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Research Article

Modeling the development of cognitive reserve in children: A residual index approach

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Abstract

Objective: To model cognitive reserve (CR) longitudinally in a neurodiverse pediatric sample using a residual index approach, and to test the criterion and construct validity of this index. **Method:** Participants were $N = 115$ children aged 9.5–13 years at baseline ($M_{Age} = 10.48$ years, $SD_{Age} = 0.61$), and $n = 43$ (37.4%) met criteria for ADHD. The CR index represented variance in Matrix Reasoning scores from the WASI that was unexplained by MRI-based brain variables (bilateral hippocampal volumes, total gray matter volumes, and total white matter hypointensity volumes) or demographics (age and sex). **Results:** At baseline, the CR index predicted math computation ability (estimate = 0.50, $SE = 0.07$, $p < .001$), and word reading ability (estimate = 0.26, $SE = 0.10$, $p = .012$). Longitudinally, change in CR over time was not associated with change in math computation ability (estimate = −0.02, $SE = 0.03$, $p < .513$), but did predict change in word reading ability (estimate = 0.10, $SE = 0.03$, $p < .001$). Change in CR was also found to moderate the relationship between change in word reading ability and white matter hypointensity volume (estimate = 0.10, $SE = 0.05$, $p = .045$). **Conclusions:** Evidence for the criterion validity of this CR index is encouraging, but somewhat mixed, while construct validity was evidenced through interaction between CR, brain, and word reading ability. Future research would benefit from optimization of the CR index through careful selection of brain variables for a pediatric sample.

Keywords: resilience; brain; MRI; pediatric; ADHD; academic

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The construct of cognitive reserve (CR) is defined as the efficiency, capacity, and flexibility of cognition, and has been outlined as an important protective factor in the context of cognitive aging and neurodegenerative disease (Stern et al., 2020). The mechanisms by which CR confers resilience to cognitive decline are poorly understood; however, several demographic/lifestyle factors, such as total years of education and occupational complexity (Chapko et al., 2018; Valenzuela & Sachdev, 2006) and participation in leisure activities (Song et al., 2022), have been identified as attenuating the effects of brain pathology on cognition later in life. It has been theorized that cognitive stimulation induced by these factors results in increased computational flexibility and/or the recruitment of cognitive structures that may be more resilient to neurological damage (Stern, 2002).

While the vast majority of research on CR has been conducted with older adult populations, there has been a shift toward investigating CR in midlife in order to elucidate its development across the lifespan. In middle-aged adult samples, studies have examined reading and vocabulary scores (Soldan et al., 2020), occupational complexity (Boots et al., 2015), and participation in cognitively stimulating leisure activities(Ihle et al., 2018; Reed et al., 2011); findings suggest that increased levels of these factors in midlife may continue to promote CR, and ultimately, mitigate late-life cognitive decline.

With precedence established that CR is active in midlife, it is reasonable to suggest that CR is being built even earlier than this (e.g., childhood/adolescence), particularly given that most formal education occurs in the first 18 years of life. While the concept of pediatric CR remains to be clearly conceptualized, Dennis and colleagues (2000) postulated a framework delineating biological risk/resilience factors (i.e., brain reserve capacity and neuro-biological integrity), and functional risk/resilience factors (i.e., cognitive reserve) that are largely in line with theories of reserve based on older adults (Stern et al., 2020). Further, according to Dennis et al. (2007), along with functional plasticity, the combined effect of brain and cognitive reserve is likely to account for the significant disparities observed in physical, cognitive-academic, neuropsychological, and psychosocial outcomes in children with acquired or congenital neurological damage.

Empirical work on CR in child samples is, again, somewhat limited compared to literature with older adults; although, higher CR has been shown to predict more favorable outcomes in

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pediatric samples afflicted with various neurological disorders, such as improved executive functioning in children with acute lymphoblastic leukemia (Kesler et al., 2010), as well as stable/improving cognitive performance in pediatric-onset multiple sclerosis (Pastò et al., 2016). Further, CR has been found to moderate relationships between brain injury severity and post-concussive symptoms (Fay et al., 2010) as well as intellectual functioning (Donders & Kim, 2019) in pediatric samples with traumatic brain injury.

Findings pertaining to CR in pediatric samples seem intriguing, although studies have typically operationalized CR through proxy variables, such as parental (Donders & Kim, 2019) or maternal education (Kesler et al., 2010), as well as full-scale IQ (Koenen et al., 2009; Pastò et al., 2016) and other general measures of cognitive ability (Fay et al., 2010). This methodology presents challenges in terms of confounding influences (Jones et al., 2011). For instance, in line with CR theory, maternal education reflects socioeconomic status of the household, and may indeed facilitate increased opportunity for exposure to cognitively stimulating environments; however, socioeconomic status also predicts child height-for-age, increased health-seeking behaviors, access to healthcare, and overall child mortality (Desai & Alva, 1998), which may influence cognitive/diagnostic outcomes through mechanisms unrelated to CR.

