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Functional Reserve: The Residual Variance in Instrumental Activities of Daily Living Not Explained by Brain Structure, Cognition, and Demographics

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Abstract

Objective: Cognitive reserve is a concept that explains individual differences in resilience to brain pathology and susceptibility to poor late-life cognitive outcomes. We evaluate the analogous concept of 'Functional Reserve,' defined as the difference between observed functional abilities and those predicted by brain structure, cognitive performance, and demographics. This study aims to validate the construct of functional reserve by testing its utility in predicting clinical outcomes and exploring its predictors.

Method: Longitudinal data collected annually for up to seven years from 1,084 older adults ($n_{dementia}$=163; n_{MCI}=333; n_{CN}=523) were analyzed. Functional reserve was operationalized as the residual variance in the Lawton-Brody Instrumental Activities of Daily Living (IADL) Scale after accounting for demographics (sex/gender, race, ethnicity, education), neuropathology (grey matter, hippocampal, and white matter hyperintensity volumes), and cognition (executive function, verbal episodic memory, semantic memory, and spatial function). Structural equation models

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estimated (1) functional reserve's associations with 7-year changes in clinical diagnosis and disease severity and (2) predictors of functional reserve.

Results: Functional reserve was lower in dementia versus cognitively normal individuals. Higher baseline functional reserve was associated with lower concurrent dementia severity and slower clinical progression, and attenuated the association of cognition with concurrent dementia severity. Physical function and apathy were the strongest predictors of functional reserve.

Conclusions: Results provide preliminary validation of functional reserve for explaining individual differences in susceptibility to IADL dysfunction independent of neuropathology, cognition, and demographics. Physical functioning and apathy are promising modifiable intervention targets to enhance functional reserve in the context of brain atrophy and cognitive decline.

Keywords

cognitive reserve; dementia; functional abilities; instrumental activities of daily living (IADLs); older adults

Older adulthood is characterized by increases in age-associated brain pathology as well as declines in cognitive and functional abilities, with substantial inter-individual heterogeneity in trajectories of decline. The concept of cognitive reserve was developed to describe observed variability in late-life cognition (Reed et al., 2010; Satz, 1993; Stern, 2002; Stern et al., 2018; Stern & Barulli, 2019), particularly with respect to cognitive health outcomes. However, less is known about variability in late-life functional ability and its relationship to clinical outcomes such as dementia, independent of cognition and neuropathology. For example, we do not yet fully understand why some individuals with relatively high degree of cognitive impairment remain functionally independent and others with comparatively lower levels of cognitive impairment are much more disabled. This has considerable clinical importance. For example, the concept of mild cognitive impairment (MCI) is defined as a transitional state between normal cognition and dementia. A primary difference between MCI and dementia is the relative absence of functional deficits and associated loss of independence in MCI compared with dementia (Albert et al., 2011). Accordingly, two individuals who have the same level of cognitive impairment and neuropathologic changes could have considerably different degrees of functional impairment, wherein one individual has intact instrumental activities of daily living (IADLs) and the other has impaired IADLs. Despite having identical brain and cognitive status, the former person would be diagnosed with MCI and the latter person would be diagnosed with dementia. Beyond the (somewhat arbitrary) diagnostic label, elucidating the mechanisms that help maintain functional independence is important for enhancing quality of life and decreasing burden on families, caregivers, and society (Callahan et al., 2015; Hurd, Martorell, Delavande, Mullen, & Langa, 2013; Kawaharada et al., 2019).

Beyond diagnositic importance, there is a large body of work demonstrating that neuropsychological performance (particularly episodic memory and executive functioning) helps to explain degree of functional impairment (Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002; Farias, Mungas, Reed, Haan, & Jagust, 2004; Grigsby, Kaye, Baxter,

Shetterly, & Hamman, 1998). However, neuropsychological performance, alone or in combination with demographic variables, typically accounts for only a quarter to a third of the variance in functional outcomes (Royall et al., 2007). Inclusion of structural and/or functional brain integrity measures may account for additional variance in functional abilities (Nadkarni, Levy-Cooperman, & Black, 2012; Overdorp, Kessels, Claassen, & Oosterman, 2016; Roy et al., 2014) beyond cognitive test performance. For example, findings from a systematic review of 20 studies conducted in older adult samples concluded that alterations in brain morphology, including hippocampal atrophy and white matter changes, were associated with poorer IADL performance independent of neuropsychological test scores (Overdorp et al., 2016). Therefore, the literature described above suggests that cognition and brain integrity contribute both shared and unique sources of variance toward maintaining intact IADLs. Nonetheless, much of the variance in IADL function remains unexplained even after accounting for these variables plus demographic data.

This remaining unexplained variance can therefore be interpreted to represent the construct of ‘functional reserve,’ which we define here as the residual variance in functional abilities after accounting for cognition, brain integrity, and demographics. One prior study measured functional reserve as the protective influence of participating in IADLs thoughout life, operationalized as a proxy variable calculated by summing participants’ history of ever conducting various IADLs (Berezuk et al., 2017). The study found that less participation in IADls was a risk for greater dependence, supporting the potential usefulness of the concept of functional reserve. Extending this prior cross-sectional work, the current study explicitly models functional reserve as the mismatch between actual and expected functional (IADL) performance predicted by brain integrity, cognitive test scores, and demographic variables (e.g., education, sex/gender, and race/ethnicity). Using this operationalization, a person with high reserve has better functional performance than predicted, and conversely, a person with low reserve has worse functional performance than predicted. This same method has been applied to defining cognitive reserve (McKenzie et al., 2020; Reed et al., 2010; Zahodne et al., 2013), which has demonstrated validity as a construct that buffers cognitive ability from the effects of brain disease.

Conceptually, functional reserve is posited to operate analogously to cognitive reserve; that is, to modify the expected association of cognitive performance with dementia-relevant clinical outcomes such as clinical diagnosis and progression. As with the residualized cognitive reserve variable (Reed et al., 2010), demographics, brain, and cognitive variables are included as covariates in our proposed functional reserve model as they represent sources of variability in IADL performance. Furthermore, all else equal, greater functional reserve should be associated with less severe dementia and a slower rate of clinical progression. Similar to theoretical and empirical work on cognitive reserve (Stern, 2002; Stern et al., 2018), functional reserve should buffer against the deleterious effects of lower cognitive performance on clinical dementia severity outcomes. Within this ‘reserve’ framework, individuals with high functional reserve are expected to demonstrate greater functional independence and lower dementia severity than would be predicted on the basis of their cognitive functioning, whereas the opposite pattern would be expected in people with low functional reserve.

One advantage of modeling functional reserve as the residual variance in IADL performance not explained by cognition, brain variables, and demographics, is that such an approach allows for the elucidation of factors that contribute to better or worse functional reserve. There are a multitude of such candidate factors (Verbrugge & Jette, 1994). For example, previous studies have shown that neuropsychiatric symptoms, particularly depression and apathy, can negatively impact functional abilities independent of cognition (Hinton, Tomaszewski Farias, & Wegelin, 2008; Okura et al., 2010; Rog et al., 2014). Depression and apathy may be particularly salient in the context of cognitive health outcomes. Indeed, they have been observed to be two of the most prevalent neuropsychiatric symptoms in a sample of older adults with normal cognition, cognitive impairment, and dementia (Okura et al., 2010). Conversely, intrapersonal characteristics and habits, such as use of good compensatory strategies (e.g., keeping a calendar and taking notes) are associated with better functional abilities and slower rates of functional decline, independent of cognitive function (Farias et al., 2019, 2018). Additionally, physical impairments that affect ambulation or other motor functions can contribute to functional disability independent of other health issues. Importantly, many of these factors are potentially modifiable and thus could be the target of interventions to support greater functional reserve and preserved independence in the context of neurodegenerative disease.

In summary, the aims of this paper are threefold: (1) to empirically operationalize the construct of functional reserve as the variance not explained by cognitive impairment and brain degeneration and examine its validity with respect to its association with clinical outcomes, (2) to test whether baseline functional reserve modifies associations between cognitive performance and clinical outcomes, and (3) to identify potentially modifiable factors that predict functional reserve. Regarding the **first aim**, we hypothesize that greater functional reserve will be associated with better clinical outcomes in terms of both dementia severity (i.e., lower initial dementia severity and slower clinical progression over the follow-up period up to seven years) and diagnosis (i.e., less impaired diagnosis concurrently and lower likelihood of conversion from cognitively normal or MCI to dementia). Regarding the **second aim**, we hypothesize that greater functional reserve will attenuate the associations of cognitive performance with clinical dementia severity outcomes. Regarding the **third aim**, we hypothesize that greater compensatory abilities, better physical function, and lower levels of depression and apathy will predict higher functional reserve.

Method

Participants

Participants (N = 1,084) underwent evaluation at the University of California, Davis Alzheimer's Disease Center as part of a longitudinal study of cognitive aging and dementia. Participants were recruited via memory clinic referrals and community outreach. All participants were tested in their preferred language of either English or Spanish. Recruitment method and cohort composition have been described elsewhere (Hinton et al., 2010); of note, the recruitment methods were designed to build a diverse cohort of participants with respect to race, ethnicity, language, referral source (clinic vs. community), and cognitive status.

Participants were included in the study if they were age 60 years or older. They were excluded if they had any unstable major medical illness, major primary psychiatric disorder (e.g., history of schizophrenia or bipolar disorder), or a substance abuse or dependence diagnosis in the last five years. Participants unable to undergo magnetic resonance imaging (MRI) scanning were excluded. All participants provided written informed consent. The study was approved by Institutional Review Boards at the University of California, Davis, the Veterans Administration Northern California Health Care System, and the San Joaquin General Hospital in Stockton, California.

Measures

Clinical Dementia Rating.—The Clinical Dementia Rating (CDR; Morris, 1993) is a structured caregiver and participant interview that assesses six functional domains, including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The current study used the CDR sum of boxes (CDR-SB) as the primary dementia severity measure, which was calculated by summing scores across the six domains (Daly et al., 2000). Higher scores reflect greater dementia severity.

Clinical Diagnosis.—Clinical diagnoses were categorized as normal cognition, MCI, or dementia, as described in detail previously (Chen et al., 2017; Farias et al., 2013; Fletcher et al., 2018). All participants received annual multidisciplinary clinical evaluations that included a physical and neurological exam, neuroimaging, lab work, and neuropsychological testing from the Alzheimer's Disease Uniform Dataset Neuropsychological Battery (Weintraub et al., 2009). Diagnosis was categorized as normal cognition, MCI, or dementia based on a multidisciplinary adjudication process according to standard clinical criteria using the current Alzheimer's Disease Centers Uniform Data Set guidelines (Morris et al., 2006).

