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RESEARCH ARTICLE

Linking cognitive and behavioral reserve: Evidence from the CAN-PROTECT study

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Abstract

INTRODUCTION: Changes to the brain due to Alzheimer's disease and other age-related neuropathologies may present with cognitive and behavioral symptoms, even during preclinical and prodromal stages. While cognitive reserve is known to mitigate cognitive decline in the preclinical stages of Alzheimer's disease, links between cognitive reserve and behavioral symptoms remain unclear. This study investigates the relationship between cognitive reserve and mild behavioral impairment (MBI), a neurodegenerative behavioral prodrome.

METHODS: We analyzed cross-sectional data from 1204 participants in the Canadian Platform for Research Online to Investigate Health, Quality of Life, Cognition, Behavior, Function, and Caregiving in Aging (CAN-PROTECT) study. A cognitive reserve score (CRS) was generated based on education, occupation, and personal cognitive reserve proxies. MBI presence (MBI+) and MBI global and domain symptom severity were eval-

uated using the self-reported MBI Checklist. Initial analyses examined the convergent validity of the CRS through associations with objective neuropsychological test performance and self-reported cognitive symptoms (Everyday Cognition [ECog-II] scale). Models were also fitted to assess MBI status and severity as functions of the CRS.

RESULTS: Higher CRS was associated with better neuropsychological test scores, lower odds of subjective cognitive decline (OR = 0.86, 95% CI: [0.76, 0.98], $p = .03$), and lower ECog-II total score. Likewise, higher CRS was associated with lower odds of MBI+ (OR = 0.81, 95% CI: [0.71, 0.93], $p = .003$), and lower MBI symptom severity globally, and in impulse dyscontrol and social inappropriateness domains.

DISCUSSION: We provide preliminary evidence that engagement in activities known to preserve cognitive function in aging and disease may also preserve behavioral function. Future research should disentangle possible pathways through which cognitive reserve may preserve both cognition and behavior, explore common etiologies for these symptoms, and observe outcomes longitudinally to better understand these relationships.

Highlights:

- Education, occupation, and personal activities are cognitive reserve proxies.
- Cognitive reserve is linked to lower subjective cognitive decline in older persons.
- Cognitive reserve is linked to lower mild behavioral impairment odds and severity.

KEYWORDS
cognitive reserve, mild behavioral impairment, Alzheimer's disease, aging

1 | INTRODUCTION

Cognitive reserve refers to the adaptability of cognitive processes that can account for variability in cognitive decline due to brain aging, pathology, or damage.[1] The theory of cognitive reserve, along with other concepts of resilience in brain aging, helps explain discrepancies between brain status and cognitive function. According to cognitive reserve theory, individuals who accumulate more cognitive reserve across their lifespan—through education, complex occupational roles, and engagement in other cognitively stimulating personal activities—are more likely to develop adaptable brains that can better compensate for, and withstand, brain diseases like Alzheimer's disease (AD).[2] Hence, individuals with higher cognitive reserve typically show a smaller degree of cognitive impairment, if any, than those with lower cognitive reserve despite similar levels of AD neuropathological burden.

Behavioral symptoms, also known as neuropsychiatric symptoms (NPS), are core features of dementia, but they often emerge alongside cognitive decline at early stages of AD, before dementia onset.[3] Mild behavioral impairment (MBI) is a construct that identifies changes in behavior (decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, abnormal perception or thought content) that are more relevant to dementia prognostication.[4] Importantly, MBI is characterized not only by a specific collection of NPS that are associated with elevated dementia risk, but by a specific natural history; NPS may be considered MBI symptoms when later-life emergent (eg, age ≥ 50 years) and persistent, which improves specificity for underlying neurodegenerative disease.[5] Indeed, MBI is linked to higher progression rates to mild cognitive impairment (MCI) and dementia, lower reversion rates from MCI to normal cognition,[6] and a greater burden of AD biomarkers, compared to non-MBI NPS (ie, not later-life emergent and persistent).[7–9]

Several parallels have been observed between cognition and behavior in preclinical and prodromal AD. Similar to MCI, persons with MBI are at higher risk of dementia,[10] show lower amyloid beta (Aβ)42/40 and higher phosphorylated tau,[8] neurofilament light,[5] and medial temporal lobe atrophy.[11] In memory clinic patients, MBI is present in as many as 37% of patients with subjective cognitive decline (SCD) and 54% of patients with MCI.[12] These data suggest high comorbidity between cognition and behavior. Still, MBI differs from MCI: associations of MBI with incident dementia and AD biomarkers persist even after accounting for individual differences in cognition.[13] Furthermore, MBI can manifest in advance of or even absent cognitive decline.[14]