To ameliorate methodological issues related to proxy variables, research investigating pediatric CR might benefit from an approach mirroring that of the literature on older adults; specifically, a residual reserve index (Reed et al., 2010). This method involves partialling out variance in cognition due to an individuals' demographic or structural brain characteristics. Ultimately, the aim is to generate a more valid operationalization of CR based on the variance in cognition that is left unaccounted for by these confounding influences. Further, in the case where longitudinal cognitive and imaging data is procured, the residual approach holds another advantage over static proxy variables (e.g., parental education) in that it allows the construction of a dynamic index that can quantify changes in CR over time (Bettcher et al., 2019; Zahodne et al., 2015).

A residual-based method seems particularly suited to measuring CR in a developing cohort, and further, it provides the opportunity to apply methods based on established geriatric residual models (e.g., Bettcher et al., 2019; Reed et al., 2010) to pediatric samples. In the case where a meaningful CR index could be generated using the same approach as in older adults, this would have both theoretical and practical implications for the CR construct. For instance, success with a residual approach would imply that CR can be modeled in children as the discrepancy between expected versus observed cognitive functioning given certain brain and demographic characteristics – a notion that has been hitherto alluded but not empirically tested, to our knowledge. Additionally, the identification of salient brain and demographic predictors for age groups at both ends of the lifespan would enable the modeling of CR across childhood and into adulthood, thereby facilitating the study of its developmental trajectory. Ultimately, this could serve to inform interventions aiming to facilitate the "growth" of CR to not only protect children afflicted with neurological disease, but also bolster the reserve of future generations and mitigate their susceptibility to late-life cognitive decline.

Alternatively, in the case where a geriatric CR index did not show the same level of validity in our pediatric cohort, this too would have implications; specifically, that the construct of CR, as it is currently conceptualized in the geriatric literature, does not directly apply to children in this form and would need to be operationalized accordingly. Further, regardless of how the geriatric model performs, a baseline would be established (i.e., certain residual model components will have been outlined as salient or irrelevant for a pediatric cohort), which would inform future attempts at optimizing – or overhauling, in the case where the geriatric model does not apply at all – a pediatric residual reserve index.

The current study utilized a residual approach to operationalise CR within a pediatric cohort that comprised children both with and without ADHD; this is a neurodiverse sample previously shown to exhibit variability in structural brain characteristics (Ball et al., 2019). The residual model was based on brain and demographic variables paralleling studies that have successfully employed this methodology in older adult samples, using latent variable (Bettcher et al., 2019; Reed et al., 2010; Zahodne et al., 2015; Zahodne et al., 2013), and regression approaches (Beyer et al., 2019; Habeck et al., 2017; van Loenhoud et al., 2019).

We aimed to adhere to successful cross-sectional (Reed et al., 2010), and longitudinal (Bettcher et al., 2019) geriatric residual models as closely as possible. However, the residual index is generated based on the decomposition of variance in "cognition", and previous studies have selected episodic memory as a cognitive domain given its sensitivity to a multitude of late-life neurodegenerative processes and diseases (e.g., Alzheimer's); given the absence of such processes in children, we opted to decompose a measure of fluid intelligence to represent cognition. This decision was based on research previously employing intellectual quotient (IQ) as a proxy for CR in pediatric samples (Koenen et al., 2009; Pastò et al., 2016). Further, intelligence – and more specifically, its fluid component – shows face validity in terms of its ability to capture the adaptability of cognitive processes that is central to Stern et al.'s (2020) definition of CR (i.e., the efficiency, capacity, and flexibility of cognition). That is, fluid intelligence has been described similarly, with the construct thought to represent novel problem-solving, abstract reasoning, and ultimately, an individual's capacity to "flow" into different forms of cognitive activities (Carroll, 1993).

In keeping with the approach taken by Reed et al. (2010) in their pilot study with older adults, we subjected a residual index to tests of criterion validity as well as more stringent tests of construct validity. We hypothesized that our residual index would predict criteria relevant to a pediatric cohort (i.e., academic outcomes; H_1), as well as moderate the relationship between structural brain characteristics and academic ability (H_2), both at baseline and longitudinally.

Method

This study received ethical approval from the University of Western Australia's Human Research Ethics Office (Ref: 4/20/6290) as well as The Royal Children's Hospital Human Research Ethics Committee, Melbourne (Ref: #34071). Research was completed in accordance with the Helsinki Declaration.

Participants

Longitudinal data were obtained from the Children's Attention Project (CAP) cohort, who were recruited by the Murdoch Children's Research Institute over a 9-year span (i.e., 2011–2019). The CAP sample was recruited in Grade 1 during 2011–2012 (i.e.,

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two consecutive cohorts) across 43 primary schools of diverse socioeconomic status near Melbourne.

Of the initial $N = 5922$ eligible participants who were contacted, 3734 returned both parent and teacher screening reports of the Conners 3 ADHD index. Potential ADHD cases were assessed via clinical interview, and participants were matched with typically developing children on sex, school, and age; this resulted in a sample of 179 children with confirmed ADHD and 212 typically developing controls from ages 6–8 years, who were followed up in regular 18-month intervals following initial recruitment. Exclusion criteria for the CAP study were as follows: intellectual disability, serious medical conditions, neurological diagnoses, genetic disorders, moderate-to-severe sensory deficits, and parents without sufficient English language competency (i.e., precluding their ability to fill out questionnaires and participate in interviews).

