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Physical reserve and its underpinning functional neural networks moderate the relationship between white matter hyperintensity and postural balance in older adults with subcortical ischemic vascular cognitive impairment

Chun Liang Hsu[1]✉, Roee Holtzer[2,3], Roger C. Tam[4,6,7,10], Walid al Keridy[4,8,9,11] & Teresa Liu-Ambrose[4,5,10]

White matter hyperintensities (WMH) are markers of subcortical ischemic vascular cognitive impairment (SIVCI) associated with impaired postural balance. Physical reserve (PR) is a recently established construct that reflects one's capacity to maintain physical function despite brain pathology. This cross-sectional study aims to map functional networks associated with PR, and examining the relationship between PR, WMH, and postural balance. PR was defined in 22 community-dwelling older adults with SIVCI. Functional networks of PR were computed using general linear model. Subsequent analyses examined whether PR and relevant networks moderated the relationship between WMH and postural balance under two conditions—eyes open while standing on foam (EOF) or on floor (EONF). We found that PR and the relevant networks—frontoparietal network (FPN) and default mode network (DMN)—significantly moderated the association between WMH and postural balance. For individuals with high PR, postural balance remained stable regardless of the extent of WMH load; whereas for those with low PR, postural balance worsened as WMH load increased. These results suggest the attenuated effects of WMH on postural stability due to PR may be underpinned by functional neural network reorganization in the FPN and DMN as a part of compensatory processes.

Keywords Physical reserve, Physical reserve neural networks, Postural balance, Subcortical ischemic vascular cognitive impairment, fMRI

[1]The Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Kowloon, Hong Kong, SAR, China. [2]Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA. [3]Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, NY, USA. [4]Djavad Mowafaghian Centre for Brain Health, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada. [5]Department of Physical Therapy, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada. [6]Department of Radiology, University of British Columbia, Vancouver, BC, Canada. [7]School of Biomedical Engineering, University of British Columbia, Vancouver, BC, Canada. [8]Division of Neurology, University of British Columbia Hospital, Vancouver, BC, Canada. [9]Geriatric Division, Department of Medicine, University of British Columbia, Vancouver, BC, Canada. [10]Centre for Aging SMART at Vancouver Coastal Health, Vancouver Coastal Health Research Institute, Vancouver, BC, Canada. [11]Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia. ✉email: chun-liang.hsu@polyu.edu.hk

White matter lesions due to cerebral small vessel disease are common among older adults and secondary to cardiovascular risk factors or neurodegenerative diseases[1,2]. White matter lesions are often referred to as white matter hyperintensities (WMH) that are represented by voxels that appeared bright on T2-weighted magnetic resonance imaging (MRI) images. Notably, WMH is associated with decreased cognitive function[3,4], executive functions, postural stability, and increase the risk of falls[5]. Therefore, individuals with subcortical ischemic vascular cognitive impairment (SIVCI), defined as having cognitive impairment and the presence of WMH or lacunes on neuroimaging, often are characterized by impaired executive functions, postural balance, and a history of falls. Evidence also suggest poorer neural efficiency and disrupted network connectivity were observed among these individuals with SIVCI[6,7].

The effects of cerebral small vessel disease do not impact all individuals equally. Some individuals are resilient and maintain function despite the presence of extensive WMH[8,9]. Resiliency is hallmarked by the ability to resist aging or pathology-related decline in cognitive and mobility function[10]. The adaptive capacity of neural networks that enable the brain to resist the negative effects of aging or disease-related brain pathology is construed as reserve[11].

Cognitive reserve (CR) is the capacity to mitigate age- or disease-related negative impact on cognitive function[12]. It has been extensively examined using self-report proxy measures (*e.g.*, years of education, occupational complexity, etc.)[13]. For example, the Rush Memory and Aging Project reported that greater CR preserved cognitive function regardless of significant brain pathologies[11,14]. Recent efforts are focusing on understanding the underlying neural basis of CR[12,15,16]. The residual approach to defining CR[17–19] offers conceptual advantages as well as considerable empirical support that demonstrated stronger protective effects against cognitive decline and dementia compared with traditional socio-demographic measures often used as proxies of this hypothetical construct[20]. Briefly, using regression models, the residual approach removes variance on cognitive tests performance explained by socio-demographic and brain pathology measures and utilizes the residuals of the remaining unexplained variance to quantify CR[17–19].