The similarities between cognitive and behavioral changes across the AD continuum suggest possible overlapping etiology. Yet, it remains unclear whether factors that protect against later-life cognitive impairment (eg, cognitive reserve) also protect against behavioral change. The primary aim of this study was to investigate the relationship

between cognitive reserve and MBI in a cohort of older persons without dementia. We hypothesized that MBI would have lower frequency and severity in those with greater cognitive reserve; in other words, cognitive reserve may help preserve behavioral function in the presence of aging or disease, analogous to its role in preserving cognitive function. To test this hypothesis, we developed a novel cognitive reserve composite measure comprising known sociobehavioral proxies of cognitive reserve. Secondary objectives were to evaluate associations of cognitive reserve with individual MBI domains and to explore specific cognitive reserve domain associations with cognitive and behavioral outcomes.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using PubMed and Google Scholar. The relationship between cognitive reserve and neuropsychiatric symptoms, especially in advance of dementia, has not been fully explored.
2. **Interpretation**: Our findings show that cognitive reserve, when operationalized using education, occupation, and personal activity proxy measures, is associated with higher scores on neuropsychological tests and everyday cognitive function. Moreover, cognitive reserve was associated with lower odds of mild behavioral impairment (MBI) and less severe MBI symptoms in dementia-free older persons, particularly for impulse dyscontrol and social inappropriateness.
3. **Future directions**: More research is needed to extend evidence that cognitive reserve may apply to behavior in addition to cognition. Future studies must disentangle possible pathways through which cognitive reserve may affect both cognitive and behavioral outcomes across the neurocognitive continuum, explore common etiologies for these symptoms, and monitor outcomes longitudinally to better understand these relationships.

2 | METHODS

2.1 | Study design

The Canadian Platform for Research Online to Investigate Health, Quality of Life, Cognition, Behavior, Function, and Caregiving in Aging (CAN-PROTECT) is an online longitudinal observational cohort study, focusing on brain aging in dementia-free community-dwelling adults. Annually, participants and their study partners are asked to complete assessments of demographics, health, cognition, behavior, function, lifestyle, and more. Participants have up to 6 months from registration to complete all assessments, and several assessments are optional. Ethics approval for the study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary (REB21-1065). A detailed description of the study has been published elsewhere.[15]

The present analysis was a complete case analysis that used baseline data from 1204 participants aged ≥50 years (Figure 1). Specifically, from the initial cohort of 2372 participants considered, exclusions were due to age <50 years ($n = 240$), as per the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment MBI criteria,[4] and incomplete neuropsychological test battery ($n = 550$), lifestyle questionnaire ($n = 365$), Everyday Cognition (ECog-II) scale ($n = 9$), and MBI Checklist (MBI-C; $n = 4$). Participants with missing data were primarily excluded for having not yet completed the required study assessments, some of which were optional, at the time of analysis.

2.2 | Cognitive reserve operationalization

We devised a cognitive reserve score (CRS) using established proxy measures grouped into three domains: education (2 items), occupation (5 items), and personal activities (6 items) (Table 1).[2] Items were from the demographic and lifestyle questionnaires in CAN-PROTECT. The education domain included highest educational level achieved and total years of education. The occupation domain covered the type of occupation, self-reported cognitive demands of the job, and the highest complexity level of work involving data, people, and objects.[16] The personal domain included musicality (playing an instrument), multilingualism, and regular participation in word/number puzzles and/or computer-based brain training games. All items were coded so that higher scores reflected greater educational attainment, occupational complexity, or leisure activity engagement.

Each cognitive reserve domain score was computed by dividing the sum of all domain item scores by the maximum possible score. The CRS was then calculated as the mean of these three normalized domain scores. As the relative influence of each domain on cognitive reserve has not yet been fully explored, we assumed equal weighting across education, occupation, and personal domains.

$$CRS = \frac{\frac{\text{Sum of education items}}{\text{Education domain maximum}} + \frac{\text{Sum of occupation items}}{\text{Occupation domain maximum}} + \frac{\text{Sum of personal items}}{\text{Leisure domain maximum}}}{3}$$

The CRS formula yielded a score ranging from 0 to 1; higher CRS indicated greater cognitive reserve.

2.3 | Cognitive function

The CAN-PROTECT neuropsychological test battery was used to evaluate objective cognitive function. The battery comprised six cognitive tests: Trail Making B (visual attention and task switching),[17] Switching Stroop (visual attention and task switching),[18] Self-Ordered Search (spatial working memory),[19] Paired Associate Learning (visual episodic memory),[20] Verbal Reasoning (general intelligence and grammatical reasoning),[21] and Digit Span (working memory).[22] These tests, validated for online use in healthy older persons,[23,24] were completed on a