The present study utilized data from a subset of the CAP sample, referred to as the Neuroimaging of the Children's Attention Project (NICAP) cohort. This comprised those participants whose parents provided further consent, prior to their 36-month follow-up, for them to take part in a neuroimaging substudy, which would be completed alongside their regular assessments. More detailed descriptions of the CAP (Sciberras et al., 2013) and NICAP (Silk et al., 2016) study protocols have been previously published.

Complete datasets (i.e., comprising cognitive assessment and neuroimaging data from at least two timepoints) were available for $N = 115$ children, of which $N = 72$ (63%) were male. At baseline, the mean age of the sample was 10.48 ($SD = 0.61$, min = 9.5, max = 13), and there were $N = 43$ (37.4%) participants who met the criteria for a DSM-IV ADHD diagnosis. Each participant had received at least two MRI scans, with $N = 86$ (74.1%) receiving three scans. In addition, completion of the Matrix Reasoning task at a minimum of two timepoints were required for all participants, with $N = 85$ (73.9%) completing three assessments; no significant difference in raw matrix reasoning scores at final scan was found between those completing two assessments ($M = 25.63$) versus those completing three ($M = 25.73$), with $t(50) = -0.10$, $p = .923$.

Materials

NIMH diagnostic interview schedule for children: fourth edition

Parents were interviewed with the NIMH Diagnostic Interview Schedule for Children: Fourth Edition (NIMH DISC-IV; Shaffer et al., 2000) to ascertain participants' ADHD diagnostic status at recruitment (age 7), at imaging baseline (age 10) and at the imaging 36-month follow-up (age 13). The parent-completed version of the NIMH DISC-IV is a widely employed and psychometrically validated structured interview for the assessment of a range of psychiatric conditions, including ADHD and related behaviors, in children aged 6–17 (Shaffer et al., 2000).

Fluid intelligence

The Matrix Reasoning subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) was administered at each wave, as part of a more comprehensive cognitive assessment. This subtest has excellent reliability and validity, and was selected as a measure of fluid intellect (Wechsler, 1999). To minimize the influence of measurement error, participants' baseline Matrix Reasoning raw scores were adjusted to produce "true" scores according to the split-half reliability of the WASI measure, which, according to previous research, is estimated at approximately $r = .92$ (Wechsler, 1999). This adjustment was done by determining the difference between observed scores from the sample mean, scaling this difference by the reliability coefficient, and summing this product with the mean (Strauss et al., 2006). Similarly, individual Matrix Reasoning score changes were converted to "true" change scores based on test-retest reliability of the WASI, which was found to be $r = .77$ in previous research (Wechsler, 1999).

Academic achievement

Math Computation and Word Reading subtests from the Wide Range Achievement Test: Fourth Edition (WRAT-4; Wilkinson & Robertson, 2006) were utilized as academic outcomes; both subtests have demonstrated high internal consistency and alternate-form reliability. Math Computation is a two-part subtest: Part 1 consists of "oral math" (15 items) while Part 2 comprises a 40-item subtest that involves basic arithmetic (e.g., number identification, counting, addition, subtraction, multiplication and division), as well as more advanced mathematical skills (e.g., decimals, fractions, and algebra); raw scores ranged from 0 to 55, with higher scores indicating greater mathematic ability. The Word Reading subtest also consists of two parts: Part 1 involves letter recognition (15 items) while Part 2 requires participants to correctly read aloud words that are shown to them in written format. A total of 55 words are present on the word card, with the range of scores being 0–70 for the full subtest; higher scores indicate more favorable word decoding and recognition ability. Raw scores from each subtest were z-transformed prior to analysis.

Neuroimaging

Brain images were acquired from the Murdoch Children's Research Institute at The Royal Children's Hospital in Melbourne. The apparatus utilized was a research-dedicated 3-Tesla Siemens MRI scanner with a 32-channel head coil (Siemens, Erlangen, Germany). Navigator-based prospective motion correction was incorporated to mitigate movement artifacts during imaging. A modified multi-echo magnetization-prepared rapidly acquired gradient-echo (MEMPRAGE; van der Kouwe et al., 2008) sequence was used to generate T1-weighted structural images of the brain. For full sequence and acquisition details, see Silk et al. (2016).

Data processing

The process of segmenting and parcellating neural structures was accomplished with the longitudinal FreeSurfer pipeline (Reuter et al., 2012). The method implemented by Reuter et al. (2012) involved processing data from each timepoint using the standard cross-sectional FreeSurfer function, and subsequently, generating an unbiased within-subjects template based on averaged information from each timepoint. Intracranial volumes were extracted from the cross-sectional analyses (i.e., at baseline), while the longitudinal pipeline was run to obtain structural information from several neural regions, including bilateral hippocampal volumes, total gray matter volumes (i.e., sum of bilateral cortical, subcortical, and cerebellar gray matter volumes), and total white matter hypointensity (WMH) volumes. These regions were selected based on a dynamic residual model shown to effectively operationalize CR in a geriatric sample (Bettcher et al., 2019).