Decomposed Functional Reserve Variables

IADL.—The Lawton-Brody Instrumental Activities of Daily Living Scale (Lawton & Brody, 1969) measures independent living skills. The informant-reported 8-item scale assesses participants' ability to complete daily tasks such as medication management and food preparation. In analytic models, scores were recoded so that higher scores reflect a higher functional level (0 = the task must now be completed by someone else, 1= the task requires some assistance, 2 = can complete the task independently), with total scores ranging from 0 to 16. The total score was computed by summing responses to each item. Scores on this measure were used to decompose variance attributed to brain health, cognitive functioning, demographic factors, and the residualized functional reserve variable. The internal consistency reliability (McDonald's omega; McDonald, 1999) of the Lawton-Brody in the current sample was $\omega = .92$.

Neuropsychological Functioning.—The Spanish and English Neuropsychological Assessment Scale (SENAS) is a comprehensive, well-developed neuropsychological battery, psychometrically matched across English and Spanish versions. Details regarding the battery and its psychometric properties have been described elsewhere (Mungas, Reed, Crane, Haan, & González, 2004; Mungas, Reed, Marshall, & González, 2000). Briefly, the current study

includes neuropsychological test performance from four cognitive domains (verbal episodic memory, semantic memory, spatial functioning, and executive functioning). Verbal episodic memory is a composite score from performance on a multi-trial word list learning test. Semantic memory is a composite of highly correlated nonverbal (Picture Association) and verbal (Object Naming) tasks. Spatial functioning is a composite of Spatial Localization and Pattern Recognition subtests. Executive functioning is a composite of Category Fluency, Phonemic (letter) Fluency, and Working Memory tasks. Z-scores were computed using means and standard deviations from the current study sample for the four cognitive domains.

Brain Variables.—MRI scans were performed at the University of California, Davis Imaging Research Center using a 1.5T GE Signa Horizon LX Echospeed system or at the Veterans Administration at Martinez on a 1.5T Marconi system. The comparability of images and scan parameters in the two sites have been previously described (DeCarli et al., 2008). Brain measures used in our analysis were obtained by a standard in-house pipeline at the Imaging of Dementia and Aging Laboratory, UC Davis. Briefly, intra-cranial masks (ICC) comprising the brain and surrounding space to the pia mater were segmented using an atlas-based segmentation approach (Aljabar, Heckemann, Hammers, Hajnal, & Rueckert, 2009). Hippocampal masks were obtained by a similar procedure applied to the hippocampus. In each of these processes, a set of atlas whole-head images with carefully segmented masks (i.e. for intra-cranial volume or hippocampus) are non-linearly matched to the target native space whole head structural MRI, followed by a voting scheme based on the transformed masks to determine the native voxels belonging to a given structure. For the ICC segmentations, human quality control is additionally used for any minor cleanup after the atlas segmentation. White matter hyperintensities (WMH) volumes were segmented from the native structural T1 and FLAIR images by an in-house Bayesian maximal likelihood procedure described previously (Decarli, Maillard, & Fletcher, 2013). WMH volumes were log transformed to normalize their distribution. Brain total gray volume measurements were taken using an in-house tissue segmentation algorithm to designate gray, white and CSF tissues in native space structural brain MRI (Fletcher, Singh, Harvey, Carmichael, & DeCarli, 2012).

Neuropsychiatric symptoms.—Depression and apathy were assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q; Kaufer et al., 2000) administered via structured clinical interview to the participant's informant, with responses ranging from 0 (no reported symptoms) to 3 (severe symptoms). The NPI-Q has been used to quantify symptoms in normal aging, MCI, and dementia samples (Geda et al., 2008; Hwang, Masterman, Ortiz, Fairbanks, & Cummings, 2004; Okura et al., 2010; Rog et al., 2014). Depression and apathy were included in the current study as single items given previous findings showing that these two neuropsychiatric symptoms in particular can negatively impact functional abilities independent of cognition (Hinton et al., 2008; Okura et al., 2010; Rog et al., 2014).

Physical Function.—Physical function was assessed using the Short Physical Performance Battery (Guralnik et al., 1994), which is a performance-based test of lower-extremity function in older adults. It has been shown to predict functional abilities

(Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995) and has high test-retest reliability (Ostir, Volpato, Fried, Chaves, & Guralnik, 2002). Scores range from 0 to 12, with higher scores indicating better physical function.

Compensation Abilities.—The Everyday Compensation (EComp) informant-reported 70-item questionnaire assesses compensation strategies used to complete IADL tasks across six domains of everyday life, including managing appointments and transportation (Farias et al., 2018). Items are rated for frequency ranging from 0 (never) to 4 (always) and averaged across all items completed for a total score (possible range = 0 to 4). Internal consistency across all EComp items is high (Cronbach's alpha = .94) and scores on this measure have been shown to predict IADL performance independent of cognition (Farias et al., 2018).

Analytic Strategy

Model for Estimating Functional Reserve—Statistical analyses were conducted using Mplus Version 8. Missing data were handled using full information maximum likelihood using all available data. The MLR (maximum likelihood estimation with robust standard errors) estimator in MPlus was employed, as this is preferred when data are not normally distributed (Yuan & Bentler, 2000). Time was parameterized as years from the baseline visit. Syntax is provided in Supplemental Material. As depicted in Figure 1, IADL scores were regressed onto independent cognitive (verbal episodic memory, semantic memory, spatial function, and executive function), brain (total gray matter and hippocampal volumes regression-adjusted for total intracranial volume, and white matter hyperintensity volume), and demographics (sex/gender with female as the reference group, ethnicity with non-Hispanic as the reference group, race with white as the reference group, and education in years) predictors. Here we extend methods previously utlilized by Reed et al. (2010) to functional reserve, which was modeled as a latent variable representing the residual variance in IADL scores not explained by and orthogonal to these predictors (Figure 1). Model fit was determined using commonly used criteria: root mean square error of approximation (RMSEA) < 0.06, standardized root mean square residual (SRMR) < .08, weighted root mean square residual (WRMR) < 1.0, comparative fit index (CFI) > 0.95, and Tucker-Lewis index (TLI)> 0.95 (Hu & Bentler, 1999).

Functional Reserve Associations with Clinical Outcomes—Next, we tested independent associations between the primary IADL components (i.e., the functional reserve residual, cognitive performance, brain characteristics, and demographics) and the clinical outcome variables, as hypothesized. Latent growth curve analysis was used to model the association between baseline functional reserve and the CDR-SB intercept (estimated initial dementia severity) and linear slope (estimated rate of change in dementia severity) over the seven-year follow-up period (Figure 2). Because of floor effects in the CDR-SB scores in cognitively healthy individuals, a Tobit regression model was used to account for the fact that CDR-SB is below-censored at 0.

In a separate analysis, the baseline functional reserve residual was regressed on concurrent clinical diagnosis (i.e., dummy-coded variables representing MCI and dementia), with cognitively normal as the reference group. Finally, logistic regression was used to determine

whether baseline functional reserve could predict subsequent conversion to dementia in a subset of participants without a baseline dementia diagnosis.

Functional Reserve as a Moderator of Cognition-Outcomes Associations—For the second aim, an interaction term (baseline functional reserve x baseline cognition) was added to the analytic models. Interaction effects with executive functioning and verbal episodic memory were explored (Figure 2). Two separate models, one for each of these two cognitive domains, tested whether baseline functional reserve modified the association of baseline cognitive performance with initial dementia severity (CDR-SB intercept) and rate of progression (CDR-SB slope) over the follow-up period. Executive function and verbal episodic memory were selected as the cognitive variables of interest given their well-documented associations with clinical outcomes in aging and dementia (Bell-McGinty et al., 2002; Farias et al., 2004; Grigsby et al., 1998).

Predictors of Functional Reserve—For Aim 3, we first tested the independent effects of predictors (i.e., physical function, apathy, depression, and compensatory abilities) on functional reserve in four univariable models (including covariates; Figure 2). Next, predictors demonstrating significant univariable associations were entered into a multivariable model to quantify their joint ability to predict functional reserve.

Results

Data from a total of 1,084 participants contributed to the analysis (163 had dementia, 333 had MCI, 523 had normal cognition, and 65 participants with missing data for diagnosis). Not all participants provided data on each instrument. As can be seen in Table 1, the dementia group was the oldest and the cognitively normal group had a higher proportion of women. As expected, cognitive, functional, and brain variables generally showed the expected gradient (greatest level of impairment and brain disease in the dementia group, followed by the MCI and then the cognitively normal groups). For compensation use, the cognitively normal and MCI groups were both very low in their use of compensatory strategies, which is consistent with our previous findings (Farias et al., 2020, 2018).

Before testing our hypotheses, we first operationally defined functional reserve using a latent variable model. This model decomposed the variance in IADL scores into four orthogonal components: (1) variance explained by three brain variables (intracranial volume-adjusted total gray matter and hippocampus volumes plus white matter hyperintensity volume), (2) four cognitive variables (measures of verbal episodic memory, executive functioning, semantic memory, and spatial skills), (3) four demographic variables (years of education, race, ethnicity, and sex/gender) and (4) a latent variable to capture the residual variance not explained by the first three classes of predictors (Figure 1).

The three observed brain variables and the four observed cognitive test scores were modeled as single indicator latent variables, which can help prevent measurement error from being included in the residual variable conceptualized as functional reserve. For the observed brain variables, measurement error was constrained to .10, which corresponds to a reliability coefficient of .90 for an indicator with a variance of 1.00; this procedure is consistent with

Reed et al. (2010). For the cognitive variables, measurement error estimates of .15 were chosen to correspond to conservatively estimated reliability coefficients of .85, as reported in previous research (Mungas et al., 2004). The measurement error of the standardized IADL score was also fixed to 1 minus its observed internal consistency reliability (i.e., 1.00 - .92 = .08).

The functional reserve decomposition model fit the data very well: RMSEA = 0.023, 90% CI [0.000, 0.041], CFI = 0.998, TLI = 0.990, SRMR = 0.022 (Figure 1), supporting its use in further validation models, whose results are summarized below.