Physical reserve (PR) is a more recent construct of reserve. It is defined as an individual's ability to maintain physical function in the face of age- or disease-related brain changes[21,22]. In conjunction with CR, PR is a constituent of "total reserve"—an overall neurocognitive-motor buffer that attenuate the negative effects of aging or disease-related neurological pathologies on both cognitive and physical function[22]. In a longitudinal study of 510 older adults over the age of 70 years, O'Brien and colleague[21] found that high baseline PR was correlated with lower incidence of falls. Physical reserve, in this study, was operationally defined as the unexplained residual variance in gait speed after removing the effects of age, sex, history of stroke, history of falls, history of knee replacement surgery, history of hip replacement and/or pinning surgery, and number of medications. O'Brien and colleague[21] hypothesized that the mechanism underlying PR may involve efficient allocation of neural resources and utilization of successful compensatory processes facilitated by large-scale functional neural networks[23].

Nevertheless, the underlying neural substrate of PR remains unexplored. This study aims to map the functional neural networks associated with PR among individuals with SIVCI, and examine the relationship between PR, WMH, and postural balance (Fig. 1). Previously, we have demonstrated that frontoparietal network (FPN) connectivity was crucial towards preventing gait speed decline[23]; and that aberrant FPN connectivity pattern was significantly associated with slower gait speed in community-dwelling older adults with mild cognitive impairment[24]. Further, among older adults with mild cognitive impairment, we showed that greater default mode network (DMN) connectivity was associated with poorer dual-task performance, slower gait speed, and postural instability[25]. Therefore, given the relevance of the FPN and DMN in cognitive function and mobility elucidated by our prior works[7,24–26], we hypothesize that: (1) the FPN and DMN would be significantly correlated to PR; and (2) functional neural networks associated with PR would significantly moderate the association between

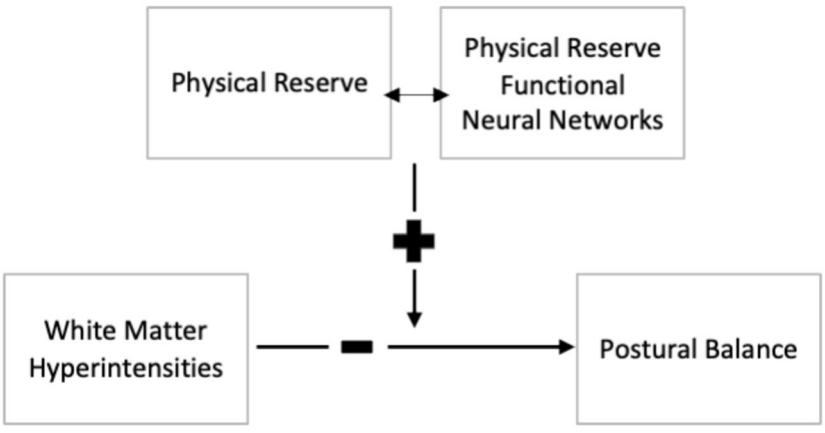

Figure 1. Moderation models. We propose that residual-derived physical reserve (PR) will moderate the association between white matter hyperintensities (WMH) and postural balance. Specifically, PR and its relevant functional neural networks (i.e., FPN and DMN) will moderate (as illustrated by the "+" symbol) the negative main effect of WMH (as illustrated by the "–" symbol) on postural balance.

WMH and postural balance, such that postural balance of those with higher PR will be less negatively impacted by WMH compared with their counterparts with lower PR.

Methods and measures

Study design

This cross-sectional study includes baseline data from a 12-month randomized controlled trial (RCT) of resistance training in 93 community-dwelling older adults who were clinically diagnosed with SIVCI. Details of the study can be found from the published study protocol (ClinicalTrials.gov; NCT02669394)[27]. All 93 participants underwent baseline magnetic resonance imaging (MRI) scanning, however, baseline resting-state functional magnetic resonance imaging (fMRI) were acquired from only a subset (n = 38, Fig. 2). Study ethics approval was obtained from the University of British Columbia Clinical Research Ethics Board (H15-00972) and Vancouver Coastal Health Research Institute (V15-00972). All methods used in the study were performed in accordance with the relevant guidelines and regulations.

Participants

Subcortical ischemic vascular cognitive impairment classification

Community-dwelling adults aged 55 years old or older who fulfilled the criteria for SIVCI were included. Subcortical ischemic vascular cognitive impairment was operationally defined as having cognitive impairment defined by Montreal Cognitive Assessment (MoCA)[28] score of < 26/30 in addition to presence of cerebral small vessel disease identified by WMH and/or lacunes on computed tomography or MRI[27]. Additional inclusion criteria were: (1) a Mini-Mental State Examination (MMSE)[29] score greater than 20/30; (2) able to communicate in English; (3) had acceptable visual and auditory acuity; (4) on a fixed dose of cognitive medication that is not expected to change during the study period, or, if not on these medication, not expected to start during the study period. Exclusion criteria were: (1) a diagnosis of dementia; (2) high risk of cardiac complications; (3) peripheral neuropathy or severe musculoskeletal or joint disease; (4) contraindications for MRI. All enrolled study participants provided written informed consent.