Statistical analyses

All data cleaning, structuring, and analysis was conducted using the R programing language (v4.1.1; R Core Team, 2021).

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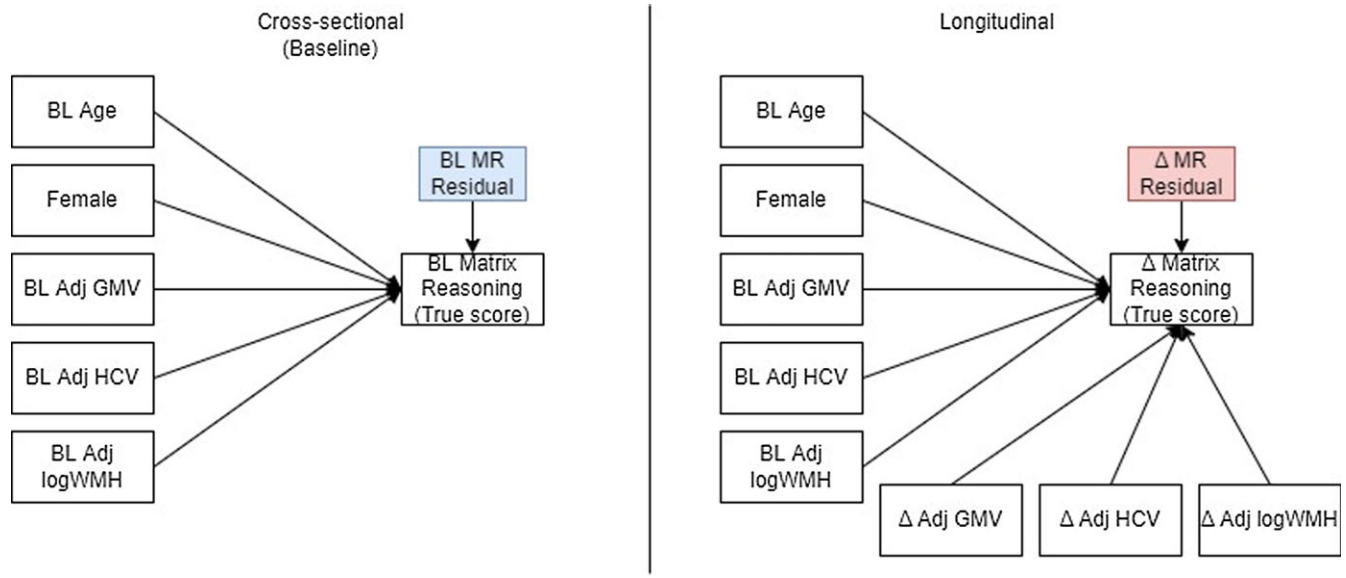

Figure 1. Regression models used to generate the baseline CR index (left) and longitudinal CR index (right). BL = baseline; Adj = adjusted for intracranial volume; GMV = gray matter volume; HCV = hippocampal volume; logWMH = log-transformed white matter hypointensities.

Generation of baseline and longitudinal CR indices

Matrix Reasoning true scores were entered as dependent variables in two separate multiple linear regressions with different sets of predictor variables involving demographic data and MRI-based brain volumes (i.e., a baseline CR model and a CR change model).

Demographic variables included age (centred at 10) and sex (coded as male = 0, female = 1). Observed MRI-based brain variables included standardized total gray matter volumes, hippocampal volumes, and WMH. Given that the original distribution was extremely skewed, WMH were log-transformed to obtain a normalized distribution. In addition, total gray matter, hippocampal volumes, and WMH volumes were scaled by intracranial volumes at baseline and adjusted accordingly. CR at baseline was estimated by regressing standardized Matrix Reasoning true scores onto demographic variables, as well as the brain variables, at the time of first scan; baseline CR was represented by the residual variance in this model.

Change in brain variables over time was estimated by calculating differences between raw morphometric data (i.e., total gray matter, hippocampal volume, and WMHs) obtained at participants' final scan from their first scan; change variables were subsequently converted to *z*-scores and annualized. To estimate a residual index representing longitudinal change in CR, Matrix Reasoning difference scores (i.e., difference between Matrix Reasoning score at first and last MRI scans) were regressed onto demographic, baseline brain, and brain change variables.

The baseline and longitudinal CR residual models are visualized in Figure 1.

Missing values

Baseline and longitudinal CR indices were computed using only observed variables. This was to maintain face validity of the CR construct and mitigate any bias that would result from deriving a CR index – which is purportedly representing discrepancy in an individual's functioning – that is generated from linear combinations of other variables in the dataset. Regressions involving outcome variables were, however, based on imputed datasets generated via multiple imputation by chained equations (MICE). Data were assumed to be missing at random. Multiple imputation was carried out using the R software package "mice" v3.14.0 with the default command, which generates $m = 5$ imputed datasets based on a fully conditional specification approach. Regression models involving outcome variables were fit across all imputed datasets; subsequently, estimates and standard errors were amalgamated to produce a single set using mice's pool() function.