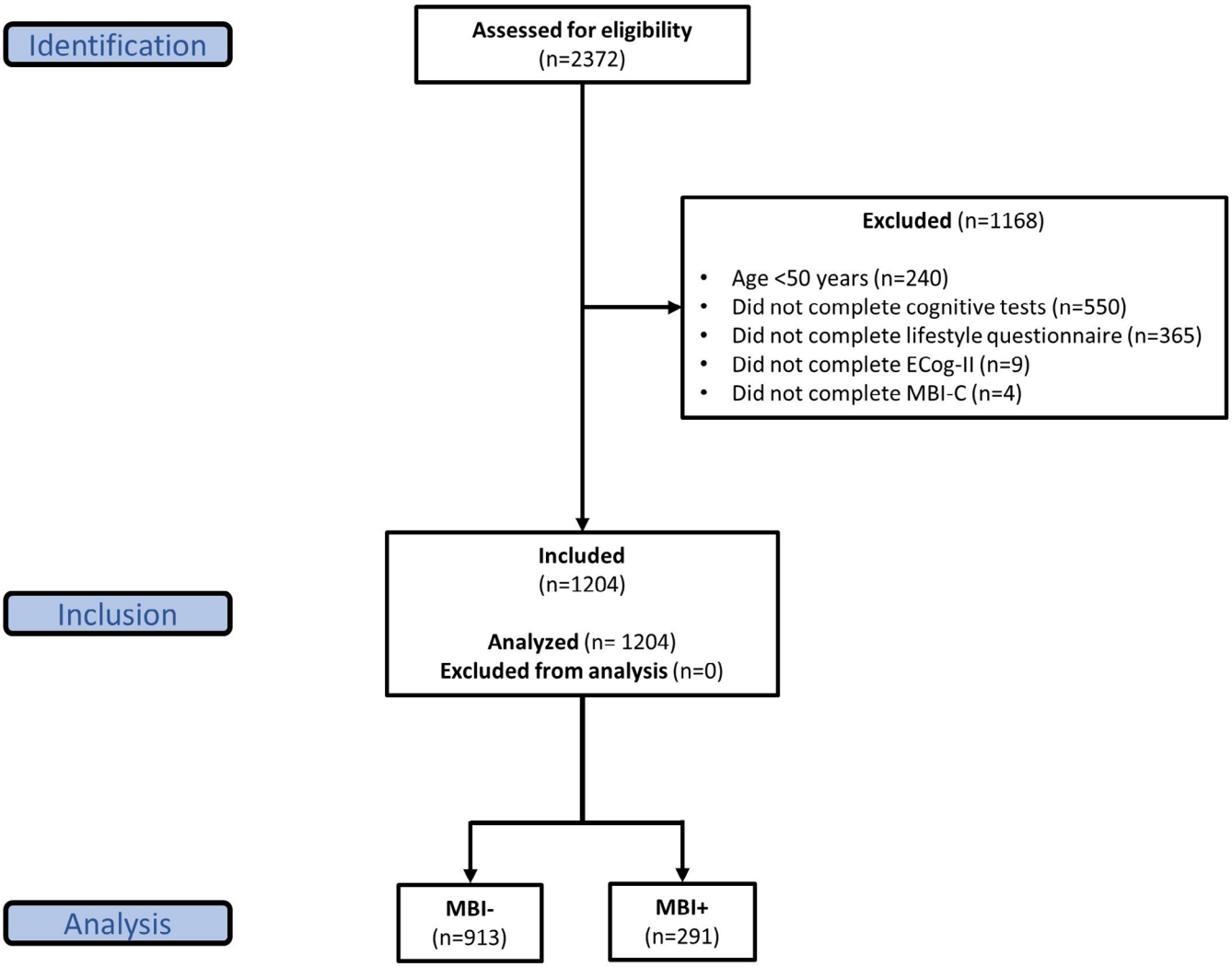

FIGURE 1 Participant flow diagram. ECog-II, Everyday Cognition II scale; MBI-C, Mild Behavioral Impairment Checklist; MBI, mild behavioral impairment.

computer device. Detailed descriptions of these tests have been published elsewhere.[15,23] Participants were instructed to complete the cognitive test battery up to three times within a 1-week period, annually throughout the duration of the study, which has been shown to reduce variability with minimal learning effects.[24] Scores were averaged across completions for participants who completed the battery more than once. Each battery session was time-restricted to ensure data quality. For the present study, cognitive test battery data were only used if the battery was completed within the time limit.

CAN-PROTECT also includes several self-reported assessments of cognitive function. The primary subjective tool was the revised Everyday Cognition (ECog-II) scale.[25] The scale evaluates changes in everyday cognition and function related to memory (9 items), language (9 items), visuospatial function (8 items), and executive function (15 items). Each item is scored 0 to 3 (0 = no change, 1 = occasionally worse, 2 = consistently a little worse; 3 = much worse) relative to a participant's own baseline. If the item does not apply, the participant can respond "I do not know" or "Not applicable." We operationalized subjective cognitive decline status (SCD+) based on a score of ≥2 (ie, consistently a little or much worse) on any ECog-II item.[26] The total ECog-II score was calculated by summing all applicable item scores.

2.4 | Mild behavioral impairment

MBI symptom severity was assessed using the self-reported MBI Checklist (MBI-C).[27] The MBI-C is designed to capture MBI symptoms in older persons without dementia according to the International Society to Advance Alzheimer's Research and Treatment–Alzheimer's Association (ISTAART-AA) MBI research diagnostic criteria. The self-reported MBI-C has been previously validated in online settings.[28]

Briefly, the MBI-C comprises 34 items pertaining to five domains: decreased motivation (6 items), affective dysregulation (6 items), impulse dyscontrol (12 items), social inappropriateness (5 items), and abnormal perception or thought content (5 items). Participants indicated whether each symptom had been present for a minimum

TABLE 1 Cognitive reserve score operationalization.

Domain	Domain range	Item	Item range
Education	1–35	Highest level of education completed	1–9
		Total number of years of education	0–26
Occupation	0–41	Type of occupation	0–15
		Self-reported cognitively demanding occupation	0, 5
		Highest level of complexity of work related to data	0–7
		Highest level of complexity of work related to people	0–7
		Highest level of complexity of work related to things	0–7
Personal	1–31	Musical instrument playing	0–5
		Number of languages spoken	1–6
		Word puzzles	0–5
		Number puzzles	0–5
		Computer brain training games	0–5

Note: The domain score for each cognitive reserve domain is calculated by dividing the domain sum by the corresponding domain maximum. The total cognitive reserve score is the average of the three domain scores.

of 6 months and represented a change from longstanding patterns of behavior, thereby fulfilling MBI criteria. If these symptoms were present, participants then rated symptom severity on a scale from 1 to 3, with higher scores indicating greater severity. Domain scores were calculated by summing all items within each domain, and global MBI symptom severity (range = 0 to 104) was calculated as the sum of domain scores. Participants with an MBI-C score of ≥8 were classified as MBI+, consistent with past studies in pre-dementia samples.[29] Although ISTAART-AA MBI criteria traditionally exclude persons with psychiatric conditions from MBI case ascertainment,[4] this was not necessary here as the MBI-C was developed to operationalize the MBI-C criteria, purposefully eliciting later-life emergent and persistent symptoms that represent change from longstanding behavior or personality.[27]

