults appear more heterogeneous in their CR variables than their younger counterparts. Although included in the theoretical model, Fig. 1, but not tested here, it is plausible that the cognitive variables are sensitive to age-related neural changes which are causing this heterogeneity. The correlations in Table 2 do not demonstrate any significant correlations between the structural brain measures of the current study and the cognitive measures; however, other unmeasured structural correlates of cognition may exist.

The conceptual model presented is very general and easily used with multiple data sets and across laboratories. We provide supportive evidence with a single instantiation of the model and continue to use it as a starting point for developing ideas related to the role of CR. The greatest benefit of the conceptual model is its generalizability such that each node can be operationalized differently without altering the overall structure or the theoretical underpinnings of the model. The structural measures are expandable to include measures of white matter integrity, blood flow, cortical thickness, or amyloid burden and additional measures of functional activity may be included (e.g. measures from other tasks, activity within regions of interest or measures of functional connectivity). Although our measure of CR was based on education and IQ scores, this could be expanded to include other factors (e.g. lifetime occupation (Y. Stern et al. 1995), or life time cognitive activities (Wilson et al. 2002). In addition, it could include expression of task non-specific networks related to CR (Y. Stern et al. 2008). Finally, we used task performance during the functional task as our clinical outcome variable which may also be represented with other indices of current cognitive/functional capacity or clinical outcomes (such as cognitive decline or incident dementia).

The implementation of the model incorporated previous findings from neuroimaging studies conducted in our laboratory, where consecutive studies independently tested one or two pathways of the model. To test the model as a whole, the current path analyses incorporated many of the findings in a single analysis with the additional inclusion of CR. Ongoing work in our group continues to use this conceptual model to integrate information across these different domains. We offer this approach as particularly useful for multi-modal studies of the aging phenomenon. This approach provides a straightforward way of assimilating multi-modal imaging data with clinical and performance measures. Its implementation can provide greater insight into the age-related neural alterations that lead to cognition changes and illuminate how CR mediates their effects.

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