Predicting academic outcomes

To assess whether the CR index could predict relevant academic outcomes both cross-sectionally and longitudinally, a series of multiple linear regression models were run. Cross-sectional analyses of outcome variables involved each academic variable (i.e., standardized mathematical computation and word reading *z*-scores) entered as dependent variables in two separate multiple regressions with identical sets of predictors, including demographics, structural brain variables, and CR at baseline. A moderation effect of baseline CR on the relationship between baseline brain characteristics and each academic outcome was also assessed. Similarly, two longitudinal models were run, each of which involved either math computation and word reading change scores as dependent variables. Differences in math computation or word reading between first and last MRI scan were regressed onto the CR change variable, as well as baseline CR, baseline brain variables, and annualized change in brain variables. This was to estimate unique effects of CR at baseline, as well as CR change, on change in each academic variable. Similar to the cross-sectional analysis, a moderation effect of CR change on the relationship between change in brain variables and change in each academic outcome, was also analysed.

The described baseline and longitudinal models involving academic outcomes variables are visualized in Figure 2.

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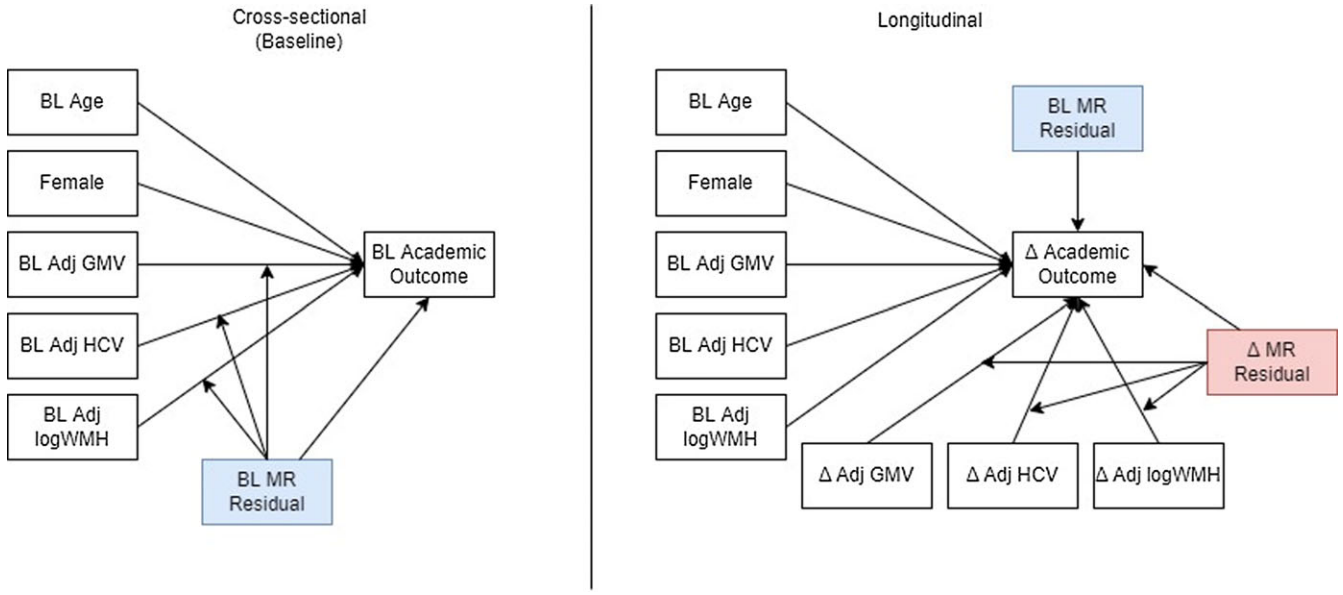

Figure 2. Regression models assessing unique effects of brain characteristics, demographics, and cognitive reserve on academic outcomes, as well as moderation of cognitive reserve on brain and academic outcomes, at baseline (left) and longitudinally (right). BL = baseline; Adj = adjusted for intracranial volume; GMV = gray matter volume; HCV = hippocampal volume; logWMH = log-transformed white matter hypointensities; Academic Outcome = Math Computation or Word Reading *z*-scores from the WRAT-4 (each entered as dependent variables in separate models).

Results

Descriptive statistics

Sample characteristics are presented in Table 1, including demographic information as well as baseline and change (i.e., from first to last scan) for cognitive, academic, and MRI-based brain variables.

Baseline and longitudinal residual models

For the baseline CR model, results of a multiple linear regression indicated that there was no significant collective effect of structural brain variables and demographics on fluid intellect (i.e., Matrix Reasoning true score), with $F(5, 109) = 2.05$, $p = .077$, $R^2 = .09$ (adjusted $R^2 = .04$). Regarding the performance of individual predictors in the model, baseline gray matter explained a significant amount of variance in fluid intellect (estimate = 1.68, standard error [*SE*] = 0.73, $p = .023$), while other baseline predictors including hippocampal volume (estimate = 0.12, $SE = 0.62$, $p = .847$), log-transformed WMHs (estimate = −0.81, $SE = 0.51$, $p = .115$), sex (estimate = 0.97, $SE = 1.14$, $p = .397$), and age (estimate = 0.62, $SE = 0.76$, $p = .818$), were nonsignificant.