Descriptors

Age and education were recorded in years. Height and weight were measured in units of centermeters (cm) and kilograms (kg). Global cognitive function was assessed with the MoCA[28] and the MMSE[29]. The MoCA is a 30-point test that assesses multiple cognitive domains[28]. The MoCA can accurately discern 90% of a large sample of individuals with mild cognitive impairment[28]. Scores of 18–25/30 are indicative of mild cognitive impairment (MCI); scores > 25/30 indicate normal cognition and scores < 18 indicate dementia[28].

Quantification of physical reserve

We used residual variance modelling in this study to quantify PR[21,22]. We selected the Timed Up and Go test (TUG) to derive PR because of its relevance to postural balance[30], as well as its ability to capture critical elements of physical function that discriminate higher vs lower functioning individuals among older clinical populations[31]. The Timed Up and Go Test (TUG) is a validated functional mobility assessment tool that assesses the ability to rise from seated position on a chair, walk for 3 m, turn, and return to seated position. A cut-off of > 13.5 s taken to complete the test is indicative of risk of falling for community-dwelling older adults[30].

In the study, PR was operationally defined as the unexplained residual variance in Timed Up and Go test (TUG; i.e., dependent variable) after accounting for the effects of age, cognitive capacity, and brain structural integrity (i.e., regressors). Within the context of the current analysis, the Alzheimer's Disease Assessment Scale-Cognitive-13 (ADAS-Cog-13)[32] was selected to reflect cognitive capacity, and hippocampal volume was selected to reflect structural integrity.

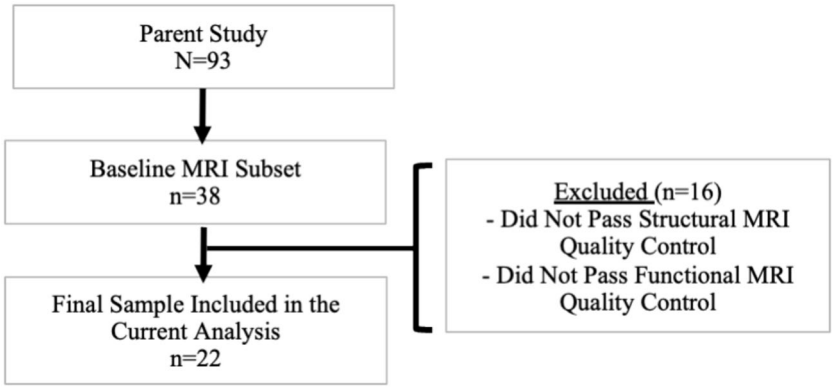

Figure 2. Flow Chart for Data Inclusion. Of the 38 study participants that underwent MRI scanning, 22 passed imaging quality assurance/control assessment, therefore, a final total of 22 participants were included in the analyses.

Cognitive capacity was assessed by the ADAS-Cog-13[32]. The ADAS-Cog-13 is a global cognitive function scale that assesses mutliple cognitive domains including memory, language, attention, concentration, and praxis. It is a more sensitive than the original ADAS-Cog (to subtle changes in cognitive function in those with MCI[32]. The scores range from 0 to 84 points; higher score indicates poorer cognitive function.

Total hippocampal volume was selected to reflect brain structural integrity for the calculation of PR as the hippocampus is involved in cognitive function, memory, spatial navigation[33–35], and postural balance[36]. Estimated intracranial volume (ICV) was also included to adjust for variability in head size.

As such, the residuals—or the variance in TUG not explained by age, ADAS-Cog-13, hippocampal volume, and ICV—from the model is reflective of the variance in TUG explained by PR. Notably, all variables were demeaned (i.e., mean-centered) to minimize multicollinearity before inserted into the regression model. Given that TUG is a time-dependent assessment, standardized residual greater than zero was categorized as low physical reserve, whereas the opposite is labelled as high physical reserve.

Postural balance

Postural balance was assessed by eyes open sway while standing on foam (EOF) and eyes open sway while standing on floor (EONF) components of the Physiological Profile Assessment (PPA)[37]. Instructions were given to the participants to stand with feet at hip width apart for 30 s on a 3-inch high-density foam cushion, as well as on floor. A pen is attached to the participants' waists via custom apparatus that is horizontally aligned in parallel to the floor for marking the extent of bodily sway in the anterior–posterior, and medial–lateral planes. Total postural balance is determined by the largest distance marked by the pen in mm. For the details on the PPA apparatus, see Lord, S.R., H.B. Menz, and A. Tiedemann, *A physiological profile approach to falls risk assessment and prevention.* Phys Ther, 2003. **83**(3): p. 237–52.