Functional Reserve and Clinical Outcomes

The structural equation model regressing the baseline functional reserve residual on concurrent clinical diagnosis fit very well: RMSEA = 0.023, 90% CI [0.000, 0.040], CFI = 0.998, TLI = 0.990, SRMR = 0.020. A baseline diagnosis of dementia was associated with lower baseline functional reserve ($b = -1.695$, SE = 0.328, $p < .001$) compared to cognitively normal older adults. Although baseline functional reserve was not significantly lower in participants with a baseline diagnosis of MCI compared to those with normal cognition ($b = -0.189$, SE = 0.174, $p = .278$), the pattern of association was in the expected direction (slightly higher in those who were cognitively normal).

Latent growth curve modeling was used to estimate the intercept and slope of dementia severity, as measured by CDR-SB scores, and to determine the impact of functional reserve on these outcomes after accounting for the effects of brain, cognitive, and demographic covariates. Higher functional reserve at baseline was associated with lower initial dementia severity ($b = 1.243$, SE = 0.141, $p < .001$) and predicted slower clinical progression over the seven-year follow-up period ($b = -0.163$, SE = 0.065, $p = 0.012$) (Figure 3). Results for the covariates are shown in Table 2.

In a logistic regression model, higher baseline functional reserve was associated with reduced odds of conversion to dementia over the follow-up period; however, this effect did not reach statistical significance (OR = 0.765, 95% CI [0.562, 1.042]), in part because the parameters were not estimated precisely.

Functional Reserve Modifies Cognition-Outcome Associations

Baseline functional reserve interacted with baseline executive functioning to influence initial dementia severity ($b = 0.483$, SE = 0.159, $p = .002$). Specifically, the negative association between low executive function and concurrent dementia severity was mitigated by high baseline functional reserve (Figure 4). In contrast, baseline functional reserve did not interact with baseline executive functioning to influence rate of clinical progression ($b = 0.060$, SE = 0.112, $p = .591$). However, there were main effects of baseline functional reserve on initial disease severity ($b = -1.088$, SE = 0.135, $p < .001$) and rate of clinical progression ($b = -0.154$, SE = 0.063, $p = .014$). A similar pattern of associations was found for the interaction between baseline functional reserve and verbal episodic memory on initial dementia severity and subsequent clinical progression (Table 3), but without a significant baseline functional reserve by baseline episodic memory interaction effect on the CDR-SB intercept. In a logistic regression model, baseline functional reserve did not significantly

interact with baseline executive function or baseline verbal episodic memory to influence the odds of conversion to dementia (functional reserve by executive function: OR=1.210, 95% CI [0.762, 1.922]; functional reserve by verbal episodic memory: OR=1.239, 95% CI [0.197, 7.798]), in large part due to imprecision (i.e., large standard errors and associated confidence intervals) in estimating these effects.

Predictors of Functional Reserve

Separate univariable models (with covariates) showed that better physical function (β = 0.303, SE = 0.125, $p = .015$), less severe informant-rated apathy (β = −0.241, SE = 0.069, $p < .001$), and less severe informant-rated depression (β = −0.160, SE = 0.066, $p = .016$), were associated with higher functional reserve concurrently, whereas compensation ability was not associated (β = 0.169, SE = 0.465, $p = .717$). In a multivariable model that included these three significant predictors of functional reserve, patterns of association persisted for physical function (β = 0.325, SE = 0.116, $p = .005$) and apathy (β = −0.236, SE = 0.073, $p = .001$) but not depression symptoms (β = −0.044, SE = 0.075, $p = .556$).

Secondary Analyses

As a measure of dementia severity, the CDR contains some items that more strongly emphasize cognition (memory, judgment and problem solving, orientation) and others that more strongly emphasize functioning (community activities, personal care, home and hobbies; Cedarbaum et al. 2013; Tractenberg et al., 2005). Results from secondary analyses revealed similar patterns of association between functional reserve and the intercepts and slopes for both CDR components (data not shown).

Discussion

Extending previous work on the residual-based approach to estimating cognitive reserve (Reed et al., 2010; McKenzie et al., 2020; Zahodne et al., 2013), the current study defined the construct of functional reserve in a similar way: the discrepancy between observed and expected functional performance based on three brain volume measures (derived from structural MRI), cognitive function, and relevant demographics. Functional reserve quantified by this IADL residual variable predicted important clinical outcomes related to cognitive aging and dementia. Specifically, greater functional reserve was concurrently associated with lower dementia severity and, importantly, it predicted subsequently slower clinical progression. A 1-SD increase in functional reserve was also associated with approximately a 25% reduction in odds of converting from non-demented to clinically-diagnosed dementia during the seven-year follow-up period. Although this finding suggests that functional reserve may be associated with a meaningful reduction in future dementia risk, the effect was not estimated precisely enough to be considered statistically significant due to its large standard errors. The functional reserve residual variable also mitigated the negative effects of low baseline executive function on initial dementia severity, although it did not mitigate the impact of baseline cognitive (i.e., memory or executive) function on subsequent rate of clinical progression. Nonetheless, even when cognitive ability was accounted for in a model predicting clinical progression, functional reserve had an independent main effect on rate of clinical progression.

The term ‘functional reserve’ has been used to describe individual differences in reserve capacities of other aspects of everyday functioning in the context of aging. For instance, in studies of physical fitness, functional reserve has been separately operationalized to capture interindividual differences in one’s capacity to mitigate cardiovascular health and musculoskeletal system deterioration (Goldspink, 2005) and to maintain physical fitness (Gonzalez, Cofré, & Cabello, 2016). Functional reserve has also been operationalized as a variable to determine person-specific oxygen uptake values (Arnett et al., 2008). The current study extends prior work on functional reserve to IADLs in older adulthood, highlighting the application and potential utility of functional reserve in cognitive aging and dementia research.

How does functional reserve differ from cognitive reserve? Cognitive reserve would, in theory, be captured by the neuropsychological test scores used to predict IADL functioning. In fact, Reed et al. (2010) defined cognitive reserve by decomposing the variance in the same episodic memory test that was used to create the residual in the current study (SENAS Verbal Episodic Memory). Thus, by ensuring that our functional reserve residual was modeled as orthogonal to SENAS Verbal Episodic Memory, we could ensure that it was – at least from a measurement perspective – independent from cognitive reserve. In other words, functional reserve here is defined as the variance in IADL performance not explained by brain, cognition/cognitive reserve, and demographics. Measurement issues aside, it is possible that cognitive reserve and functional reserve may share some of the same mechanisms and associations with relevant outcomes. This study thus sets the stage for future research that can test these and other hypotheses.

This study also lays important groundwork in terms of identifying the importance of functional reserve on clinical outcomes. However, another valuable attribute of the residual approach may lie in its ability to identify factors that contribute to higher or lower functional reserve. In turn, these factors may ultimately inform the development of interventions to improve cognitive health and functional outcomes in older adulthood. To this end, in the current study we evaluated different factors that may account for higher or lower functional reserve. Specifically, three types of predictors were evaluated: neuropsychiatric symptoms, physical functioning, and behavioral compensation tendencies. In clinical contexts, it is often observed that some older adults present as more functionally impaired than expected given their neuropsychological performance (i.e., major loss of independence in various activities of daily function in the setting of relatively mild cognitive deficits). In this case, the question about the impact of depression or other neuropsychiatric symptoms is often considered. In fact, a large number of studies have found that depressive symptoms are often negatively associated with IADLs, independent of cognition (Baune et al., 2010; Hybels, Pieper, & Blazer, 2009; Lenze et al., 2005). Additionally, apathy is a multidimensional construct comprising cognitive, affective, and behavioral components (Marin, Biedrzycki, & Firinciogullari, 1991; Robert et al., 2018) and has well-established associations with late-life functional independence and neurocognitive health (for a review, see Lanctôt et al., 2017). Furthermore, in a sample of older adults with normal cognition, cognitive impairment, and dementia, depression and apathy were observed to be two of the most prevalent neuropsychiatric symptoms (Okura et al., 2010). In the current study, while we also found that both depression and apathy were associated with lower functional reserve in univariable

models, in a multivariable model, only apathy had an independent effect on functional reserve. Previous studies examining the impact of both depression and apathy on functional outcomes have been mixed, with some studies finding an independent association for both (Rog et al., 2014) and others suggesting a more important role of apathy (Ruthirakuhan, Herrmann, Vieira, Gallagher, & Lanctôt, 2019; Vicini Chilovi et al., 2009; Zahodne & Tremont, 2013). Differences in results may be attributable to different methodologies used to measure psychiatric symptoms and/or functional outcomes.

Excessive IADL difficulties compared to degree of cognitive impairment may also occur in the context of physical limitations. Physical limitations such as reduced gait, balance, or strength have been previously associated with poor functional outcomes (Kojima, 2017; Paterson & Warburton, 2010; Vaughan et al., 2016). Most often, these limitations are more strongly associated with basic activities of daily living, such as dressing, grooming and other activities that have a major physical component but relatively less of a cognitive component (Beswick et al., 2008; Vaughan et al., 2016). However, instrumental activities such as shopping, driving, completing household chores, and cooking can be impacted by physical limitations. Consistent with this idea, we found that functional reserve was predicted by performance on the Short Physical Performance Battery, which is a combined score based on gait, balance, and lower body strength.

In contrast to low functional reserve or excessive disability, patients can also present as less functionally impaired than expected given their degree of deficits on neuropsychological testing and degree of brain atrophy. In this case, one potential explanation may be the use of behavioral strategies in daily life that assist in compensating for cognitive loss. Such compensatory strategies may include increasing reliance on the use of lists, calendars, and other internal or external aids. Previous studies have shown that more frequent use of compensatory strategies was associated with both a higher level of concurrent functional abilities (Farias et al., 2018) and slower subsequent decline in functional abilities over time (Farias et al., 2020); furthermore, these relationships were independent of cognitive function. Similarly, in other studies using behaviorally observed measures of compensation, those who use more compensatory strategies seemed to function better (Weakley, Weakley, & Schmitter-Edgecombe, 2019). Based on these previous findings, we hypothesized that functional reserve would be explained, in part, by degree of compensation. However, we did not find evidence to support this hypothesis in the current study. One possible reason for this finding is that the variance in IADL function that could have been attributable to compensatory strategies may at least be partially accounted for by variance ultimately attributable to brain or cognitive variables (which was regressed out of the functional residual variable but not accounted for in our previous work on compensation).