2.5 | Statistical analysis

Demographic, CRS, cognitive, and behavioral measures were summarized for the entire cohort and stratified by MBI status using means, standard deviations (SDs), ranges, and percentages. To compare participants with or without MBI in these descriptive variables, we used independent samples *t*-tests for continuous variables or chi-squared tests for categorical variables. As several CAN-PROTECT questionnaires were optional, we attempted to identify potential self-selection bias by comparing the demographics of participants excluded due to incomplete assessments with those included for analysis.

Prior to statistical modeling, neuropsychological test scores were normalized by age and sex within the CAN-PROTECT cohort. Specifically, each neuropsychological test was modelled as a function of age and sex using linear regression. The resulting standardized residuals for each participant were treated as a measure of test performance relative to the expected value given their demographic profile. A global cognitive measure was calculated as the sum of standardized scores across all six tests. Education was excluded from this normalization procedure as it was a component of the CRS. Moreover, this data-driven approach was employed as there are no existing normative data for the CAN-PROTECT neuropsychological battery.

We examined convergent validity of the CRS by modeling CRS associations with neuropsychological test performance, SCD status, and ECog-II total score using linear, logistic, and negative binomial regressions, respectively. Model selection was based on the distribution of residuals, linearity or non-linearity of the relationship, and the presence of heteroscedasticity or overdispersion informed by visual inspection of scatter and residual plots. As the residuals in the linear regression models for Trail Making B, Self-Ordered Search, and Digit Span were not normally distributed, the reported 95% confidence intervals (95% CIs) for these models were bias corrected using bootstrapping with 5000 simulations; this procedure does not make any assumptions about normality.

To test our hypothesis, we modeled the association between CRS and MBI status using a logistic regression. For MBI total symptom severity, a negative binomial regression was used, given that the statistical distribution of the MBI-C total scores resembled a Poisson distribution (ie, right-skewed whole numbers) with overdispersion (variance > mean). Coefficients were exponentiated (exp[b]), and as such, represent the factor change in the outcome variable for every 1 SD rise in CRS. Good model fit of each negative binomial model was confirmed prior to reporting results based on visual inspection of rootograms. Where relevant, we explored the effect of controlling for MBI-C in models of ECog-II, and measures of cognition in models of MBI, to discern if CRS associations could be explained by changes in behavior or cognition, respectively.

Inverse probability of treatment weighting (IPTW) was used to address potential confounders by balancing observed covariates including age, sex, marital status, and ethnocultural origins within the sample. As the CRS was continuous, generalized propensity scores were derived from multivariable linear regression. These scores were then applied as regression weights to adjust each model accordingly. The overall performance of IPTW was confirmed by inspecting the coefficient of variance, effective sample sizes, and standardized mean differences of covariates.

A secondary analysis examined CRS associations with individual MBI domain symptom severities. Further, individual CRS domain associations with global neuropsychological test performance, ECog-II total score, and MBI-C total score were also explored. Secondary analyses

used the same statistical modeling approaches described previously, only varying the outcome or exposure variables, as appropriate. A statistical significance threshold of $p < 0.05$ was used for primary hypothesis tests. All analyses were conducted using *R* version 4.3.0.

3 | RESULTS

3.1 | Sample characteristics

Table 2 presents the demographic and clinical characteristics of participants ($n = 1204$). The cohort predominantly consisted of participants who self-reported being assigned female sex at birth (80.5%) and being married (77.7%), with a mean ± SD age of 64.6 ± 7.3 years and 15.8 ± 4.4 years of education completed. Participants mainly identified themselves as having North American (48.5%) or European (84.6%) ethnocultural origins (multi-select origins allowed). SCD+ and MBI+ were present in 27.4% and 24.2% of all participants, respectively. Compared to those excluded for not completing the assessments required for analysis, included participants were more likely to have been assigned female sex at birth (75.4% vs 80.5%, $p = 0.006$), but there were no significant differences in any other demographic variables.

3.2 | Cognitive reserve and cognitive performance

The CRS showed convergent validity with neuropsychological test performance (Figure 2), with each SD rise in CRS associated with higher normalized global neuropsychological test performance ($\beta = 0.09$, 95% confidence interval [CI]: [0.07, 0.12], $p < 0.001$) (Table 3). These associations were also present for each individual neuropsychological test: Each SD rise in CRS was associated with a shorter Trail Making B time ($\beta = -0.12$, 95% CI: [−0.16, −0.07], $p < 0.001$) and higher scores on Switching Stroop ($\beta = 0.16$, 95% CI: [0.11, 0.21], $p < 0.001$), Self-Ordered Search ($\beta = 0.12$, 95% CI: [0.07, 0.18], $p < 0.001$), Paired Associates Learning ($\beta = 0.09$, 95% CI: [0.04, 0.14], $p < 0.001$), Verbal Reasoning ($\beta = 0.19$, 95% CI: [0.14, 0.24], $p < 0.001$), and Digit Span ($\beta = 0.12$, 95% CI: [0.07, 0.16], $p < 0.001$). In other words, higher CRS was associated with better performance across the domains of executive function, attention, task-switching, visual episodic memory, verbal reasoning, and working memory.