MRI acquisition

Functional and structural brain MRI was performed with an 8-channel phased array head coil in the research dedicated Philips 3.0-Tesla Achieva scanner at the University of British Columbia MRI Research Center. High-resolution structural T1w imaging was collected with one 6-min three-dimensional 1 mm isotropic T1 MPRAGE (TR = 1800 ms, TE = 3.50 ms, TI = 800 ms, flip angle = 8°, FOV = 256 × 200 × 170 mm). Resting-state functional imaging was collected with one 8-min T2* weighted echoplanar imaging sequence sensitive to blood oxygenation level-dependent contrast (TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 240 × 240 × 143 mm, 3 × 3 × 3 mm).

Structural MRI analysis

As a hallmark of SIVCI[38], higher WMH is significantly correlated with poorer postural stability[5,39]. Hippocampal, WMH, and ICV were calculated and obtained from previous analysis. Briefly, ICV was estimated by normalizing each brain image to the MNI atlas template. To ascertain hippocampal and WMH volumes, cortical reconstruction and volumetric segmentation were performed using the FreeSurfer image analysis suite[40] developed at the Martinos Center for Biomedical Imaging by Laboratory for Computational Neuroimaging (http://surfer.nmr.mgh.harvard.edu/). The structural MRI analysis stream incorporated skull-stripping, motion correction, Talairach transformation, registration to standard atlas, and brain parcellation. WMH labels were determined through a probabilistic process in which total WMH volume was calculated on each hemisphere and summed to generate a single WMH value for each study participant. All scans underwent manual checking following the automated segmentation. A Jacobian white matter correction was applied to provide better estimation of regional cortical and subcortical volumes.

Functional MRI analysis

Functional imaging analysis was conducted with a custom pipeline that incorporated toolboxes from FSL (version 6.0.6.2), SPM12, and Matlab (R2022b). Data preprocessing included rigid body motion correction, spatial smoothing with a 6.0 mm Full-Width-Half-Maximum Gaussian kernel, high-pass temporal filtering to exclude confounding physiological signals from frequencies below 0.008 Hz. Abnormal spikes in signals due to motion were first removed from the time-series data through FSL's motion outlier tool, followed by Independent Component Analysis based Automatic Removal of Motion Artifacts to remove remaining motion-related artifacts. Nuisance signals from the cerebral spinal fluid and white matter were included as regressors and their effects were removed via general linear model. Preprocessed time-series data will be extracted from established network templates[41], which will be utilized as seeds for a whole-brain voxelwise correlation to derive voxelwise functional connectivity maps for each associated networks. Fisher's r-to-z transformation was performed to normalize the extracted seed-voxel correlation to construct the final connectivity matrix.

Functional neural networks associated with physical reserve functional neural networks

After functional connectivity maps of the networks of interest (i.e., FPN and DMN) were calculated for each study participant, a higher-level group analysis was carried out via FSL's general linear model (GLM) and FMRI's Local Analysis of Mixed Effects (FLAME) to establish group level functional connectivity maps of PR associated with the FPN and DMN. Similar to the steps used for PR quantification described earlier, functional brain mapping for PR were extrapolated as TUG-correlated FPN and DMN connectivity maps computed using two separate GLMs (i.e., one for FPN and one for DMN) that removed the effects of age, cognitive capacity (i.e., ADAS-Cog-13), and brain structural integrity (i.e., hippocampal volume). All regressors were demeaned prior to model fitting. Subsequently, whole-brain voxelwise connectivity maps for PR were derived and statistically thresholded at $Z > 2.3$ with a cluster correction p threshold of 0.05.

Moderation analysis

Moderation analysis was performed via the PROCESS package in SPSS (version 29.0.1.0)[42]. Three separate moderation models were constructed to examine the moderating effects of PR variable/intranetwork FPN connectivity/intranetwork DMN connectivity on the association between WMH and postural balance: (1) postural balance was set as the dependent variable (i.e., variable Y), WMH was set as the independent variable (i.e., variable X), and TUG-derived physical reserve was set as the moderator (i.e., variable W); (2) postural balance was set as the dependent variable (i.e., variable Y), WMH was set as the independent variable (i.e., variable X), and intranetwork FPN connectivity was set as the moderator (i.e., variable W); and (3) postural balance was set as the dependent variable (i.e., variable Y), WMH was set as the independent variable (i.e., variable X), and intranetwork DMN connectivity was set as the moderator (i.e., variable W).

As computation of PR already adjusted for the effects of age, cognitive capacity, and brain structural integrity, no additional covariates were adjusted for in the moderation analysis. All statistical significance was set at $\alpha < 0.05$.

Results

Participants characteristics

Participant descriptors and outcomes of interest are reported in Table 1. Of the 38 study participants included, 22 had a complete set of resting-state fMRI, structural MRI data that passed imaging quality assurance/control assessment. Thus, 22 participants were included in the our analyses (Fig. 2). The sub-sample in this cross-sectional study did not differ significantly from the parent RCT except the mean body mass in participants with lower PR was greater than both the parent cohort and the participants with higher PR (79.0 kg, 73.2 kg, and 70.2 kg respectively). The average age of the 22 participants was 73 years, with a mean MoCA and MMSE score of 21.2 and 27.1 respectively.