Examining other predictors of functional reserve will be an important future direction. There are likely a variety of intrapersonal characteristics, behavioral and lifestyle patterns, and personality factors that contribute to greater or lower functional reserve. For example, a number of previous studies have demonstrated that personality traits such as conscientiousness are associated with a host of health outcomes including IADL disability (Bogg & Roberts, 2013; Chapman, Roberts, & Duberstein, 2011; Kaup, Harmell, & Yaffe, 2019). A sense of mastery and self efficacy may also be important predictors of functional

status (Chang, Latham, Ni, & Jette, 2015) not attributable to cognitive and disease/brain variables.

Another potential advantage of our approach to quantifying functional reserve is that it can be measured longitudinally (e.g., change in functional reserve after residualizing out change in cognition and brain variables) to examine how it fluctuates in relation to various factors. This parallels an approach already applied to change in cognitive reserve (Bettcher et al., 2019). Measuring functional reserve longitudinally would allow characterization of intra- and inter-individual differences in stability versus decline in functional reserve. Specifically, a longitudinal investigation may show that reductions in functional reserve may not necessarily occur in conjunction with greater brain pathology and/or decreasing cognitive performance. In some cases, worsening pathology and cognitive performance may minimally affect IADL performance, resulting in minor change in the reserve variable. Identifying factors that are associated with maintaining a stable level of functional reserve over time will likely be even more important in informing interventions than factors that influence a static measure of functional reserve.

As with previous studies using the residual-reserve approach (McKenzie et al., 2020; Reed et al., 2010; Zahodne et al., 2013), the model is dependent on accurate and comprehensive assessment of cognition and brain variables. Any improvements in either or both of these variables would be expected to potentially decrease the amount of residual variance in IADL function that is left unexplained. Total gray matter, hippocampal, and white matter hyperintensity volumes were selected as general markers of brain integrity, consistent with a well-established body of research documenting the sensitivity of these markers to age-related neurodegenerative disease and their associations with cognitive trajectories of aging. However, it is possible that more precise measurement of brain structures – for example, brain “signature regions” associated with cognition (Bakkour, Morris, & Dickerson, 2009; Dickerson et al., 2009) – and brain and lifestyle factors, for example, as outlined in scaffolding theories (Park & Reuter-Lorenz, 2008; Reuter-Lorenz & Park, 2014), known to impact cognition and function – could change the residual measure of functional reserve we propose here. Indeed, very recent work shows the ability of the signature region approach to produce a maximized accounting of brain contributions to cognition (Fletcher et al., 2020), thereby reducing the magnitude of unmeasured brain factors in the residual measure of reserve. This same approach could be applied for developing more precise brain signatures of functional outcomes. Further, incorporation of functional brain imaging measures, which have been associated with functional capacities (Halawa et al., 2019; Nadkarni et al., 2012), may impact the residualized functional reserve variable. Future work should evaluate other neuroimaging methodologies such as tau or amyloid PET (e.g., Marshall et al., 2019).

Although participants’ cognitive abilities were measured across multiple domains by an instrument with extensive previous validation, we did not measure some aspects of cognition including processing speed, prospective memory, and executive functioning subdomains like reasoning and problem solving, which could be important to everday functions (Beaver & Schmitter-Edgecombe, 2017; Brown et al., 2013). In particular, processing speed has been shown to mediate the cross-sectional association between depression and everyday function (Brown et al., 2013). Future work could incorporate tests of cognitive domains not included

in the current study and examine how they impact the measurement of functional reserve. Furthermore, as with most longitudinal studies, not all participants had complete data. However, missing data in the current study were managed with full information maximum likelihood, which makes use of all available data.

Finally, the IADL measure used in the current study may be less sensitive to the early manifestations of neurodegenerative changes than some other functional measures that have been specifically developed for early disease (Farias et al., 2008). Functional abilities in the current study were reported by an informant. Performance-based measures provide another method of measurement that has both strengths (less subject to recall bias) and limitations (functional tasks are often not performend in real-world settings) (Schmitter-Edgecombe, Parsey, & Cook, 2011). The current study also does not consider the role of basic activities of daily living (ADL) as measures of ADLs have well-documented ceiling effects among older adults with no or mild cognitive impairment and are weakly associated with cognition (Cahn-Weiner et al., 2007; Hopman-Rock, vam Hirtum, de Vreede, & Freiberger, 2019; West, McCue, & Golden, 2012). Future investigations are needed to determine whether the current study's findings can be replicated using other functional measures.

In conclusion, the functional reserve construct quantified as the residual variance in IADL performance after accounting for brain, cognitive, and sociodemographic variables predicted the clinical progression of dementia and attenuated the impact of poor cognition on initial dementia severity. Physical function and apathy were the strongest predictors of functional reserve. Thus, the quantified functional reserve variable has potential to facilitate research regarding the pathways and predictors of functional reserve. Future investigations using this method are needed to examine how this residualized variable relates to worsening neuropathology and cognition over time in older adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, … Phelps CH (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia : The Journal of the Alzheimer's Association, 7(3), 270–279. 10.1016/j.jalz.2011.03.008

Aljabar P, Heckemann RA, Hammers A, Hajnal JV, & Rueckert D (2009). Multi-atlas based segmentation of brain images: Atlas selection and its effect on accuracy. NeuroImage, 46(3), 726–738. 10.1016/J.NEUROIMAGE.2009.02.018 [PubMed: 19245840]

Arnett SW, Laity JH, Agrawal SK, & Cress ME (2008). Aerobic reserve and physical functional performance in older adults. Age and Ageing, 37(4), 384–389. 10.1093/ageing/afn022 [PubMed: 18287178]

Bakkour A, Morris JC, & Dickerson BC (2009). The cortical signature of prodromal AD: Regional thinning predicts mild AD dementia. Neurology, 72(12), 1048–1055. 10.1212/01.wnl.0000340981.97664.2f [PubMed: 19109536]

Baune BT, Miller R, McAfoose J, Johnson M, Quirk F, & Mitchell D (2010). The role of cognitive impairment in general functioning in major depression. Psychiatry Research, 176(2–3), 183–189. 10.1016/j.psychres.2008.12.001 [PubMed: 20138370]

Bell-McGinty S, Podell K, Franzen M, Baird AD, & Williams MJ (2002). Standard measures of executive function in predicting instrumental activities of daily living in older adults. International Journal of Geriatric Psychiatry, 17(9), 828–834. 10.1002/gps.646 [PubMed: 12221656]

Berezuk C, Zakzanis KK, Ramirez J, Ruocco AC, Edwards JD, Callahan BL, & Black SE (2017). Functional Reserve: Experience Participating in Instrumental Activities of Daily Living is Associated with Gender and Functional Independence in Mild Cognitive Impairment. Journal of Alzheimer's Disease, 58, 425–434. 10.3233/JAD-161227

Beswick AD, Rees K, Dieppe P, Ayis S, Gooberman-Hill R, Horwood J, & Ebrahim S (2008). Complex interventions to improve physical function and maintain independent living in elderly people: a systematic review and meta-analysis. The Lancet, 371(9614), 725–735. 10.1016/S0140-6736(08)60342-6

Bettcher BM, Gross AL, Gavett BE, Widaman KF, Fletcher E, Dowling NM, … Mungas D (2019). Dynamic change of cognitive reserve: associations with changes in brain, cognition, and diagnosis. Neurobiology of Aging, 83, 95–104. 10.1016/j.neurobiolaging.2019.08.016 [PubMed: 31585371]

Bogg T, & Roberts BW (2013). The Case for Conscientiousness: Evidence and Implications for a Personality Trait Marker of Health and Longevity. Annals of Behavioral Medicine, 45(3), 278–288. 10.1007/s12160-012-9454-6 [PubMed: 23225322]

Brown PJ, Liu X, Sneed JR, Pimontel MA, Devanand DP, & Roose SP (2013). Speed of processing and depression affect function in older adults with mild cognitive impairment. The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry, 21(7), 675–684. 10.1016/j.jagp.2013.01.005 [PubMed: 23567401]

Callahan CM, Tu W, Unroe KT, LaMantia MA, Stump TE, & Clark DO (2015). Transitions in Care in a Nationally Representative Sample of Older Americans with Dementia. Journal of the American Geriatrics Society, 63(8), 1495–1502. 10.1111/jgs.13540 [PubMed: 26200764]

Cedarbaum JM, Jaros M, Hernandez C, Coley N, Andrieu S, Grundman M, … Alzheimer's Disease Neuroimaging Initiative. (2013). Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. Alzheimer's & Dementia : The Journal of the Alzheimer's Association, 9(1 Suppl), S45–55. 10.1016/j.jalz.2011.11.002

Chang F-H, Latham NK, Ni P, & Jette AM (2015). Does self-efficacy mediate functional change in older adults participating in an exercise program after hip fracture? A randomized controlled trial. Archives of Physical Medicine and Rehabilitation, 96(6), 1014–1020.e1. 10.1016/j.apmr.2015.02.009 [PubMed: 25701101]

Chapman BP, Roberts B, & Duberstein P (2011). Personality and longevity: knowns, unknowns, and implications for public health and personalized medicine. Journal of Aging Research, 2011, 759170. 10.4061/2011/759170 [PubMed: 21766032]

Chen Y, Denny KG, Harvey D, Farias ST, Mungas D, DeCarli C, & Beckett L (2017). Progression from normal cognition to mild cognitive impairment in a diverse clinic-based and community-based elderly cohort. Alzheimer's and Dementia 10.1016/j.jalz.2016.07.151

Daly E, Zaitchik D, Copeland M, Schmahmann J, Gunther J, & Albert M (2000). Predicting Conversion to Alzheimer Disease Using Standardized Clinical Information. Archives of Neurology, 57(5), 675. 10.1001/archneur.57.5.675 [PubMed: 10815133]

Decarli C, Maillard P, & Fletcher E (2013). Four Tissue Segmentation in ADNI II Retrieved March 29, 2020, from http://adni.loni.usc.edu/methods/mri-tool/

DeCarli C, Reed BR, Jagust W, Martinez O, Ortega M, & Mungas D (2008). Brain behavior relationships among African Americans, whites, and Hispanics. Alzheimer Disease and Associated Disorders 10.1097/WAD.0b013e318185e7fe

Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, … Buckner RL (2009). The Cortical Signature of Alzheimer's Disease: Regionally Specific Cortical Thinning Relates

to Symptom Severity in Very Mild to Mild AD Dementia and is Detectable in Asymptomatic Amyloid-Positive Individuals. Cerebral Cortex, 19(3), 497–510. 10.1093/cercor/bhn113 [PubMed: 18632739]

Farias ST, Gravano J, Weakley A, Schmitter-Edgecombe M, Harvey D, Mungas D, … Giovannetti T (2019). The Everyday Compensation (EComp) Questionnaire: Construct Validity and Associations with Diagnosis and Longitudinal Change in Cognition and Everyday Function in Older Adults. Journal of the International Neuropsychological Society, 1–11. 10.1017/s135561771900119x

Farias ST, Gravano J, Weakley A, Schmitter-Edgecombe M, Harvey D, Mungas D, … Giovannetti T (2020). The Everyday Compensation (EComp) Questionnaire: Construct Validity and Associations with Diagnosis and Longitudinal Change in Cognition and Everyday Function in Older Adults. Journal of the International Neuropsychological Society, 26(3), 303–313. 10.1017/S135561771900119X [PubMed: 31668159]

Farias ST, Mungas D, Reed BR, Cahn-Weiner D, Jagust W, Baynes K, & Decarli C (2008). The measurement of everyday cognition (ECog): Scale development and psychometric properties. Neuropsychology, 22(4), 531–544. 10.1037/0894-4105.22.4.531 [PubMed: 18590364]

Farias ST, Mungas D, Reed BR, Haan MN, & Jagust WJ (2004). Everyday functioning in relation to cognitive functioning and neuroimaging in community-dwelling Hispanic and Non-Hispanic older adults. Journal of the International Neuropsychological Society, 10(03), 342–354. 10.1017/S1355617704103020 [PubMed: 15147592]

Farias ST, Park LQ, Harvey DJ, Simon C, Reed BR, Carmichael O, & Mungas D (2013). Everyday Cognition in Older Adults: Associations with Neuropsychological Performance and Structural Brain Imaging. Journal of the International Neuropsychological Society, 19(4), 430–441. 10.1017/S1355617712001609 [PubMed: 23369894]

Farias ST, Schmitter-Edgecombe M, Weakley A, Harvey D, Denny KG, Barba C, … Willis S (2018). Compensation Strategies in Older Adults: Association With Cognition and Everyday Function. American Journal of Alzheimer's Disease and Other Dementias, 33(3), 184–191. 10.1177/1533317517753361

Fletcher E, Gavett BE, Crane PK, Soldan A, Hohman T, Farias ST, … Mungas D (2020). A robust brain signature region approach for episodic memory performance in older adults under review

Fletcher E, Gavett B, Harvey D, Farias ST, Olichney J, Beckett L, … Mungas D (2018). Brain volume change and cognitive trajectories in aging. Neuropsychology 10.1037/neu0000447

Fletcher E, Singh B, Harvey D, Carmichael O, & DeCarli C (2012). Adaptive image segmentation for robust measurement of longitudinal brain tissue change In 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society (Vol. 2012, pp. 5319–5322). IEEE. 10.1109/EMBC.2012.6347195

Geda YE, Roberts RO, Knopman DS, Petersen RC, Christianson TJH, Pankratz VS, … Rocca WA (2008). Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. Archives of General Psychiatry, 65(10), 1193–1198. 10.1001/archpsyc.65.10.1193 [PubMed: 18838636]

Goldspink DF (2005). Ageing and activity: their effects on the functional reserve capacities of the heart and vascular smooth and skeletal muscles. Ergonomics, 48(11–14), 1334–1351. 10.1080/00140130500101247 [PubMed: 16338704]

González PM, Cofré RM, & Cabello ME (2016). Functional reserve in functionally independent elderly persons: a calculation of gait speed and physiological cost. Revista Brasileira de Geriatria e Gerontologia, 19(4), 577–589. 10.1590/1809-98232016019.150136

Grigsby J, Kaye K, Baxter J, Shetterly SM, & Hamman RF (1998). Executive Cognitive Abilities and Functional Status Among Community-Dwelling Older Persons in the San Luis Valley Health and Aging Study. Journal of the American Geriatrics Society, 46(5), 590–596. 10.1111/j.1532-5415.1998.tb01075.x [PubMed: 9588372]

Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, & Wallace RB (1995). Lower-Extremity Function in Persons over the Age of 70 Years as a Predictor of Subsequent Disability. New England Journal of Medicine, 332(9), 556–562. 10.1056/NEJM199503023320902

Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, … Wallace RB (1994). A short physical performance battery assessing lower extremity function: association

with self-reported disability and prediction of mortality and nursing home admission. Journal of Gerontology, 49(2), M85–94. 10.1093/geronj/49.2.m85 [PubMed: 8126356]

Halawa OA, Gatchel JR, Amariglio RE, Rentz DM, Sperling RA, Johnson KA, … Alzheimer's Disease Neuroimaging Initiative, A. D. N. (2019). Inferior and medial temporal tau and cortical amyloid are associated with daily functional impairment in Alzheimer's disease. Alzheimer's Research & Therapy, 11(1), 14. 10.1186/s13195-019-0471-6

Hinton L, Carter K, Reed BR, Beckett L, Lara E, DeCarli C, & Mungas D (2010). Recruitment of a Community-based Cohort for Research on Diversity and Risk of Dementia. Alzheimer Disease & Associated Disorders, 24(3), 1. 10.1097/WAD.0b013e3181c1ee01 [PubMed: 19571730]

Hinton L, Tomaszewski Farias S, & Wegelin J (2008). Neuropsychiatric symptoms are associated with disability in cognitively impaired Latino elderly with and without dementia: results from the Sacramento Area Latino study on Aging. International Journal of Geriatric Psychiatry, 23(1), 102–108. 10.1002/gps.1952 [PubMed: 18058994]

Hopman-Rock M, van Hirtum H, de Vreede P, & Freiberger E (2019). Activities of daily living in older community-dwelling persons: a systematic review of psychometric properties of instruments. Aging Clinical and Experimental Research, 31(7), 917–925. 10.1007/s40520-018-1034-6 [PubMed: 30191453]

Hu LT, & Bentler PM (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Structural Equation Modeling 10.1080/10705519909540118

Hurd MD, Martorell P, Delavande A, Mullen KJ, & Langa KM (2013). Monetary Costs of Dementia in the United States. New England Journal of Medicine, 368(14), 1326–1334. 10.1056/NEJMsa1204629

Hwang TJ, Masterman DL, Ortiz F, Fairbanks LA, & Cummings JL (2004). Mild Cognitive Impairment is Associated With Characteristic Neuropsychiatric Symptoms. Alzheimer Disease & Associated Disorders, 18(1), 17–21. 10.1097/00002093-200401000-00004 [PubMed: 15195459]

Hybels CF, Pieper CF, & Blazer DG (2009). The complex relationship between depressive symptoms and functional limitations in community-dwelling older adults: the impact of subthreshold depression. Psychological Medicine, 39(10), 1677. 10.1017/S0033291709005650 [PubMed: 19356260]

Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, … DeKosky ST (2000). Validation of the NPI-Q, a Brief Clinical Form of the Neuropsychiatric Inventory. The Journal of Neuropsychiatry and Clinical Neurosciences, 12(2), 233–239. 10.1176/jnp.12.2.233 [PubMed: 11001602]

Kaup AR, Harmell AL, & Yaffe K (2019). Conscientiousness Is Associated with Lower Risk of Dementia among Black and White Older Adults. Neuroepidemiology, 52(1–2), 86–92. 10.1159/000492821 [PubMed: 30602170]

Kawaharada R, Sugimoto T, Matsuda N, Tsuboi Y, Sakurai T, & Ono R (2019). Impact of loss of independence in basic activities of daily living on caregiver burden in patients with Alzheimer's disease: A retrospective cohort study. Geriatrics & Gerontology International, 19(12), 1243–1247. 10.1111/ggi.13803 [PubMed: 31638736]

Kojima G (2017). Frailty as a predictor of disabilities among community-dwelling older people: a systematic review and meta-analysis. Disability and Rehabilitation, 39(19), 1897–1908. 10.1080/09638288.2016.1212282 [PubMed: 27558741]

Lanctôt KL, Agüera-Ortiz L, Brodaty H, Francis PT, Geda YE, Ismail Z, … Abraham EH (2017). Apathy associated with neurocognitive disorders: Recent progress and future directions. Alzheimer's & Dementia, 13(1), 84–100. 10.1016/J.JALZ.2016.05.008

Lawton MP, & Brody EM (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. The Gerontologist, 9(3), 179–186. [PubMed: 5349366]

Lenze EJ, Schulz R, Martire LM, Zdaniuk B, Glass T, Kop WJ, … Reynolds CF (2005). The Course of Functional Decline in Older People with Persistently Elevated Depressive Symptoms: Longitudinal Findings from the Cardiovascular Health Study. Journal of the American Geriatrics Society, 53(4), 569–575. 10.1111/j.1532-5415.2005.53202.x [PubMed: 15817000]

Marin RS, Biedrzycki RC, & Firinciogullari S (1991). Reliability and validity of the apathy evaluation scale. Psychiatry Research, 38(2), 143–162. 10.1016/0165-1781(91)90040-V [PubMed: 1754629]

Marshall GA, Gatchel JR, Donovan NJ, Muniz MC, Schultz AP, Becker JA, … Johnson KA (2019). Regional Tau Correlates of Instrumental Activities of Daily Living and Apathy in Mild Cognitive Impairment and Alzheimer's Disease Dementia. Journal of Alzheimer's Disease : JAD, 67(2), 757–768. 10.3233/JAD-170578 [PubMed: 30689584]

McDonald RP (1999). Test theory: A unified treatment (1st ed.). Psychology Press. 10.4324/9781410601087

McKenzie C, Bucks RS, Weinborn M, Bourgeat P, Salvado O, & Gavett BE (2020). Cognitive reserve predicts future executive function decline in older adults with Alzheimer's disease pathology but not age-associated pathology. Neurobiology of Aging 10.1016/J.NEUROBIOLAGING.2019.12.022

Morris JC (1993). The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology, 43, 2412–2414.