For the longitudinal CR model, a multiple linear regression analysis indicated a significant collective effect of brain change variables and demographics on change in fluid intellect, with $F(8, 106) = 2.23$, $p = .031$, $R^2 = .14$ (adjusted $R^2 = .08$). Regarding individual predictors, only gray matter change exhibited a significant unique effect on fluid intellect change (estimate = 1.08, $SE = 0.34$, $p = .002$). Other brain change variables yielded no unique effects on change in fluid intellect, namely hippocampal volume change (estimate = −0.19, $SE = 0.33$, $p = .557$) and log-transformed WMH change (estimate = −0.40, $SE = 0.37$, $p = .284$), while baseline gray matter (estimate = 0.04, $SE = 0.22$, $p = .876$), baseline hippocampal volume (estimate = −0.14, $SE = 0.18$, $p = .426$), baseline log-transformed WMH (estimate = 0.05, $SE = 0.18$, $p = .804$), female sex (estimate = 0.13, $SE = 0.35$, $p = .716$), and age (estimate = −0.43, $SE = 0.23$, $p = .059$) also had no unique effect on change in fluid intellect.

Reserve predicting academic functioning

To investigate whether our calculated index of CR would vary with related constructs, such as academic ability (H_1), CR at baseline and change were entered with brain and demographic variables as predictors of math computation and word reading ability, in a series of multiple linear regressions. Interaction effects between CR and brain characteristics on academic variables were also assessed in order to address H_2. Full regression outputs can be seen in the online Supplemental Materials.

Math computation

Baseline CR was found to positively predict baseline math computation (estimate = 0.50, $SE = 0.07$, $p < .001$), as was baseline gray matter volume (estimate = 0.24, $SE = 0.12$, $p = .040$), while age negatively predicted math computation change (estimate = −0.11, $SE = 0.04$, $p = .017$). Change in CR was not found to be related to change in math computation ability (estimate = −0.02, $SE = 0.03$, $p = .513$).

Word reading

Both baseline CR (estimate = 0.26, $SE = 0.10$, $p = .012$) and baseline gray matter (estimate = 0.35, $SE = 0.17$, $p = .041$), were found to positively predict baseline word reading. In addition, change in CR was found to positively predict change in word reading ability (estimate = 0.10, $SE = 0.03$, $p < .001$), Further, an interaction effect was also present between CR change and WMH change on change in word reading ability (estimate = 0.10, $SE = 0.05$, $p = .045$); this is plotted in Figure 3. The plot suggests that for individuals with higher change in WMH volume, word reading trajectories are more favorable for those with higher rather than lower change in CR.

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Table 1. Sample characteristics for cognitive, academic, and brain variables

	All ($N = 115$)
Age (years)	
Baseline, Mean (*SD*)	10.48 (0.61)
Female	
n (%)	43 (37.40%)
ADHD diagnosis	
n (%) at baseline	41 (35.70%)
n (%) at final scan	31 (27.00%)
Follow-up time	
Mean (*SD*)	2.56 (0.67)
WASI Matrix Reasoning score	
Baseline, Mean (*SD*)	22.40 (5.38)
Change, Mean (*SD*)	3.30 (3.85)
WRAT-4 Word Reading score	
Baseline, Mean (*SD*)	45.06 (8.32)
Change, Mean (*SD*)	8.15 (4.46)
WRAT-4 Math Computation score	
Baseline, Mean (*SD*)	31.14 (4.95)
Change, Mean (*SD*)	6.48 (4.32)
Intracranial Volume (cm^3)	
Baseline, Mean (*SD*)	1590.97 (139.81)
Gray Matter Volume (cm^3)	
Baseline, Mean (*SD*)	788.92 (62.99)
Change, Mean (*SD*)	−0.96 (16.36)
WMH (cm^3)	
Baseline, Mean (*SD*)	0.97 (0.42)
Change, Mean (*SD*)	0.23 (0.18)
Number of visits	
n (%) with two visits	29 (25.22%)
n (%) with three visits	86 (74.78%)

Note: *SD* = standard deviation; ADHD = attention-deficit/hyperactivity disorder; WMH = white matter hypointensities; MRI = magnetic resonance imaging.

Discussion

The current study sought to operationalize an index of CR in a diverse pediatric cohort comprising children with and without ADHD. It was hypothesized that our CR index would satisfy criterion validity checks; specifically, that CR would predict academic variables at baseline and longitudinally (H_1). Baseline CR predicted math computation and word reading ability at baseline, but only word reading ability over time, lending partial support to H_1. It was also predicted that our CR index would moderate the relationship between structural brain characteristics and academic variables cross-sectionally, as well as over time (H_2). Partial support for this hypothesis was also observed, where change in CR moderated the relationship between change in WMH volume and change in word reading ability.