Functional mobility, cognitive function, hippocampal volume, white matter hyperintensity, and postural balance

Regression model for PR quantification is displayed in Table 2. Participants with lower PR showed significantly slower TUG performance ($p < 0.05$; Table 1), which was expected as PR was quantified with TUG as the dependent variable in the regression model. Otherwise, the groups were statistically comparable ($p > 0.05$; Table 1) in ADAS-Cog-13 score, hippocampal volume, WMH volume, and postural balance.

Resting-state fMRI

Whole-brain voxelwise functional connectivity analysis using FPN as the seed network revealed distinct connectivity patterns associated with PR (Fig. 3A). Specifically, participants with lower PR exhibited greater intranetwork connectivity between FPN-inferior frontal lobe, whereas those with higher PR exhibited greater internetwork connectivity between FPN-postcentral gyrus, and FPN-supramarginal gyrus ($Z > 2.3$, $p < 0.05$).

Using DMN as the seed network (Fig. 3B), we found that those with lower PR demonstrated greater connectivity between DMN-paracingulate gyrus, and DMN-inferior temporal gyrus. Conversely, individuals with higher PR demonstrated greater connectivity between DMN-frontal medial cortex, DMN-precentral gyrus, and DMN-orbitofrontal cortex ($Z > 2.3$, $p < 0.05$).

	Main parent cohort (N = 93; Mean; SD)	Participants included in current analysis (N = 22; Mean; SD)	Participants with lower PR (n = 11; Mean; SD)	Participants with higher PR (n = 11; Mean; SD)
Age (years)	74.9 (5.9)	73.0 (3.9)	73.3 (4.6)	72.7 (3.3)
Sex (m/f)	31/62	4/18	1/10	3/8
Height (cm)	162.8 (10.1)	160.4 (8.9)	159.7 (8.4)	161.0 (9.8)
Weight (kg)	73.2 (16.5)	74.6 (19.9)	79.0 (23.3)	70.2 (15.6)
Education (years)	5.2 (1.3)	5.1 (1.2)	4.8 (1.3)	5.4 (1.0)
MoCA (max 30)	21.1 (3.4)	21.2 (2.5)	21.7 (2.7)	20.7 (2.3)
MMSE (max 30)	27.3 (1.9)	27.1 (1.7)	26.9 (1.9)	27.4 (1.5)
TUG (sec)	9.6 (2.5)	9.4 (2.2)	11.1 (1.6)	7.8 (1.2)
ADAS-Cog-13 (max 85)	13.8 (5.4)	12.5 (5.4)	12.9 (5.0)	12.2 (6.0)
Hippocampus (mm^3)	–	3656.8 (460.2)	3602.7 (485.9)	3711.0 (449.7)
WMH (mm^3)	–	4587.83 (6772.5)	4559.7 (8106.3)	4615.9 (5532.4)
ICV	–	1518267.79 (198055.0)	1488248.14 (154636.0)	1548287.44 (237653.7)
EOF Sway (mm)	229.6 (221.7)	176.0 (89.0)	158.6 (46.1)	193.4 (117.9)
EONF Sway (mm)	68.2 (42.5)	84.6 (65.3)	102.8 (84.7)	66.3 (32.2)

Table 1. Study participant characteristics. MoCA, Montreal cognitive assessment; MMSE, Mini-Menta State examination; TUG, Timed-Up-and-GO test; ADAS-Cog-13, Alzheimer's disease assessment scale-cognitive-13, higher score reflects poorer cognitive performance; WMH, White matter hyperintensities; ICV, estimated intracranial volume; EOF Sway, Eyes open foam sway; EONF, Eyes open no foam sway.

Independent variables*	TUG				
	R	R^2	Unstandardized beta	Standardized beta	*p*-value
Model 1	0.49	0.22			< 0.01
Constant (intercept)			3.60		0.53
Age			7.67	0.21	0.08
ADAS-Cog-13			0.96	0.15	0.21
Hippocampus			− 6.58	− 0.27	0.03
ICV			3.96	0.17	0.16

Table 2. Regression models to quantify physical reserve. *TUG, Timed-Up-and-Go test; ADAS-Cog-13, Alzheimer's Disease Assessment Scale-Cognitive-13; ICV, estimated intracranial volume. All varibales displayed were demeaned before inserted into the regression model. Physical Reserve is quantified as the standardized residual variance output from the model.