Morris JC, Weintraub S, Chui HC, Cummings J, DeCarli C, Ferris S, … Kukull WA (2006). The Uniform Data Set (UDS): Clinical and Cognitive Variables and Descriptive Data From Alzheimer Disease Centers. Alzheimer Disease & Associated Disorders, 20(4), 210–216. 10.1097/01.wad.0000213865.09806.92 [PubMed: 17132964]

Mungas D, Reed BR, Crane PK, Haan MN, & González H (2004). Spanish and English Neuropsychological Assessment Scales (SENAS): Further Development and Psychometric Characteristics. Psychological Assessment, 16(4), 347–359. 10.1037/1040-3590.16.4.347 [PubMed: 15584794]

Mungas D, Reed BR, Marshall SC, & González HM (2000). Development of psychometrically matched English and Spanish language neuropsychological tests for older persons. Neuropsychology, 14(2), 209–223. 10.1037/0894-4105.14.2.209 [PubMed: 10791861]

Nadkarni NK, Levy-Cooperman N, & Black SE (2012). Functional correlates of instrumental activities of daily living in mild Alzheimer's disease. Neurobiology of Aging, 33(1), 53–60. 10.1016/j.neurobiolaging.2010.02.001 [PubMed: 20359778]

Okura T, Plassman BL, Steffens DC, Llewellyn DJ, Potter GG, & Langa KM (2010). Prevalence of neuropsychiatric symptoms and their association with functional limitations in older adults in the United States: the aging, demographics, and memory study. Journal of the American Geriatrics Society, 58(2), 330–337. 10.1111/j.1532-5415.2009.02680.x [PubMed: 20374406]

Ostir GV, Volpato S, Fried LP, Chaves P, & Guralnik JM (2002). Reliability and sensitivity to change assessed for a summary measure of lower body function. Journal of Clinical Epidemiology, 55(9), 916–921. 10.1016/S0895-4356(02)00436-5 [PubMed: 12393080]

Overdorp EJ, Kessels RPC, Claassen JA, & Oosterman JM (2016). The Combined Effect of Neuropsychological and Neuropathological Deficits on Instrumental Activities of Daily Living in Older Adults: a Systematic Review. Neuropsychology Review, 26(1), 92–106. 10.1007/s11065-015-9312-y [PubMed: 26732392]

Park DC, & Reuter-Lorenz P (2008). The Adaptive Brain: Aging and Neurocognitive Scaffolding Https://Doi.Org/10.1146/Annurev.Psych.59.103006.093656 https://doi.org/10.1146/ANNUREV.PSYCH.59.103006.093656

Paterson DH, & Warburton DE (2010). Physical activity and functional limitations in older adults: a systematic review related to Canada's Physical Activity Guidelines. International Journal of Behavioral Nutrition and Physical Activity, 7(1), 38. 10.1186/1479-5868-7-38

Reed BR, Mungas D, Farias ST, Harvey D, Beckett L, Widaman K, … DeCarli C (2010). Measuring cognitive reserve based on the decomposition of episodic memory variance. Brain, 133(8), 2196–2209. 10.1093/brain/awq154 [PubMed: 20591858]

Reuter-Lorenz PA, & Park DC (2014). How Does it STAC Up? Revisiting the Scaffolding Theory of Aging and Cognition. Neuropsychology Review, 24(3), 355–370. 10.1007/s11065-014-9270-9 [PubMed: 25143069]

Robert P, Lanctôt KL, Agüera-Ortiz L, Aalten P, Bremond F, Defrancesco M, … Manera V (2018). Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018

international consensus group. European Psychiatry, 54, 71–76. 10.1016/j.eurpsy.2018.07.008 [PubMed: 30125783]

Rog LA, Park Q, Harvey DJ, Huang C-J, Mackin S, & Farias ST (2014). The Independent Contributions of Cognitive Impairment and Neuropsychiatric Symptoms to Everyday Function in Older Adults. The Clinical Neuropsychologist, 28(2), 215–236. 10.1080/13854046.2013.876101 [PubMed: 24502686]

Roy K, Pepin LC, Philiossaint M, Lorius N, Becker JA, Locascio JJ, … Initiative, for the A. D. N. (2014). Regional fluorodeoxyglucose metabolism and instrumental activities of daily living across the Alzheimer's disease spectrum. Journal of Alzheimer's Disease : JAD, 42(1), 291–300. 10.3233/JAD-131796 [PubMed: 24898635]

Royall DR, Lauterbach EC, Kaufer D, Malloy P, Coburn KL, & Black KJ (2007). The Cognitive Correlates of Functional Status: A Review From the Committee on Research of the American Neuropsychiatric Association. The Journal of Neuropsychiatry and Clinical Neurosciences, 19(3), 249–265. 10.1176/jnp.2007.19.3.249 [PubMed: 17827410]

Ruthirakuhan M, Herrmann N, Vieira D, Gallagher D, & Lanctôt KL (2019). The Roles of Apathy and Depression in Predicting Alzheimer Disease: A Longitudinal Analysis in Older Adults With Mild Cognitive Impairment. The American Journal of Geriatric Psychiatry, 27(8), 873–882. 10.1016/J.JAGP.2019.02.003 [PubMed: 30910421]

Satz P (1993). Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. Neuropsychology, 7, 273–295.

Schmitter-Edgecombe M, Parsey C, & Cook DJ (2011). Cognitive Correlates of Functional Performance in Older Adults: Comparison of Self-Report, Direct Observation, and Performance-Based Measures. Journal of the International Neuropsychological Society, 17(05), 853–864. 10.1017/S1355617711000865 [PubMed: 21729400]

Stern Y (2002). What is cognitive reserve? Theory and research application of the reserve concept. Journal of the International Neuropsychological Society, 8(3), 448–460. 10.1017/S1355617702813248 [PubMed: 11939702]

Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G, … Vuoksimaa E (2018). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimer's & Dementia 10.1016/j.jalz.2018.07.219

Stern Y, & Barulli D (2019). Cognitive reserve. In Handbook of clinical neurology (Vol. 167, pp. 181–190). 10.1016/B978-0-12-804766-8.00011-X [PubMed: 31753132]

Tractenberg RE, Weiner MF, Cummings JL, Patterson MB, & Thal LJ (2005). Independence of changes in behavior from cognition and function in community-dwelling persons with Alzheimer's disease: a factor analytic approach. The Journal of Neuropsychiatry and Clinical Neurosciences, 17(1), 51–60. 10.1176/jnp.17.1.51 [PubMed: 15746483]

Vaughan L, Leng X, La Monte MJ, Tindle HA, Cochrane BB, & Shumaker SA (2016). Functional Independence in Late-Life: Maintaining Physical Functioning in Older Adulthood Predicts Daily Life Function after Age 80. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 71(Suppl 1), S79–S86. 10.1093/gerona/glv061

Verbrugge LM, & Jette AM (1994). The disablement process. Social Science & Medicine, 38(1), 1–14. 10.1016/0277-9536(94)90294-1 [PubMed: 8146699]

Vicini Chilovi B, Conti M, Zanetti M, Mazzù I, Rozzini L, & Padovani A (2009). Differential Impact of Apathy and Depression in the Development of Dementia in Mild Cognitive Impairment Patients. Dementia and Geriatric Cognitive Disorders, 27(4), 390–398. 10.1159/000210045 [PubMed: 19339777]

Weakley A, Weakley AT, & Schmitter-Edgecombe M (2019). Compensatory strategy use improves real-world functional performance in community dwelling older adults. Neuropsychology, 33(8), 1121–1135. 10.1037/neu0000591 [PubMed: 31448941]

Weintraub S, Salmon D, Mercaldo N, Ferris S, Graff-Radford NR, Chui H, … Morris JC (2009). The Alzheimer's Disease Centers' Uniform Data Set (UDS): the neuropsychologic test battery. Alzheimer Disease and Associated Disorders, 23(2), 91–101. 10.1097/WAD.0b013e318191c7dd [PubMed: 19474567]

West S, Mc Cue R, & Golden C (2012). Does memory predict decline in activities of daily living in older adults with Alzheimer's disease. Archives of Assessment Psychology, 2(1), 32–43.

Yuan K-H, & Bentler PM (2000). Three Likelihood-Based Methods for Mean and Covariance Structure Analysis with Nonnormal Missing Data. Sociological Methodology, 30(1), 165–200. 10.1111/0081-1750.00078

Zahodne LB, Manly JJ, Brickman AM, Siedlecki KL, Decarli C, & Stern Y (2013). Quantifying cognitive reserve in older adults by decomposing episodic memory variance: replication and extension. Journal of the International Neuropsychological Society : JINS, 19(8), 854–862. 10.1017/S1355617713000738 [PubMed: 23866160]

Zahodne LB, & Tremont G (2013). Unique effects of apathy and depression signs on cognition and function in amnestic mild cognitive impairment. International Journal of Geriatric Psychiatry, 28(1), 50–56. 10.1002/gps.3789 [PubMed: 22368079]

Key Points

- Question: Is there a functional analogue to cognitive reserve ("functional reserve") that explains individual differences in performance of activities of daily living?
- Findings: Functional reserve is a construct that represents the variance in instrumental activities of daily living performance that is not accounted for by brain variables, cognition, and demographics, and is associated with apathy severity and physical functioning.
- Importance: This study provides preliminary validation for the construct of functional reserve and provides a method for evaluating other modifiable factors that influence functional independence despite brain and cognitive changes.
- Next Steps: Examining how functional reserve changes in parallel with age-related brain and cognitive decline and identifying factors that promote maintence of functional reserve over time will inform future interventions aimed at helping older adults remain independent.

