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Cognitive reserve moderates the association between cerebral blood flow and language performance in older adults with mild cognitive impairment

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ABSTRACT

Higher cognitive reserve (CR) may offer protection from cognitive changes associated with reduced cerebral blood flow (CBF). We investigated CR as a moderator of the effect of CBF on cognition in older adults with mild cognitive impairment (MCI; N = 46) and those who are cognitively unimpaired (CU; N = 101). Participants underwent arterial spin labeling MRI, which was used to quantify CBF in 4 a priori regions. Estimated verbal intelligence quotient (VIQ) served as a proxy for CR. Multiple linear regressions examined whether VIQ moderated associations between CBF and cognition and whether this differed by cognitive status. Outcomes included memory and language performance. There were 3-way interactions (CBF*VIQ*cognitive status) on category fluency when examining hippocampal, superior frontal, and inferior frontal CBF. Follow-up analyses revealed that, within the MCI but not CU group, there were CBF*VIQ interactions on fluency in all a priori regions examined, where there were stronger, positive associations between CBF and fluency at higher VIQ. Conclusion: In MCI, higher CR plays a role in strengthening CBF-fluency associations.

1. Introduction

The concept of cognitive reserve (CR) has been proposed to explain how 2 individuals with differing brain pathology can perform at the same cognitive level. It was developed from the repeated observation that there is no consistent one-to-one relationship between degree of brain pathology and its clinical manifestations (Stern et al., 1999). Although CR has been widely studied, there is no consistent way that it has been measured. One common method involves using education level as a proxy, and this work has shown that individuals with higher levels of education are at lower risk of developing dementia (Meng and D'Arcy, 2012). Other proxies for CR include occupational attainment (Mortel et al., 1995), leisure activities (Scarmeas et al., 2001), and literacy (Manly et al., 2003). One common method of measuring CR has been to use an estimate of premorbid intelligence as a proxy (Albert and Teresi, 1999); this continues to be a common method (Stern et al., 2020).

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CR has been applied to several disorders and conditions, but it has been studied perhaps most widely in aging and dementia. Early research suggested that higher education level and occupational attainment lower one's risk of developing dementia (Stern et al., 1994), as does engagement in leisure activities (Scarmeas et al., 2001). One review paper examining studies that operationalized CR via measures of education, occupational attainment, premorbid intelligence, or mental activities found that higher reserve, regardless of how it was defined, was associated with lowered risk for dementia (Valenzuela and Sachdev, 2006). However, once a critical threshold of Alzheimer's disease (AD) pathology is evident, individuals with higher CR then exhibit faster rates of cognitive decline (Stern et al., 1999). Thus, CR is thought to postpone clinical onset of dementia but is also then associated with a greater rate of decline once symptoms consistent with dementia appear. CR has also been studied in healthy older adult populations with mixed results. A recent meta-analysis found that associations between CR and cognition in cognitively unimpaired (CU) older adults were overall positive but modest, and depended on the specific CR proxy used (Opdebeeck et al., 2016).

CR has been examined as a moderator of brain-behavior relationships using a variety of neuroimaging methodologies. Functionally, CR is associated with increased connectivity in the cognitive control network in patients with mild cognitive impairment (MCI) (Franzmeier et al., 2017a). It has also been demonstrated that connectivity between the left lateral frontal cortex and default mode network, as well as between the left frontal cortex and dorsal attention network, is associated with CR in patients with MCI (Franzmeier et al., 2017b). CR has also been shown to be protective against the damaging effect of white matter hyperintensities (WMH) on cognitive functioning (Brickman et al., 2011), and has been shown to differentially regulate the frontoparietal control network in people with and without WMH (Chen et al., 2022).