In terms of self-reported cognitive function, each SD rise in CRS corresponded to a 0.86-fold (95% CI: [0.76, 0.98], $p = 0.03$) lower odds of SCD+ status and a 0.94-fold (95% CI: [0.89, 0.99], $p = 0.03$) lower ECog-II total score; equivalent to approximately a 1-point decrease for participants with a ECog-II score of 16. Neither association remained statistically significant upon controlling for the MBI-C total score (Table 3).

All CRS domains were associated with higher global neuropsychological test performance, but only the education domain was associated with a lower ECog-II total score (Table 4).

3.3 | Cognitive reserve and behavior

In analyzing CRS as a predictor of MBI, we found that each SD rise in CRS corresponded to a 0.81-fold (95% CI: [0.71, 0.93], $p = 0.003$) lower odds of MBI+ status and a 0.90-fold [95% CI: [0.83, 0.97], $p = 0.008$) lower MBI-C total score; equivalent to a 1-point decrease for participants with an MBI-C score of 10. None of these associations could be fully explained by changes in cognition as measured by global neuropsychological test performance or ECog-II total score (Table 3). The secondary analysis exploring MBI domains revealed similar associations between greater CRS and lower MBI symptom severity in the domains of impulse dyscontrol and social inappropriateness (Figure S1): Each SD rise in CRS was linked to 0.87-fold (95% CI: [0.79, 0.95], $p = 0.002$) and 0.82-fold (95% CI: [0.69, 0.97], $p = 0.02$) lower domain severity scores, respectively. CRS associations with other MBI domains can be found in Table 3. Only the education domain was associated with a lower MBI-C total score (Table 4).

4 | DISCUSSION

In this study, cognitive reserve was operationalized using a combination of factors related to education, occupation, and personal factors. The CRS demonstrated convergent validity with better performance on various neuropsychological tests and fewer changes in self-reported cognitive function. Importantly, higher cognitive reserve was linked to lower odds and severity of MBI symptoms among dementia-free older persons, even after accounting for individual differences in cognition, with the greatest effects for impulse dyscontrol and social inappropriateness. These findings suggest that engagement in activities known to preserve cognitive function in aging and disease may also prevent the emergence of behavioral symptoms.

MBI has been linked to numerous adverse health and social outcomes. These include greater caregiver burden,[30] hearing loss,[31] gait deficits,[32] and frailty.[33] Engaging in activities that enrich cognitive reserve throughout one's life may not only protect against cognitive decline but also mitigate negative consequences associated with MBI.

To our knowledge, few studies have explored cognitive reserve theory in relation to NPS across the neurocognitive spectrum. Previous research on the relationship between cognitive reserve and NPS have been conducted mostly in persons with AD, where lower levels of education were associated with apathy, depression, and psychosis.[34–37] More recently, these relationships have been extended to populations earlier in the AD continuum, such as amnestic MCI, where lower education was associated with apathy and aggression.[38] The concept of "behavioral reserve," particularly in the context of frontotemporal dementias, has linked higher educational levels to less disinhibition, but not to other behavioral symptoms.[39,40]

However, several older studies on AD dementia did not find an association between education and specific NPS, or observed associations in the opposite direction.[41–43] These inconsistencies have been attributed to limitations in the operationalization of cognitive reserve

TABLE 2 Study participant characteristics.

Variable	Total	MBI−	MBI+	*p*
N	1204	913	291	
Age in years	64.6 (7.3), 50–89	65.2 (7.1), 50–89	62.7 (7.6), 50–88	<0.001
Sex (% female)	969 (80.5)	741 (81.2)	228 (78.4)	0.33
Years of education	15.8 (4.4), 0–30	16 (4.4), 0-30	15.2 (4.5), 2–30	0.004
MCI status	9 (0.7)	4 (0.4)	5 (1.7)	0.07
Marital status				0.03
Married	935 (77.7)	723 (79.2)	212 (72.9)	
Other	269 (22.3)	190 (20.8)	79 (27.1)	
Ethnocultural group				
North America	581 (48.3)	437 (47.9)	144 (49.5)	0.68
Europe	1016 (84.4)	767 (84.0)	249 (85.6)	0.59
Caribbean	10 (0.8)	6 (0.7)	4 (1.4)	0.42
South America	9 (0.7)	6 (0.7)	3 (1.0)	0.80
Africa	11 (0.9)	8 (0.9)	3 (1.0)	1
Asia	38 (3.2)	31 (3.4)	7 (2.4)	0.52
Oceania	6 (0.5)	6 (0.7)	0 (0)	0.36
Cognitive reserve score				
Total	0.49 (0.11), 0.16–0.83	0.50 (0.11), 0.16–0.83	0.48 (0.11), 0.21–0.82	0.01
Education	0.74 (0.17), 0.1–1.00	0.75 (0.17), 0.1–1.00	0.70 (0.17), 0.23–1.00	<0.001
Occupation	0.48 (0.18), 0.02–0.98	0.48 (0.18), 0.02–0.98	0.47 (0.18), 0.07–0.95	0.79
Personal	0.27 (0.17), 0.03–0.87	0.27 (0.17), 0.03–0.87	0.26 (0.16), 0.03–0.71	0.40
Cognitive tests				
Trail making (sec)	61.3 (20.7), 26.9–258	61.5 (20.6), 26.9–258	60.8 (20.9), 29.3–210.2	0.62
Switching Stroop	38.1 (14.2), 0–83.3	38.3 (14.3), 0–83.3	37.6 (14), 0–74.7	0.49
Self-ordered search	6.6 (2.6), 0–12	6.6 (2.5), 0–12	6.6 (2.7), 0–12	0.90
Paired associates learning	3.9 (0.9), 0–7	4 (0.9), 0–7	3.9 (0.8), 0–7	0.50
Verbal reasoning	31.7 (9.6), −1–67	31.6 (9.5), −1–67	32.0 (10), 7–60	0.53
Digit span	7.0 (1.9), 0–20	7 (20), 0–20	6.8 (1.7), 0–15	0.17
SCD status	330 (27.4)	177 (19.4)	153 (52.6)	<0.001
ECog-II total	11.8 (11.4), 0–99	9.2 (8.5), 0–74	20 (14.9), 0–99	<0.001
MBI-C severity				
Global	5.2 (7.1), 0–65	2.1 (2.1), 0–7	14.9 (8.2), 8–65	<0.001
Decreased motivation	1.6 (2.5), 0–18	0.6 (1.0), 0–5	4.8 (3), 0–18	<0.001
Affective dysregulation	1.7 (2.5), 0–16	0.7 (1.0.), 0–6	4.7 (3.2), 0–16	<0.001
Impulse dyscontrol	1.4 (2.3), 0–20	0.6 (0.9), 0–5	4.1 (3.2), 0–20	<0.001
Social inappropriateness	0.2 (0.7), 0–8	0.1 (0.3), 0–2	0.7 (1.2), 0–8	<0.001
Psychosis	0.2 (0.6), 0–5	0.1 (0.3), 0–2	0.7 (1), 0–5	<0.001