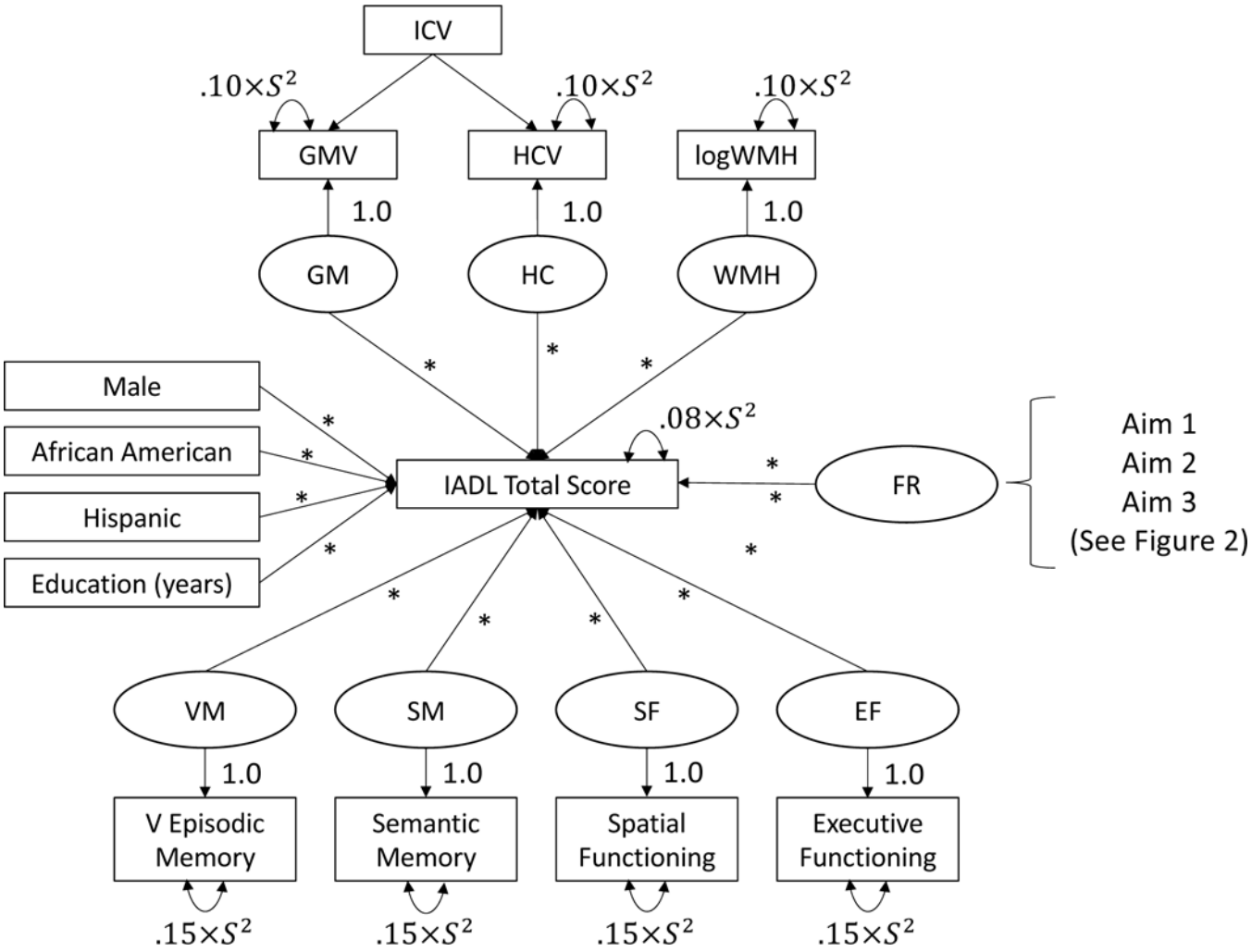

Figure 1.

Legend: Schematic of the functional reserve conceptual model. EF=executive function. FR=functional reserve. GM=grey matter. GMV=grey matter volume. HC=hippocampus. HCV=hippocampal volume. ICV=intracranial volume. SF=spatial function. SM=semantic memory. VM=verbal episodic memory. WMH=white matter hyperintensities.

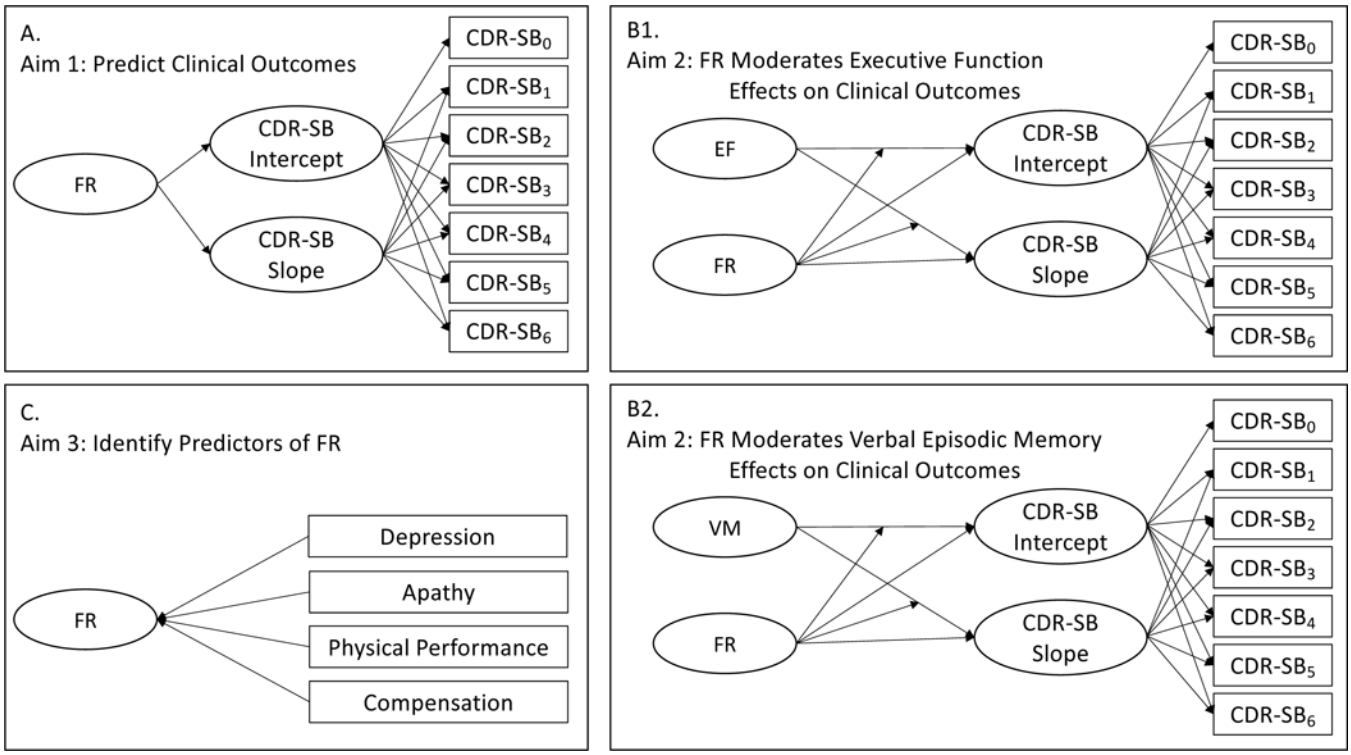

Figure 2.

Legend: Schematic of conceptual models depicting study aims. For simplicity, covariates are not depicted. CDR-SB=clinical dementia rating sum of boxes score. EF=executive function. FR=functional reserve. VM=verbal episodic memory.

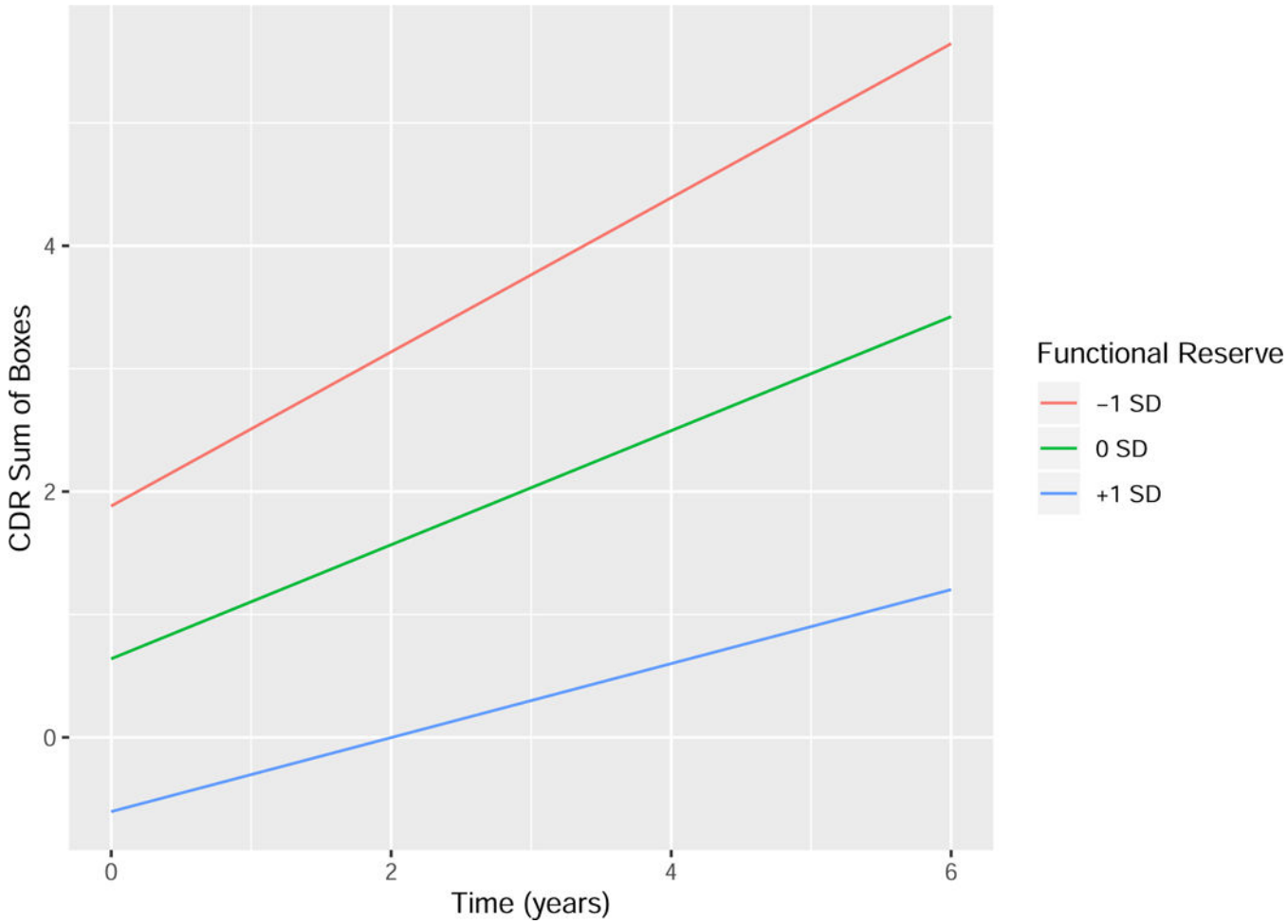

Figure 3.