Arterial spin labeling (ASL) is a non-invasive functional MRI technique that measures cerebral blood flow (CBF). This imaging technique labels water molecules in arterial flow as an endogenous tracer to quantify brain oxygen perfusion (Detre and Wang, 2002). In the aging literature, CBF has emerged as a potential biomarker for AD risk, with research showing that hypoperfusion measured using ASL can predict cognitive decline (Bangen et al., 2021; Sanchez et al., 2020) as well as progression from MCI to AD (Chao et al., 2010). These studies were also able to use CBF measurements to differentiate healthy older adults from those at risk for or diagnosed with AD. Investigating preclinical AD pathologic markers is crucial to increase the possibility of early identification and consequently intervention for AD.

No studies to date have used ASL to investigate the relationship between CBF, CR, and cognition. The primary aim of this study was to examine CR as a moderator of the relationship between CBF and cognition and to investigate whether this moderation is dependent on cognitive status (MCI or CU).

2. Materials and methods

2.1. ADNI Data Set

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

2.2. Participants

All participants included in ADNI were between the ages of 55 and 90 years, had completed at least 6 years of education, were Spanish or English speakers, had Geriatric Depression Scale scores <6 (possible score range 0–15) (Sheikh and Yesavage, 1986), had modified Hachinski Ischemic Scale scores <4, and were free from any significant neurological disease or systemic illness. ADNI was approved by the institutional review boards at participating institutions and written informed consent was obtained. Participants were included in this study if they were not diagnosed with clinical dementia and had arterial spin labeling data collected. This resulted in 200 participants. Of these, 61 met criteria for MCI and 139 were classified as CU (see Table 1 for demographics). Participants were classified as cognitively unimpaired or MCI according to Jak/Bondi actuarial neuropsychological MCI criteria (Bondi et al., 2014; Jak et al., 2009).

2.3. Neuropsychological scores

Confrontation naming was measured as score on the Boston Naming Test (BNT) or Multilingual Naming Test (MINT), depending on the cognitive battery administered at different ADNI recruitment waves. Category fluency was measured by the Animals category fluency test. Memory recall was measured by the Rey Auditory Verbal Learning Test (RAVLT) as number of words recalled following a 30-minute delay. Recognition memory was calculated from the RAVLT by subtracting false-positive errors from the number of words correctly recognized. Each of these measures was converted to a z-score that adjusted for age, sex, and education based on performance of a sample of cognitively normal ADNI participants who remained cognitively normal throughout their participation in the study ($n = 274$), consistent with previously published results (Weigand et al., 2021). Estimated verbal intelligence quotient (VIQ) from the American National Adult Reading Test (AmNART) was used as a proxy for CR (Rentz et al., 2017; Ryan and Paolo, 1992).

2.4. MR image acquisition and analysis

A description of ADNI MRI imaging data acquisition and processing is available online (www.loni.usc.edu). All images were acquired on 3T MR scanners from a single vendor (MAGNETOM Trio, Verio, and Skyra, Siemens). A resting state pulsed ASL scan was acquired utilizing QUIPS II with thin-slice TI1 periodic saturation sequence ("Q2TIPS") with echo-planar imaging (Luh et al., 1999). The sequence included the following parameters: inversion time of arterial spins (TI1) 700 ms, total transit time of the spins (TI2) 1900 ms, tag thickness 100 mm, tag to proximal slice gap 25.4 mm, repetition time 3400 ms, echo time 12 ms, field of view 256 mm, 64×64 matrix, 24 4 mm thick axial slices [52 tag + control image pairs], time lag between slices 22.5 ms. The ADNI protocol was validated across platforms and all imaging sites passed scanner validation tests (Jack Jr et al., 2008). A more detailed description of this has been previously reported (Bangen et al., 2017).

Detailed information describing the ASL MRI data acquisition and processing is available online at www.loni.usc.edu. In summary, the pipeline involves motion correction, using a rigid body transformation to align each ASL frame to the first frame, and conducting least squares fitting using SPM8. Perfusion weighted images are calculated as the difference between the mean of tagged and untagged ASL data sets. In order to account for signal decay during acquisition and allow for intensities in meaningful physiological units, perfusion weighted images were intensity scaled. Next, following geometric distortion correction, ASL images were

Table 1
Demographic Characteristics.