Note: MBI− and MBI+ groups were defined according to a score of ≥8 on the MBI-C. Numeric variables are shown in the mean (standard deviation), range. Categorical variables are shown in *n* (%). All values are rounded to one decimal place, except for cognitive reserve scores (ranging 0–1) and *p*-values which are rounded to two or three decimals, as appropriate.

Abbreviations: ECog-II, revised Everyday Cognition scale; MBI, mild behavioral impairment; MBI-C, Mild Behavioral Impairment Checklist; MCI, mild cognitive impairment; SCD, subjective cognitive decline.

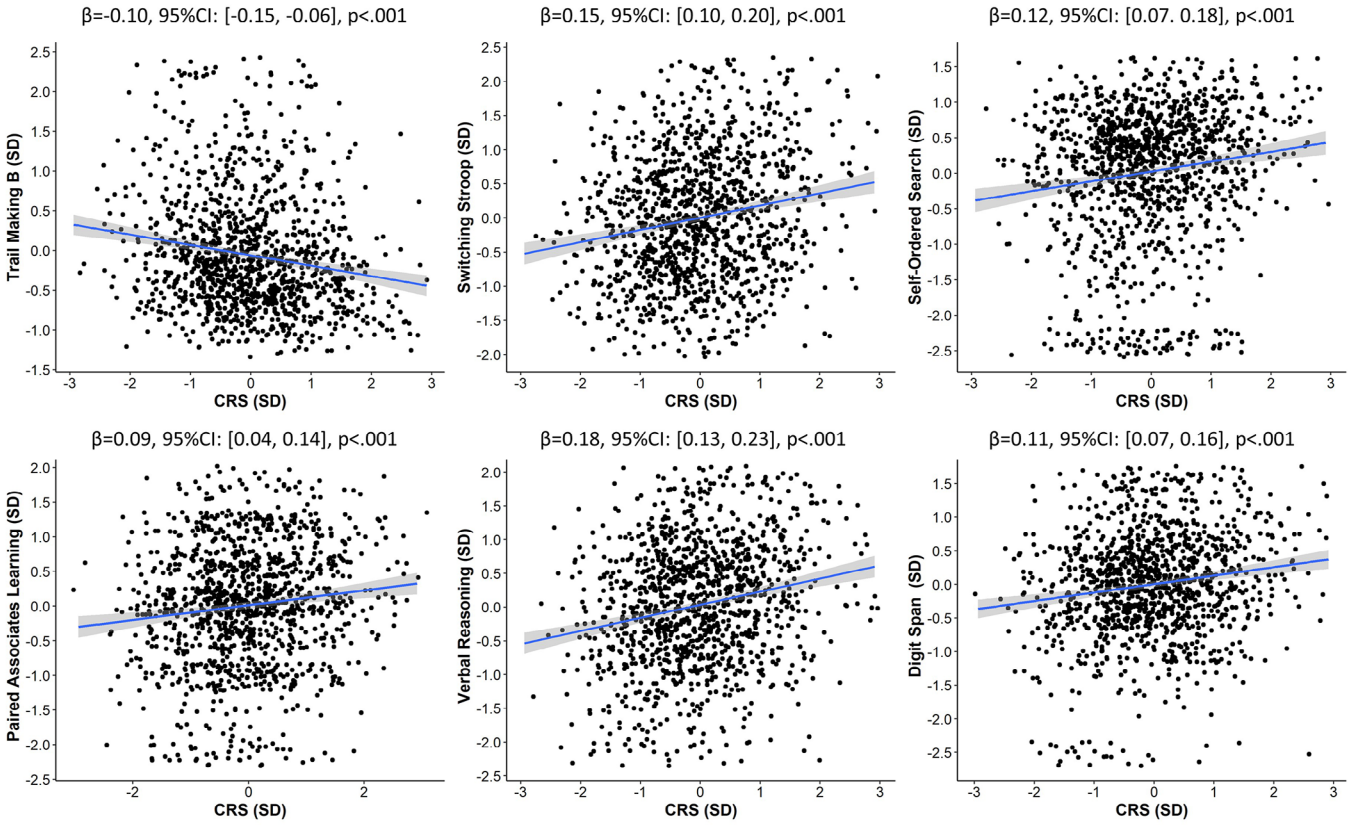

FIGURE 2 Scatterplots for associations between CRS and neuropsychological test performance. All exposure and outcome variables have been standardized to have a mean of 0 and a SD of 1. Neuropsychological test scores were normalized by age and sex. Higher CRS values indicate greater cognitive reserve. Higher scores on all neuropsychological tests indicate better performance except for Trail Making B, where lower scores indicate better performance. Shaded boundaries surrounding the line of best fit indicate 95% confidence intervals. Size of points indicate the inverse probability of treatment weight used for linear regression. CRS, cognitive reserve score; SD, standard deviation.

(ie, not accounting for non-educational reserve proxies like occupational attainment and leisure activities).[37] We propose two further explanations. First, faster rates of cognitive decline are frequently observed in persons with higher cognitive reserve after symptom onset, consistent with cognitive reserve theory, as they tend to be at more advanced disease stages before showing symptoms than their low reserve counterparts.[44] In other words, the benefits of cognitive reserve are less pronounced, and may sometimes even appear deleterious by the time patients receive an AD dementia diagnosis. Second, NPS has historically been measured in a manner that was not necessarily specific to underlying neurodegenerative disease, which the MBI construct aims to address. Key differences between the present study and previous investigations are in our operationalization of cognitive reserve (which accounts for education, occupation, and leisure), sample (all dementia-free and mostly cognitively normal), and use of MBI—a conceptualization of NPS that leverages risk associated specifically with symptoms that emerge de novo in late life and persist—to improve specificity as a neurodegenerative disease marker.[8,9]

A plausible mechanism through which cognitive reserve may indirectly influence NPS might involve the protective effect of cognitive reserve on cognition. Individuals with lower cognitive reserve are more prone to cognitive impairment, which may exacerbate existing NPS, making symptoms more easily detected. However, previous research on cognitive reserve and NPS did account for cognitive impairment, either through cognitive assessments or dementia staging, and still observed a cognitive reserve-NPS relationship.[37,39,40] Similarly, in the present study, cognitive reserve continued to show a significant association with MBI after adjusting for both measures of neuropsychological test performance and self-reported cognitive function. These findings suggest that the link between cognitive reserve and MBI cannot be fully accounted for by individual differences in cognition.