Based on results from a multiple linear regression, baseline CR predicted baseline math computation scores with a strong effect (.50), although, change in CR did not predict change in math computation, possibly suggesting that while math computation and CR are found to correlate cross-sectionally at specific junctures in the developmental period, the factors contributing to change in CR may not overlap with those conferring changes in numerical reasoning ability across this phase of development (e.g., age 10–13). This result is somewhat in line with those of Arcara et al. (2017), who noted that mathematical ability was not related to CR in a sample of older adults; instead, they found that aging performance in mathematics was mostly attributable to level of education, the latter of which was largely constant in our sample.

Regarding word reading ability, both baseline CR and CR change predicted baseline word reading and change in word reading ability, respectively. This result is particularly encouraging regarding the criterion validity of the CR index. Word reading ability demands a relatively intensive knowledge-base of phonological rulesets and prerequisite exposure to words, and is often used to represent premorbid ability and crystallised intelligence; both of these constructs have been previously conceptualized as adjacent to CR, given that the adaptability/efficiency of one's cognition is likely to be related to the accrual of crystallised knowledge and strategies acquired through cognitive stimulation and exposure to learning environments (Alexander et al., 1997; Richards & Sacker, 2003).

In addition, change in CR was found to moderate the effect of WMH volume change on word reading trajectory. Individuals with low change (−1 *SD*) in WMH volume performed similarly regardless of change in CR across time; however, those with higher change (1 *SD*) in WMH volume and higher change in CR (1 *SD*) showed a more favorable word reading trajectory compared to those with low change in CR (−1 *SD*). The capacity for change in CR to moderate the relationship between change in a measure of brain pathology and change in an academic outcome, in a pediatric sample, is a novel finding. This result demonstrates preliminary evidence of construct validity of the CR index, and is in line with how we would expect the index to behave in the case where it had appropriately operationalized the CR construct. Although, the aetiological mechanisms and functional implications represented by WMHs in pediatric samples requires elucidation, given that this mode of neuropathology is typically associated with age-related degenerative processes (e.g., hypertension, diabetes, and arterio/atherosclerosis). In saying this, some research has linked increased WMH with higher prevalence of suicidality (Ehrlich et al., 2004), as well as ADHD, conduct disorder, and depression (Lyoo et al., 2002), in pediatric samples.

Implications

Our findings satisfy the foundational aims of the current study, which was predominantly concerned with initial proof-of-concept; that is, the generation of a meaningful residual index in a pediatric cohort based on a methodology developed to measure CR in older individuals. Indeed, our adapted pediatric residual index showed a somewhat similar performance to the residual geriatric model upon which it was based: Reed and colleagues' (2010) index also predicted word reading ability independently of brain. Further, numerous papers have shown CR to moderate the association between change in structural brain characteristics and change in cognition (Bettcher et al., 2019; Reed et al., 2010; Zahodne et al., 2015), within older adult samples. Taken with findings from geriatric studies, there seem to be two possible implications: firstly, it seems plausible that CR may be consistently operationalized with a residual approach at both ends of the lifespan; secondly, in terms of operationalizing CR in children, fluid intellect appears to be a suitable substitute for cognitive variables (e.g., episodic memory performance) that are typically employed in geriatric residual models.

Limitations & future research

The results of the current study are preliminary, and any implications are pending more rigorous validation of the residual index, as well as optimization in terms of its "purity" as a measure of CR. Indeed, perhaps the most salient shortcoming of the study relates to the relatively low amount of variance explained in fluid intellect for both baseline and longitudinal CR models, compared to past research (Reed et al., 2010). Our CR index seems to mostly represent variance in fluid intellect, suggesting that results may