	MCI (N = 61)	CU (N = 139)	Between-group differences
Age	73.59 ± 7.20	73.60 ± 6.91	t = -0.045, p = 0.964, d = 0.002
Education	15.82 ± 2.91	16.26 ± 2.71	t = -2.89, p = 0.004, d = 0.16
Sex	32 M; 29 F	69 M; 70F	X^2 = 1.92, p = 0.166, V = 0.37
Race	57 White, 2 Black, 2 More Than One	129 White, 5 Black, 3 Asian, 2 More Than One	X^2 = 10.29, p = 0.113, V = 0.086
APOE e4 Frequency	None (51%), 1 (41%), 2 (8%)	None (67%), 1 (28%), 2 (4%)	X^2 = 68.47, p < 0.001, V = 0.221

Welch 2-sample *t*-tests were used for evaluating differences in age and education between the CU and MCI groups. X^2 tests were used to evaluate differences in sex, race, and APOE e4 carrier status between CU and MCI groups. "V" indicates Cramer's V. "d" indicates Cohen's d.

aligned to structural T1-weighted images. Given that we are interested in CBF in gray matter and therefore want to minimize the effects of the lower perfusion in white matter on our CBF estimates, we conducted a partial volume correction that assumes that CBF in gray matter is 2.5 times greater than in white matter. We then normalized the partial volume corrected perfusion weighted images by the reference image (i.e., an estimate of blood water magnetization) to convert the signal into physical units (mL/100 g tissue/min). Quality control procedures involved inspecting image quality and rating quality as pass or fail.

Four bilateral CBF ROIs were chosen for analyses as predilection sites for early AD: hippocampus, superior frontal gyrus, inferior frontal gyrus, and inferior temporal gyrus (Alafuzoff et al., 2008; Braak and Braak, 1997, 1991; Thal et al., 2002) . These variables were FreeSurfer derived and residualized by precentral gyrus CBF.

2.5. Statistical analyses

Prior to analyses, data were examined for violations of assumptions of the statistical procedures employed. Age, sex, and APOE ε4 status (carrier, single ε4 allele-carrier, double ε4 allele-carrier) were entered into all models as covariates. Cognitive measures were Box-cox transformed to improve normality of their distributions, and outliers greater or less than 3 standard deviations away from the mean were removed from all independent and dependent variables. Models that included CBF additionally adjusted for cerebral metabolism (baseline FDG-PET composite).

We examined 3-way interactions between regional CBF, VIQ, and cognitive status (MCI or CU) on each of the neuropsychological measures. We also examined the 2-way interaction between CBF and VIQ within each cognitive group on any of the cognitive measures that yielded a significant model in the 3-way interactions (category fluency). When examining main effects, VIQ was dichotomized by median splitting into high and low groups. All interaction models included the interaction, simple main effects, and covariates. All analyses were conducted in R.

Finally, to address potential inflation of type I error resulting from multiple comparisons, we applied the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995). We assessed results when the false discovery rate (FDR) was controlled at 0.05 across all 16 statistical tests.

3. Results

3.1. Demographic characteristics

Demographic characteristics of each group can be viewed in Table 1. The CU and MCI groups did not differ by average age, gender, or race. The MCI group had a significantly higher frequency of APOE ε4 carriers, and the CU group on average had a higher education level than the MCI group.

3.2. 3-Way interaction between CBF, VIQ, and cognitive status

Adjusting for age, gender, APOE status, and FDG uptake, there were significant 3-way interactions between regional CBF, VIQ, and cognitive status on category fluency performance when examining hippocampal (t = 2.98, p = 0.003), superior frontal (t = 3.76, p < 0.001), and inferior frontal CBF (t = 2.93, p == 0.004; Table 2) such that regional CBF was more strongly positively associated with category fluency in participants with high VIQ, yet who were classified as MCI. The same 3-way interaction involving inferior temporal CBF had a similar pattern but was statistically nonsignificant (t = 1.94, p == 0.055). The 3-way interactions between regional CBF, VIQ, and cognitive status on all other measures of cognition (naming, delayed recall, and recognition) were not significant. Statistical significance of all results described above was retained using a 0.05 FDR.