Several other mechanisms may explain the link between cognitive reserve and MBI. Greater cognitive reserve may buffer against both cognitive and behavioral decline through enhanced efficiency or flexibility of the default mode network (DMN).[45–47] Notably, reduced functional connectivity within the DMN has been observed in dementia-free older persons with MBI.[7] Additionally, individuals with higher cognitive reserve may engage more frequently in lifestyle activities linked to lower AD and MBI risk, like physical exercise and healthy diet.[48] These lifestyle factors have been suggested as other potential cognitive reserve proxies,[49] although their effect on cognition and behavior may be challenging to isolate from their effect on vascular risk factors and inflammation, both known to influence cognition, NPS, and dementia risk.[50,51] To further elucidate how cognitive reserve

TABLE 3 Cognitive reserve score associations with cognition and behavior.

Outcome variable	β	95% CI	p
Neuropsychological test performance			
Global	0.09	0.07–0.12	<0.001
Trail making	−0.12	−0.16 to −0.07	<0.001
Switching Stroop	0.16	0.11–0.21	<0.001
Self-ordered search	0.12	0.07–0.18	<0.001
Paired associate learning	0.09	0.04–0.14	<0.001
Verbal reasoning	0.19	0.14–0.24	<0.001
Digit span	0.12	0.07–0.16	<0.001
	OR	**95% CI**	**p**
SCD status	0.86	0.76–0.98	0.03
SCD status *(adj. MBI-C total score)*	0.91	0.79–1.04	0.18
MBI status	0.81	0.71–0.93	0.003
MBI status *(adj. neuropsychological tests)*	0.81	0.70–0.93	0.003
MBI status *(adj. ECog-II total score)*	0.83	0.71–0.96	0.01
	exp(b)	**95% CI**	**p**
ECog-II total score	0.94	0.89–0.99	0.03
ECog-II total score *(adj. MBI total score)*	0.98	0.93–1.02	0.33
MBI-C scores			
Total	0.90	0.83–0.97	0.008
Total *(adj. neuropsychological tests)*	0.90	0.84–0.98	0.01
Total *(adj. ECog-II total score)*	0.93	0.87–1.00	0.05
Decreased motivation	0.91	0.83–1.00	0.05
Affective dysregulation	0.93	0.85–1.01	0.09
Impulse dyscontrol	0.87	0.79–0.95	0.002
Social inappropriateness	0.82	0.69–0.97	0.02
Psychosis	0.92	0.78–1.10	0.37

Note: The exposure variable for all models was standardized CRS. Standardized coefficients (β) were estimated from linear regression and represent the standard deviation change in global neuropsychological test performance for every SD rise in the CRS. Confidence intervals for Trail Making B, Self-Ordered Search, and Digit Span were bias-corrected using bootstrapping to account for non-normally distributed residuals. Logistic regression models were used to estimate ORs, indicating a change in odds per 1 SD rise in CRS. Exponentiated coefficients (exp[b]) were estimated from negative binomial regression, and as such, represent the factor change in the outcome variable for every SD rise in CRS. All models were conducted on a propensity score-weighted sample to account for age, sex, ethnocultural origin, and marital status.
Abbreviations: adj, additionally adjusting for; CI, confidence interval; CRS, cognitive reserve score; ECog-II, Everyday Cognition II scale; MBI, mild behavioral impairment; MBI-C, Mild Behavioral Impairment Checklist; OR, odds ratio; SCD, subjective cognitive decline.