Moderation analysis

There was a significant main effect of WMH on EOF (b = 0.05, SE = 0.01, t = 3.40, $p < 0.01$), where greater WMH was associated with increased EOF sway. With the inclusion of PR as a moderator, we observed a r-square change of 0.23 (F = 6.95, $p = 0.02$), suggesting there is a significant WMH*PR interaction (b = 0.07, SE = 0.03, t = 2.64, $p = 0.02$). This interaction effect was not observed with postural balance on floor (i.e., EONF; $p = 0.99$). Specifically, compared with individuals with lower PR, those with higher PR were able to maintain balance even at high WMH load (conditional effect = − 0.02, SE = 0.02, t = − 1.36, $p = 0.19$, LLCI = − 0.06, ULCI = 0.01; Fig. 4A), whereas the amount of postural sway (i.e., affected postural balance) was positively correlated with the level of WMH burden among the participants with lower PR (conditional effect = 0.12, SE = 0.04, t = 3.03, $p = 0.01$, LLCI = 0.04, ULCI = 0.21; Fig. 4A). With the inclusion of overall intranetwork FPN connectivity as a moderator, we observed a r-square change of 0.72 (F = 14.88, $p < 0.01$), suggesting there is a significant WMH*FPN connectivity interaction (b = 0.07, SE = 0.01, t = 5.51, $p < 0.01$). Compared with individuals with higher intranetwork FPN connectivity (conditional effect = 0.06, SE = 0.01, t = 6.45, $p < 0.01$, LLCI = 0.04, ULCI = 0.08; Fig. 4B), those with lower intranetwork FPN connectivity was able to maintain postural balance at high WMH load (conditional effect = − 0.01, SE = 0.01, t = − 1.16, $p = 0.26$, LLCI = − 0.03, ULCI = 0.01; Fig. 4B). No statistically significant moderating effect was observed for intranetwork DMN connectivity (b = − 0.05, SE = 0.05, t = − 0.89, $p = 0.06$).

Discussion

In this cross-sectional study, we mapped connectivity patterns of large-scale functional neural networks associated to PR among older adults clinically diagnosed with SIVCI. To our knowledge, this is the first study to have leveraged from the conceptualized computation of PR through residual variance modelling[18,21,22], in combination with resting-state fMRI for a whole-brain voxelwise quantification of TUG-dependent physical reserve.

To date, there is a scarcity of studies examining physical reserve. One study reported that higher residual-derived CR was associated with more efficient brain activation patterns assessed during dual-task walking[43]. Another study reported that higher cognitive reserve derived from residual variance modelling was correlated with a lower odds of mobility dysfunction as identified by slow gait (i.e., ≤ 0.8 m/sec), as well as significant reduction in the incidence of slow gait[18]. Although as the effects from physical function were not removed from the proposed cognitive reserve residual-variance model, it is plausible that PR may have a role in reducing the incidence of slow gait reported by the authors. Extending from the previous findings, we found that high PR significantly moderated the association between postural balance and WMH, where study participants with higher PR were able to maintain similar level of postural stability regardless of WMH load; whereas those with lower PR significantly increased postural sway (i.e., poorer postural balance) as the extent of WMH increased. Current understanding of the reserve framework postulates that greater reserve may protect against WMH via enhanced neural efficiency and compensation[10]; therefore, we contend that the observed attenuated effects of WMH on postural stability due to PR may be underpinned by functional network reorganization in the FPN and DMN as a part of the compensatory processes.

FrontoParietal network configuration with physical reserve

We found that participants with lower PR exhibited greater connectivity between FPN-inferior frontal lobe, whereas those with higher PR exhibited greater connectivity between FPN-postcentral gyrus, and FPN-supramarginal gyrus. Given that inferior frontal lobe is a major hub within the FPN, and that the postcentral gyrus and supramarginal gyrus are regions within the sensorimotor network and attentional networks respectively, these connectivity patterns represented differences between engagement in intranetwork coupling exhibited by the participants with lower PR, versus enhanced internetwork connections exhibited by the participants with higher PR. This may be reflective of a successful adaptive intrinsic mechanism by which those with higher PR were able to flexibly recruit neural resources from regions in close proximity located in other similarly goal-oriented functional networks. The moderating relationship demonstrated in Fig. 4B further elucidate the role of FPN in PR as well as its involvement in mitigating the detrimental effects of WMH on postural balance in those with SIVCI.