3.3. 2-Way interactions between CBF and VIQ on category fluency stratified by cognitive group

In the CU group, adjusting for age, gender, APOE status, and FDG uptake, there was a statistically nonsignificant but quantitatively similar interaction between VIQ and superior frontal CBF on category fluency (t = -1.83, p = 0.069; Fig. 1), such that as VIQ increased, the strength of the association between CBF and fluency decreased. There were no significant main effects in either the low (t = 1.02, p = 0.308) or high (t = -0.67, p = 0.504) VIQ groups. There were no significant interactions between VIQ and CBF on category fluency across any of the other a priori ROIs (all p-values >0.05). A summary of results on category fluency in the CU group is available in Table 3.

In the MCI group, controlling for age, gender, APOE status, and FDG uptake, there were significant interactions between VIQ and CBF on category fluency when examining the hippocampal CBF (t = 3.11, p = 0.004), inferior temporal CBF (t = 2.49, p = 0.018), superior frontal CBF (t = 3.23, p = 0.002), and inferior frontal CBF (t = 4.85, p < 0.001; Fig. 2) such that there was a stronger positive relationship between CBF and category fluency in participants with higher VIQ. For hippocampal CBF, there was no significant main effect in either the low CR group (t = -0.93, p = 0.362) or high CR group (t = 1.69, p = 0.113) when assessing CR via median split. However, for inferior temporal, superior frontal, and inferior frontal CBF, there were significant main effects in the high CR group (t = 2.17, p = 0.0495; t = 2.60, p = 0.019; t = 3.15, p = 0.006, respectively) but not the low CR group (t = 0.55, p = 0.587; t = 1.29, p = 0.214; t = 0.29, p = 0.777, respectively). A summary of results on category fluency in the MCI group is available in Table 4. Statistical significance of all results described above was retained using a 0.05 FDR.

4. Discussion

Our results demonstrate that VIQ plays an important moderating role in the associations between CBF and category fluency. We

Table 2
VIQ, CBF, and cognitive status prediction of category fluency.

3-Way Interactions					
			Category fluency		
	Estimate	Standardized β	SE	t	*p*
VIQ*HIPP*CogStatus	2.69E-05	0.63	9.03E-06	2.98	**0.003**
VIQ*SFG*CogStatus	4.62E-05	0.77	1.23E-05	3.76	**0.000238**
VIQ*IFG*CogStatus	2.83E-05	0.55	9.66E-06	2.93	**0.004**
VIQ*ITG*CogStatus	1.85E-05	0.61	9.52E-06	1.94	0.055

Bold values are statistically significant, $p < 0.05$.
Key: CogStatus, cognitive status (CU or MCI); HIPP, Hippocampal CBF; IFG, inferior frontal gyrus CBF; ITG, inferior temporal gyrus CBF; SFG, superior frontal gyrus CBF