TABLE 4 Cognitive reserve domain associations with cognition and behavior.

Outcome variable CRS domain	β	95% CI	p
Global neuropsychological test performance			
CRS—Education	0.08	0.05–0.10	<0.001
CRS—Occupation	0.06	0.03–0.08	<0.001
CRS—Personal	0.05	0.03–0.08	<0.001
	exp(b)	**95% CI**	**p**
ECog-II Total score			
CRS—Education	0.93	0.88–0.98	0.004
CRS—Occupation	0.99	0.94–1.04	0.62
CRS—Personal	0.97	0.92–1.03	0.34
MBI-C Total score			
CRS—Education	0.84	0.78–0.91	<0.001
CRS—Occupation	0.96	0.89–1.04	0.32
CRS—Personal	1.01	0.93–1.09	0.88

Note: Standardized coefficients (β) were estimated from linear regression and represent the SD change in global neuropsychological test performance for every SD rise in the CRS domain. Exponentiated coefficients (exp[b]) were estimated from negative binomial regression, and as such, represent the factor change in the outcome variable for every SD rise in the CRS domain. All models were conducted on a propensity score-weighted sample to account for age, sex, ethnocultural origin, and marital status.
Abbreviations: CI, confidence interval; CRS, cognitive reserve score; ECog-II, Everyday Cognition II scale; MBI, mild behavioral impairment; MBI-C, Mild Behavioral Impairment Checklist; SD; standard deviation.

influences behavioral changes linked to dementia risk in older persons, future neuroimaging and lifestyle research, particularly involving longitudinal designs, are essential.

A key feature of the present study is the comprehensive operationalization of cognitive reserve, encompassing education, occupation, and personal activities as proxy measures. This approach, validated against neuropsychological test performance and self-reported measures of cognitive function in CAN-PROTECT, considers a wider variety of cognitive reserve-enriching activities across the entire lifespan. While education and occupational complexity are commonly used as cognitive reserve proxies,[1] the literature also supports specific personal activities as significant contributors to cognitive reserve.[49] Our findings demonstrate that all three cognitive reserve domains are linked to better neuropsychological test performance, but only the education domain was associated with self-reported cognitive function and MBI. These discrepancies suggest that, while all cognitive reserve domains may support better cognitive performance cross-sectionally in later life, early-life contributors to cognitive reserve like education may protect more strongly against cognitive and behavioral changes in older persons. Nevertheless, the relative protective strength of various cognitive reserve proxies may be the target of future investigation.

The inclusion of physical activity and other proxy measures of cognitive reserve into the composite CRS should be considered for future research, with an awareness of the complex interactions that could be at play. Furthermore, it should be acknowledged that several other methods to quantify cognitive reserve exist, including structural and functional imaging approaches, some of which have been proposed as more direct measures of cognitive reserve.[1] Imaging measures are not currently available in CAN-PROTECT, and hence could not be used to quantify cognitive reserve in the present study. Finally, the

cross-sectional design of this study precludes inferences about causal mechanisms.

5 | CONCLUSION

The traditional application of cognitive reserve theory has been able to account for variability in the relationship between brain aging or brain disease and cognitive function, thus the moniker "cognitive reserve." However, our study provides preliminary evidence for a broader conceptualization of cognitive reserve, extending its applicability to behavior. We found that behavioral symptoms were less prevalent and severe in those with greater cognitive reserve, independent of cognitive changes. Future work must disentangle possible pathways through which cognitive reserve may affect both cognition and behavior, explore common etiologies for these symptoms, and monitor outcomes longitudinally to better understand these relationships.

AUTHOR CONTRIBUTIONS

Dylan X. Guan: Conceptualization, software, formal analysis, investigation, data curation, writing—original draft, visualization. Moyra E. Mortby: Writing—review & editing. G Bruce Pike: Writing—review & editing. Clive Ballard: Software, writing—review & editing. Byron Creese: Software, writing—review & editing. Anne Corbett: Software, writing—review & editing. Ellie Pickering: Software, writing—review & editing. Adam Hampshire: Software, writing—review & editing. Pamela Roach: Investigation, writing—review & editing. Eric E. Smith: Investigation, writing—review & editing. Zahinoor Ismail: Conceptualization, investigation, resources, writing—original draft, writing—review & editing, supervision, funding acquisition

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CONFLICT OF INTEREST STATEMENT

E.E.S. reported consulting (unpaid) for Alnylam Pharmaceuticals and Eli Lilly, and an advisory board (unpaid) for Eisai. Z.I. has served as an advisor/consultant to CADTH, Eisai, Lilly, Lundbeck/Otsuka, Novo Nordisk, and Roche. The other authors have no relevant conflicts of interest to disclose. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants provided informed consent. The Conjoint Health Research Ethics Board at the University of Calgary Ethics provided approval for CAN-PROTECT (REB21-1065).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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