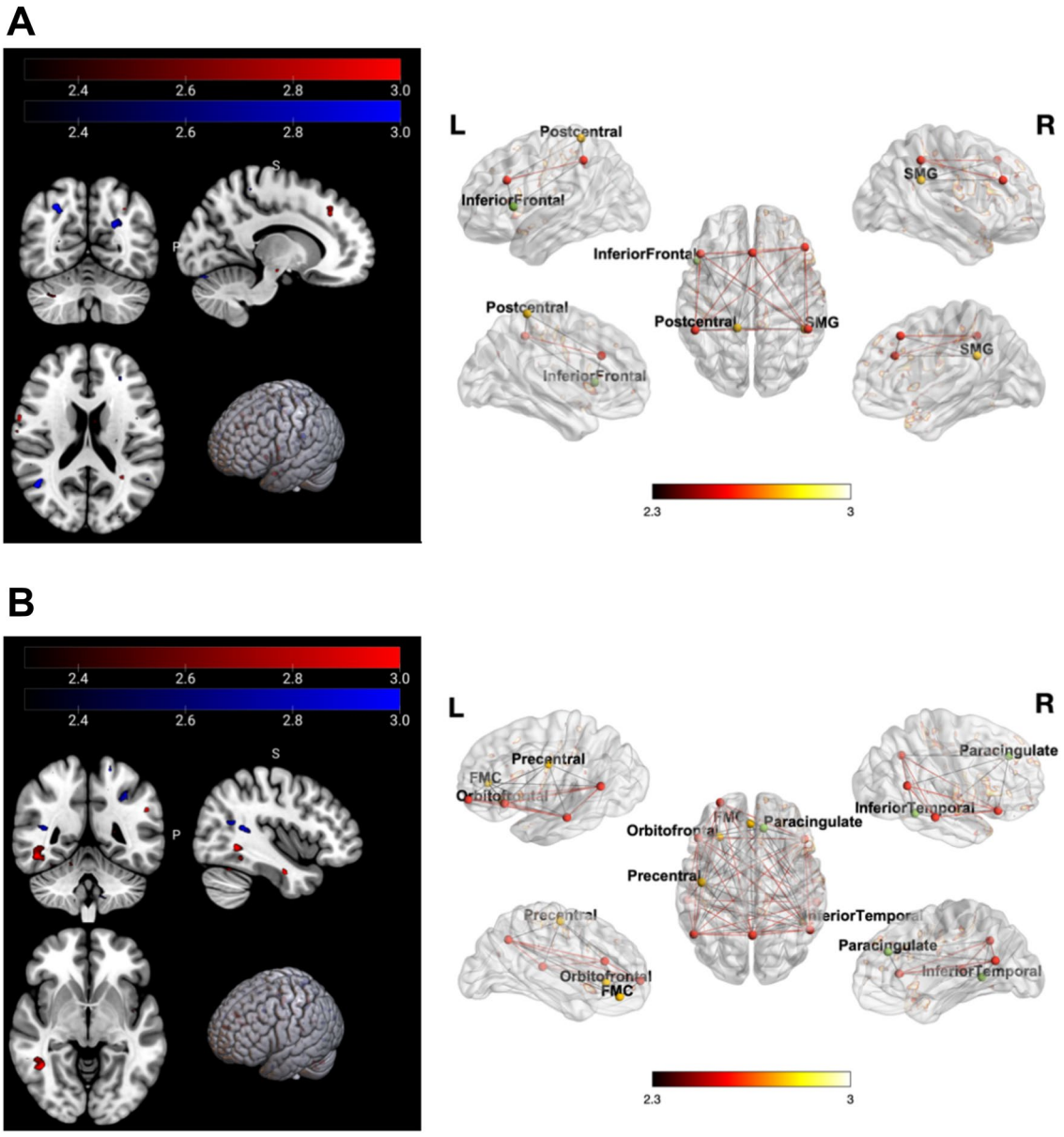

Figure 3. (**A**) Physical Reserve Related Whole Brain Voxelwise FPN Connectivity. Thresholded at Z > 2.3 with a cluster correction *p* threshold set at 0.05; multiple comparisons adjusted. Red and blue color bars represent connectivity strength for the FPN for individuals with low PR and high PR respectively; brighter colors reflect greater connectivity. Left image: red-colored clusters reflect regions with greater connectivity to the FPN connectivity among individuals with low PR (i.e., low > high contrast); blue-colored clusters reflect regions with greater connectivity to the FPN among individuals with high PR (i.e., high > low contrast). Right image: Compared with individuals with high physical reserve, those with low PR demonstrated greater connectivity between FPN-inferior frontal lobe. Conversely, individuals with high PR demonstrated greater connectivity between FPN-postcentral gyrus, and FPN-supramarginal gyrus. (**B**) Physical Reserve Whole Brain Voxelwise DMN Connectivity. Thresholded at Z > 2.3 with a cluster correction *p* threshold set at 0.05; multiple comparisons adjusted. Red and blue color bars represent connectivity strength for the DMN for individuals with low PR and high PR respectively; brighter colors reflect greater connectivity. Left image: red-colored clusters reflect regions with greater connectivity to the DMN among individuals with low PR (i.e., low > high contrast); blue-colored clusters reflect regions with greater connectivity to the DMN among individuals with high PR (i.e., high > low contrast). Right image: Compared with individuals with high physical reserve, those with low PR demonstrated greater connectivity between DMN-paracingulate and DMN-inferior temporal gyrus. Conversely, individuals with high PR demonstrated greater connectivity between DMN-frontal medial cortex, DMN-precentral gyrus, and DMN-orbitofrontal cortex.