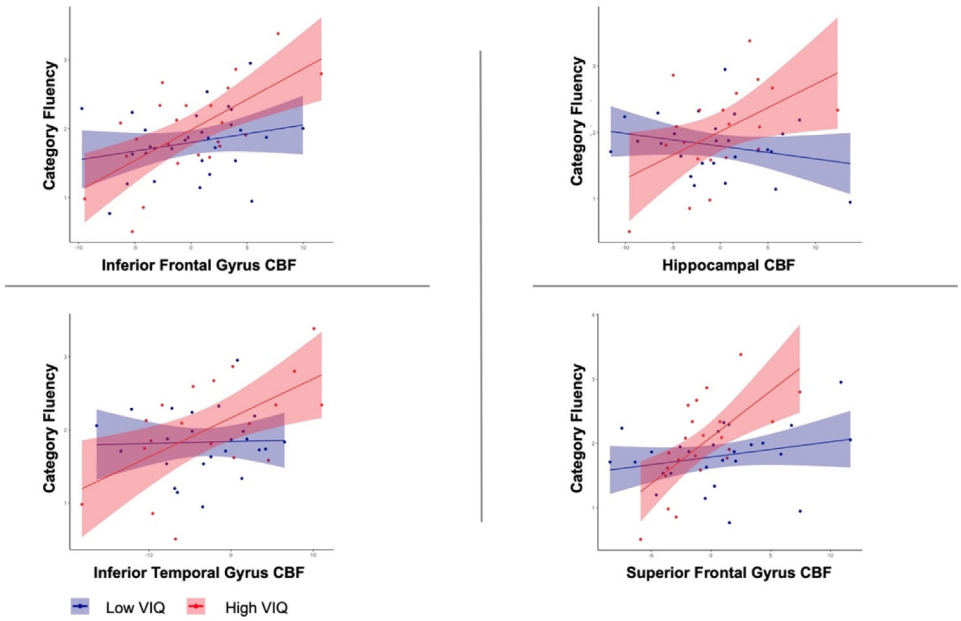

Fig. 1. Interactions Between *a priori* CBF Regions and VIQ on Category Fluency in MCI Group. Abbreviations: CBF, cerebral blood flow; MCI, mild cognitive impairment; VIQ, Verbal intelligence quotient. Y-axes reflect model-predicted category fluency, specifically. Low and high VIQ were median split.

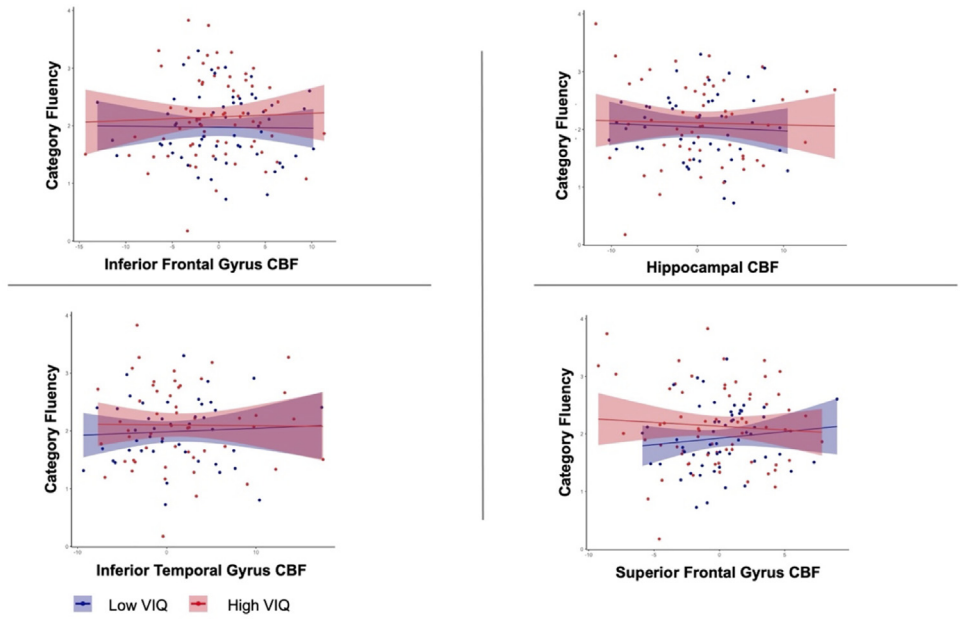

Fig. 2. Interactions Between *a priori* CBF Regions and VIQ on Category Fluency in CU Group. Abbreviations: CBF, cerebral blood flow; CU, Cognitively unimpaired; VIQ, Verbal intelligence quotient. Y-axes reflect model-predicted category fluency, specifically. Low and high VIQ were median split.

Table 3
VIQ, CBF, and VIQ*CBF prediction of category fluency in CU group.