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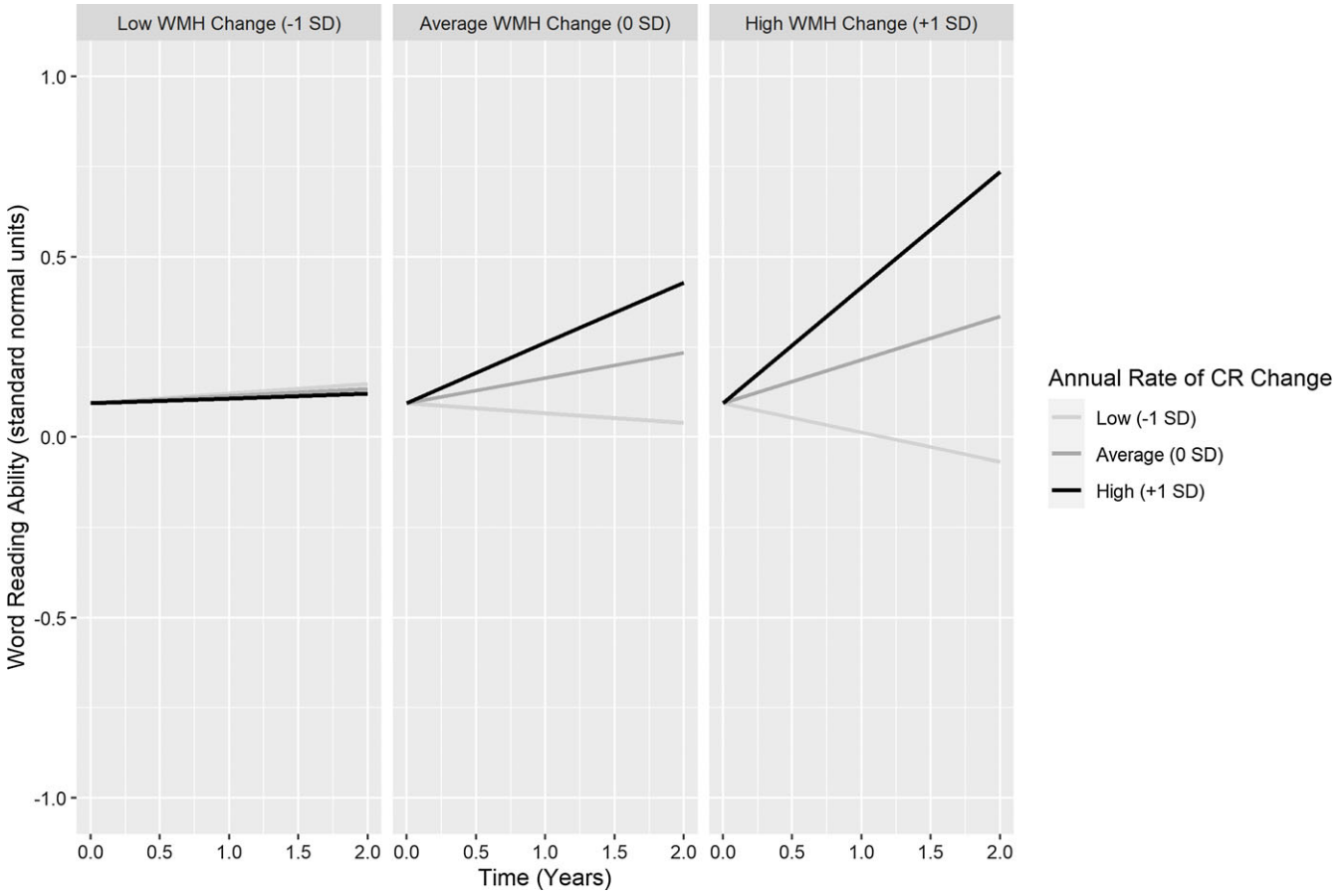

Figure 3. Interaction between change in cognitive reserve by change in log-transformed white matter hypointensity volume (WMH) on word reading ability scores.

instead pertain to this construct, rather than CR. Having said this, if the current selection of MRI-based brain variables (i.e., gray matter volume, WMHs, and hippocampal volume) and demographic variables (i.e., age and sex), are explaining only 9% of the variance in fluid intellect at baseline and 14% of the variance in its longitudinal change, this raises the question as to what other factors may be constituting such substantial residual variance.

In saying this, the study shows several strengths, including rigorous study recruitment procedures, as well as the comprehensive neuroimaging, cognitive, and academic data procured at multiple timepoints, which are necessary to generate a dynamic residual CR index (i.e., that which can track changes in CR over time; Bettcher et al., 2019).

Further research is necessary to develop a residual model that is optimized for children, which may involve, for instance, careful selection of brain variables that sufficiently partial out brain reserve. A model with higher face validity (e.g., a "purer" CR index), will facilitate the interpretability of analyses concerning criterion and construct validity, and subsequently, permit more rigorous inquiry regarding its clinical utility among pediatric samples. Notably, while the participants in this study were largely representative of a community sample, there is a high portion of children with ADHD included by design. This likely provided great variance in the measures, although the specific effect on CR is unknown and was not specifically tested. Following optimization of the residual model for a pediatric cohort, future research would benefit from investigating associations with diagnostic status and/or symptom severity among children with neurodevelopmental disorders (e.g., ADHD). Ultimately, the effective operationalization of a dynamic residual CR index in children will likely prove to be a useful clinical tool, serving to not only elucidate prognosis and identify children more at risk for cognitive sequelae in brain-based medical conditions, but also facilitate research aiming to disentangle the contributions of functional and structural aspects of the brain that might confer neuroprotection among children and adolescents.

Conclusion

The current study has provided the first step toward the operationalization of a dynamic residual model of CR in a pediatric sample. Utilizing a residual model shown to be successful for geriatric populations, criterion validity was found to somewhat mixed, but encouraging. Indeed, the present study is the first to show change in CR to track change in word reading ability across a pediatric developmental period. Further, change in CR was also found to moderate the influence of WMH volume change on word reading ability, exerting a protective effect. Importantly, these findings were obtained with a residual model that seemed to be largely unoptimized, with the selected brain and demographic variables predicting minimal variance in our residualised variable. Future research should aim to adapt the model to a pediatric cohort for the purpose of improving criterion and construct validity, and ultimately, to yield a model that may both enable investigation into the dynamic and developmental nature of CR, as well as facilitate clinical application of CR across the lifespan.

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Competing interests. None.

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