Legend: Model predicted associations between functional reserve and longitudinal dementia trajectories. The red (black) line represents −1SD. The green (dark grey) line represents the mean (i.e., 0 SD). The blue (light grey) line represents +1SD. CDR=clinical dementia rating. SD=standard deviation.

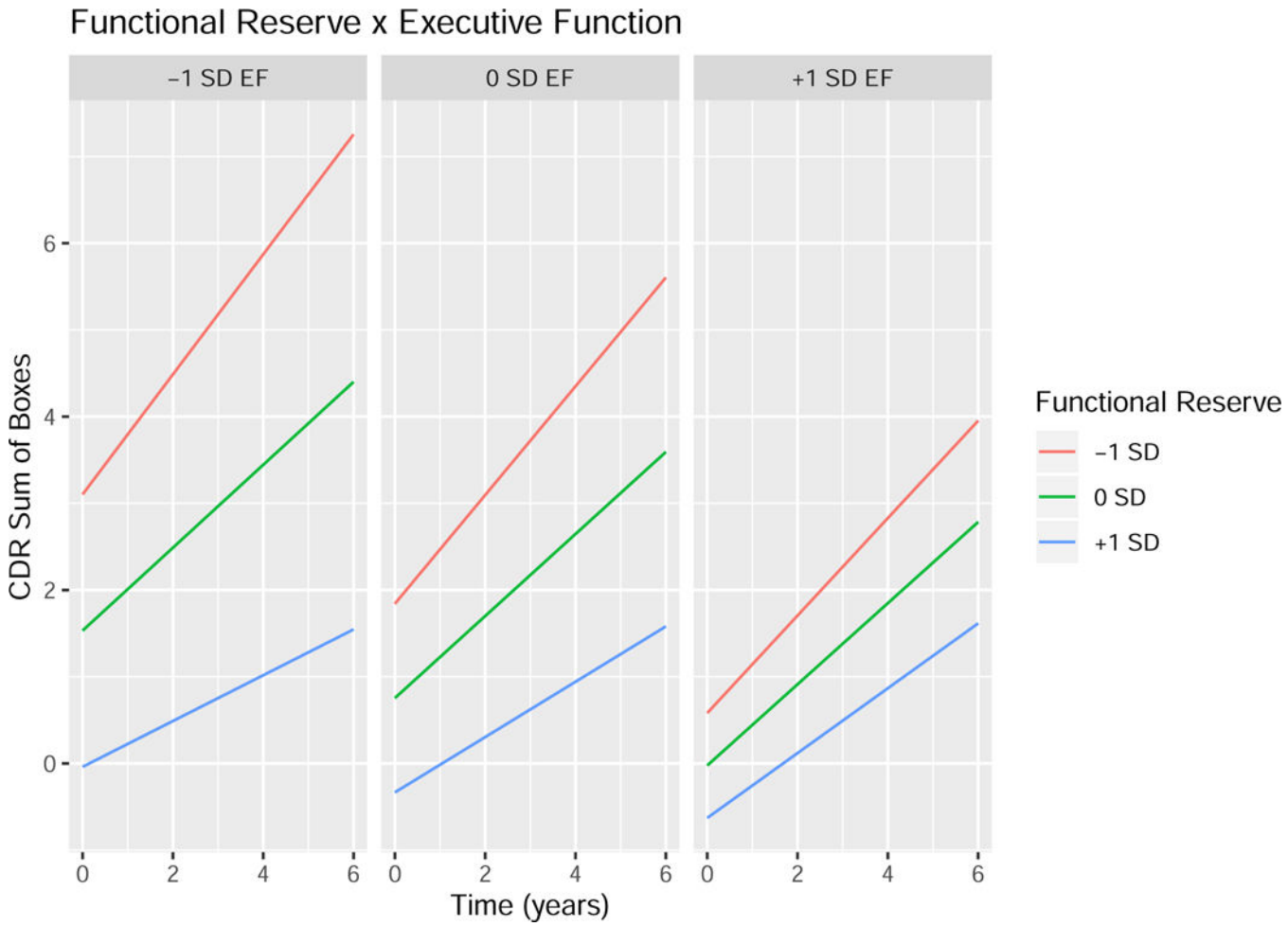

Figure 4.

Legend: Model predicted associations of the interaction between functional reserve and executive function with longitudinal dementia trajectories. The red (black) line represents −1SD. The green (dark grey) line represents the mean (i.e., 0 SD). The blue (light grey) line represents +1SD. CDR=clinical dementia rating. SD=standard deviation. EF=executive function.

Table 1

Sample characteristics

Variable	Whole Sample	Dementia	MCI	Cognitively Normal	*p*
n	1084[a]	163	333	523	
Number of cognitive assessments	3.78 ± 3.13	2.54 ± 1.91	3.56 ± 2.64	4.36 ± 3.52	< .001
Age (years)	75.67 ± 7.48	78.23 ± 7.90	76.35 ± 7.31	74.61 ± 7.32	< .001
Education (years)	13.16 ± 4.62	11.67 ± 4.74	13.47 ± 4.61	13.57 ± 4.33	< .001
Male sex (percent)	452 (41.7)	73 (44.8)	163 (48.9)	193 (36.9)	.002
AA/Black race	242 (22.3)	32 (19.6)	67 (20.1)	125 (23.9)	.313
H/L ethnicity	247 (22.8)	47 (28.8)	49 (14.7)	131 (25.0)	< .001
Verbal episodic memory	−0.29 ± 0.98	−1.34 ± 0.76	−0.71 ± 0.65	0.28 ± 0.79	< .001
Semantic memory	0.10 ± 0.91	−0.60 ± 0.98	0.05 ± 0.81	0.39 ± 0.80	< .001
Spatial function	−0.01 ± 0.99	−0.77 ± 1.11	−0.10 ± 0.99	0.27 ± 0.82	< .001
Executive function	−0.22 ± 0.74	−0.95 ± 0.73	−0.36 ± 0.61	0.11 ± 0.62	< .001
Grey matter volume	544.08 ± 62.20	516.45 ± 66.19	545.57 ± 63.02	551.13 ± 58.88	< .001
Hippocampal volume	5.94 ± 0.86	5.21 ± 0.84	5.75 ± 0.81	6.26 ± 0.72	< .001
White matter hyperintensities volume	12.64 ± 15.58	18.56 ± 20.93	14.39 ± 16.70	9.87 ± 12.09	< .001
CDR-SB	1.61 ± 2.40	5.32 ± 3.31	1.71 ± 1.60	0.45 ± 0.90	< .001
Physical function	9.11 ± 2.69	7.84 ± 2.99	8.81 ± 2.74	9.50 ± 2.54	.001
Apathy	0.26 ± 0.63	0.66 ± 0.93	0.27 ± 0.62	0.15 ± 0.48	< .001
Depression	0.47 ± 0.81	0.88 ± 1.07	0.49 ± 0.76	0.35 ± 0.72	< .001
Compensatory abilities	1.99 ± 0.79	1.91 ± 1.02	2.55 ± 0.85	1.89 ± 0.74	.05

Note. AA=African American. CDR-SB=Clinical Dementia Rating Scale – Sum of Boxes. H/L=Hispanic/Latinx. IADL=Instrumental Activities of Daily Living. Values provided are either means and standard deviations or frequencies with percentages in parentheses.

[a]65 participants were missing diagnostic information.

Table 2

Estimates of the model testing functional reserve associations with longitudinal trajectories of dementia severity (CDR-SB)

	Intercept				Slope			
Baseline Predictor	***b***	**SE**	**b/SE**	***p***	***b***	**SE**	**b/SE**	***p***
Constant	0.639	0.419	1.525	.127	0.464	0.193	2.404	.016
Functional Reserve	−1.243	0.141	−8.803	< .001	−0.163	0.065	−2.510	.012
Verbal Episodic Memory[a]	−1.048	0.230	−4.563	< .001	−0.230	0.113	−2.038	.042
Semantic Memory[a]	0.047	0.274	0.173	.863	−0.277	0.141	−1.966	.049
Spatial Functioning[a]	−0.574	0.193	−2.983	.003	−0.067	0.095	−0.706	.480
Executive Functioning[a]	−0.882	0.274	−3.225	.001	0.011	0.140	0.080	.936
Grey Matter Volume[a,b]	−0.478	0.475	−1.007	.314	−0.572	0.230	−2.483	.013
Hippocampus Volume[a,b]	−0.743	0.179	−4.142	< .001	−0.332	0.091	−3.645	< .001
WMH Volume[a]	0.063	0.144	0.439	.660	0.042	0.072	0.588	.557
Male sex	−0.077	0.202	−0.379	.705	−0.006	0.202	−0.379	.705
AA/Black race	−0.644	0.271	−2.374	.018	−0.563	0.144	−3.913	< .001
H/L ethnicity	−0.676	0.300	−2.253	.024	−0.429	0.158	−2.713	.007
Education (years)	0.028	0.028	1.001	.317	0.024	0.013	1.825	.068

Note. AA=African American. CDR-SB = Clinical Dementia Rating – Sum of Boxes. H/L=Hispanic/Latinx. SE = standard error. WMH = white matter hyperintensities.

[a]Single-indicator latent variable

[b]Adjusted for intracranial volume

Table 3

Model estimates for interactions between functional reserve and cognitive variables in predicting longitudinal trajectories of dementia severity (CDR-SB)

		Intercept				Slope			
Model	**Baseline Predictor**	***b***	**SE**	**b/SE**	***p***	***b***	**SE**	**b/SE**	***p***
1	Functional Reserve	−1.088	0.135	−8.033	< .001	−0.154	0.063	−2.462	.014
1	Executive Functioning	−0.778	0.241	−3.224	.001	−0.005	0.142	−0.034	.973
1	FR x EF	0.483	0.159	3.046	.002	0.060	0.112	0.537	0.591
2	Functional Reserve	−1.106	0.157	−7.027	< .001	−0.162	0.062	−2.624	.009
2	Verbal Episodic Memory	−1.050	0.221	−4.749	< .001	−0.244	0.114	−2.136	.033
2	FR x VEM	0.356	0.248	1.438	.150	0.023	0.104	0.218	.828

Note. CDR-SB = Clinical Dementia Rating – Sum of Boxes. EF = executive function. SE = standard error. VEM = verbal episodic memory. Model 1 examines FR x EF interaction; Model 2 examines FR x VM interaction.