Within-Group: CU		Category Fluency		
	Estimate	SE	t	*p*
VIQ	1.16E-05	3.31E-06	3.509	**<0.001**
HIPP	-0.005	0.012	-0.38	0.705
SFG	-0.002	0.018	-0.123	0.902
IFG	5.90E-05	1.28E-02	0.005	0.996
ITG	0.0006	0.012	0.052	0.959
VIQ*HIPP	-2.02E-06	2.28E-06	-0.885	0.378
VIQ*SFG	-5.25E-06	2.87E-06	-1.833	0.069
VIQ*IFG	3.97E-07	2.45E-06	0.162	0.872
VIQ*ITG	3.91E-07	2.34E-06	0.167	0.867

Bold values are statistically significant, $p < 0.05$. Main effects reported are true main effects.
Key: HIPP, Hippocampal CBF; IFG, inferior frontal gyrus CBF; ITG, inferior temporal gyrus CBF; SFG, superior frontal gyrus CBF

Table 4
VIQ, CBF, and VIQ*CBF prediction of category fluency in MCI group.

Within-Group: MCI		Category Fluency		
	Estimate	SE	t	p
VIQ	0.0003	0.00007	3.93	**<0.001**
HIPP	0.009	0.015101	0.585	0.561
SFG	0.038	0.018007	2.111	**0.041**
IFG	0.04	0.0160516	2.51	**0.016**
ITG	0.026	0.012512	2.089	**0.044**
VIQ*HIPP	0.0002	0.0000601	3.106	**0.004**
VIQ*SFG	3.00E-04	8.26E-05	3.228	**0.003**
VIQ*IFG	0.0002574	0.0000531	4.848	**<0.001**
VIQ*ITG	1.63E-04	6.54E-05	2.488	**0.018**

Bold values are statistically significant, $p < 0.05$.
Key:HIPP, Hippocampal CBF; IFG, inferior frontal gyrus CBF; ITG, inferior temporal gyrus CBF; SFG, superior frontal gyrus CBF

examined 3-way interactions between CBF, VIQ, and cognitive status on cognition. There were significant interactions between these variables on category fluency when examining hippocampal, superior frontal, and inferior frontal gyrus CBF such that MCI participants with higher VIQ scores had a stronger CBF-fluency relationship. The same 3-way interaction involving the inferior temporal gyrus was qualitatively similar. Within the MCI group specifically, there were significant interactions between VIQ and CBF on category fluency when examining all 4 *a priori* CBF regions, including bilateral hippocampus, bilateral inferior temporal gyrus, bilateral superior frontal gyrus, and bilateral inferior frontal gyrus. In the CU group, there were no significant interactions between VIQ and CBF on category fluency.

These results indicate that, in individuals with MCI, the association between CBF and category fluency is dependent on CR, even after adjusting for several relevant risk factors. In all the regions examined, as CR increased, the relationship between CBF and fluency increased, suggesting that higher CR positively strengthens the CBF-fluency association. Notably, main effects were observed in the models that included the superior frontal gyrus, inferior frontal gyrus, and inferior temporal gyrus, where there was a main effect of CBF on fluency in those with high CR but not low CR. For individuals with high CR, as CBF increased, category fluency increased, but in those with lower CR, the relationship between CBF and fluency was not significant. These findings were also dependent on cognitive status, suggesting that the effect of CR on the CBF-fluency relationship may not yet be observed in CU individuals. Interestingly, in the CU group, there was one statistically nonsignificant but quantitatively similar interaction between VIQ and superior frontal CBF on category fluency, such that as VIQ increased, the strength of the association between CBF and fluency decreased; it is of note that the directionality of this effect was opposite of the significant interactions in the MCI group.

The interactions discussed were not significant when examining memory recall or recognition. This may be in part due to our VIQ variable being more strongly associated with language measures than with memory, as word reading tests predict language functioning much more strongly than other areas of cognition (Schretlen et al., 2005). Our findings also align with previous research showing that, among older adults without dementia, poorer vascular health was associated with decline in language ability but not in other domains including memory (Nation et al., 2010). Notably, a recent study found that category fluency was sensitive to cognitive decline at the earliest stage of AD progression, where delayed memory and naming tests were not yet sensitive to change (Jutten et al., 2021). They suggested a possible explanation for the increased sensitivity of category fluency over naming in detecting early disease change is that (1) category fluency, as a timed test, may be more difficult test, and (2) the Boston Naming Test has a maximum score, making it more susceptible to a ceiling effect and thus less sensitive to detecting subtle, early changes. Thus, it is possible that we may see differential CBF-memory relationships based on levels of CR in later stages of the disease.

There are several limitations to our study worth nothing. Our sample was mostly White, relatively highly educated, and medically healthy. The relationships between VIQ, regional CBF, and language/memory may be different in more diverse individuals or those with more risk factors for cognitive decline. Also, all participants had modified Hachinski Ischemic Scale scores <4, indicating that they had relatively low vascular risk. It is additionally important to consider that, given that resources may be depleted with advancing age or encroaching pathology, CR may change dynamically over time (Bettcher et al., 2019), and the current study used a single static proxy. Other approaches have suggested modeling CR using residual cognition instead (Zahodne et al., 2013), but this method may complicate interpretability of results (Elman et al., 2022). Additionally, some researchers caution against the use of proxies, as they may contribute to CR but not necessarily directly through "reserve" mechanisms (Jones et al., 2011; Kremen et al., 2022; Reed et al., 2010). Future research is needed to further determine optimal ways to operationalize reserve and build consensus across researchers. Lastly, the ADNI dataset did not include letter fluency, so we were unable to investigate comparisons between the effect of category and letter fluency in the sample. Nevertheless, category fluency is one of the earliest cognitive changes in the progression of AD (Bondi et al., 2008), thus valuable as a variable of interest independent of letter fluency.

5. Conclusions

We examined associations between VIQ, CBF, and cognition in CU individuals and those diagnosed with MCI. There were significant interactions between VIQ, CBF, and cognitive status on category fluency, where in the MCI group, as VIQ increased, the relationship between CBF and fluency increased in all regions examined. More specifically, for the inferior frontal, superior frontal, and inferior temporal regions, those with high CR showed a stronger, positive association between CBF and fluency. These results were dependent on cognitive status and not significant in the CU group. These findings suggest that higher CR plays a role in strengthening CBF-fluency associations, specifically in people with MCI but not CU individuals. Elucidating which factors increase a person's ability to mitigate the effects of brain pathology are critical to early detection and intervention efforts. As the precise mechanism of CR

is unknown, it is imperative to examine which brain-behavior relationships it may influence and how it may affect such associations across the cognitive aging spectrum. The current work adds to the literature by illuminating the role CR plays in the association between a MR marker of cerebrovascular changes that occur in early AD, CBF, (Zlokovic, 2011) and a behavioral measure that is particularly sensitive to decline in the earliest stages of AD (Jutten et al., 2021). Future work may examine additional CBF regions in a diverse group of individuals at risk for AD. For instance, resting-state MRI studies have shown CR to be more strongly associated with frontal regions, such as the dorsal attention network and left frontal cortex, rather than posterior regions (Franzmeier et al., 2017b). Future studies should examine whether CR moderates the relationship between CBF in frontal regions and attention/executive functioning. Additionally, since category fluency may be more sensitive to early decline than memory measures (Jutten et al., 2021), future work could examine CR as a moderator of CBF-memory relationships at a later stage, such as individuals diagnosed with AD.

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CRediT authorship contribution statement

Einat K. Brenner: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Kelsey R. Thomas:** Writing – review & editing. **Alexandra J. Weigand:** Formal analysis, Data curation, Writing – review & editing. **Lauren Edwards:** Data curation, Writing – review & editing. **Emily C. Edmonds:** Writing – review & editing. **Mark W. Bondi:** Writing – review & editing. **Katherine J. Bangen:** Conceptualization, Methodology, Resources, Writing – original draft, Supervision.

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