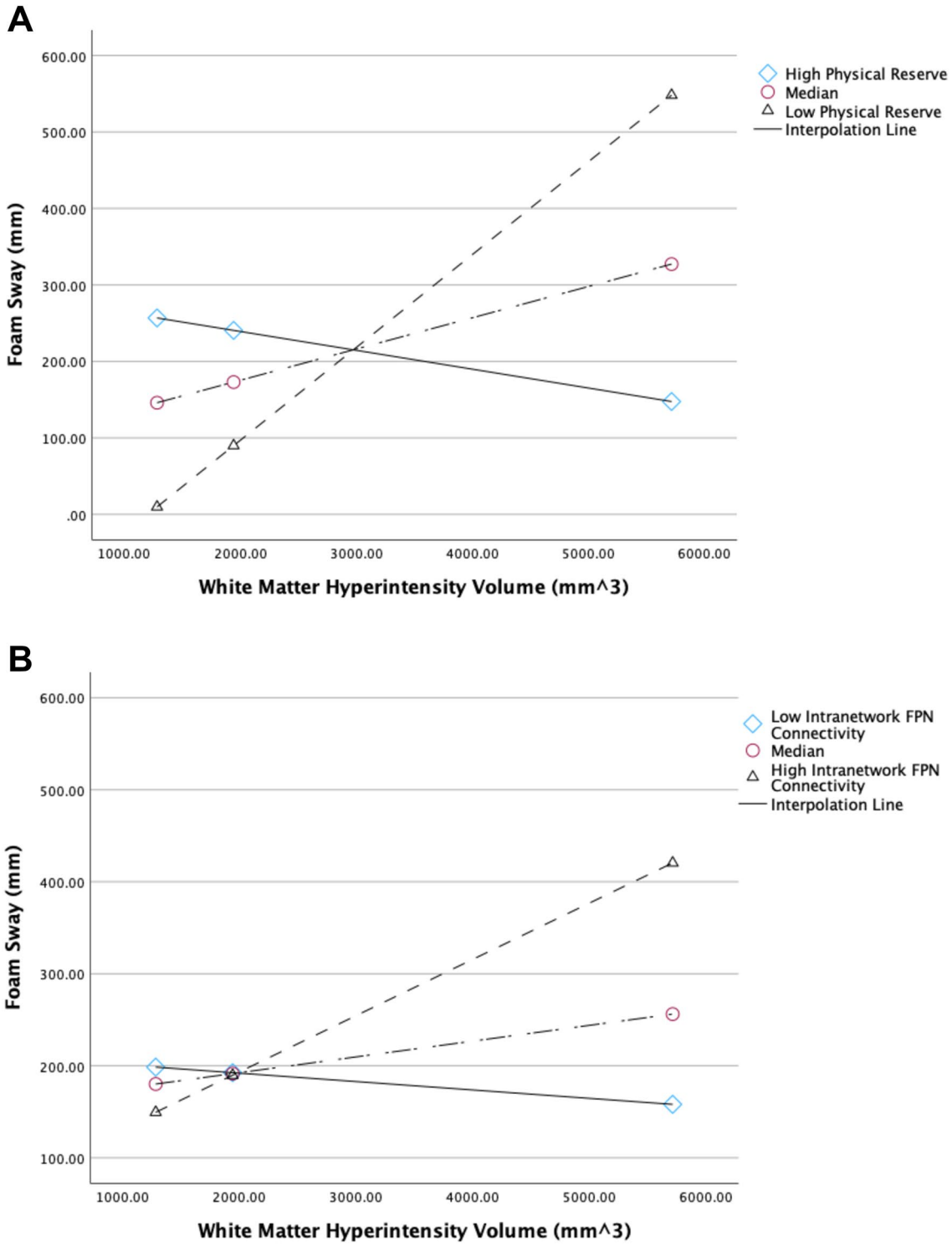

Figure 4. (**A**) Interaction between Physical Reserve and White Matter Hyperintensity Volume on Postural Balance. Foam Sway = postural balance on foam surface, units in mm; White matter hyperintensity volume units in mm^3. Compared with individuals with lower PR, those with higher PR were able to maintain balance even at high WMH load (conditional effect = − 0.02, SE = 0.02, t = − 1.36, $p = 0.19$, LLCI = − 0.06, ULCI = 0.01), whereas the amount of postural sway (i.e., affected postural balance) was positively correlated with the level of WMH burden among the participants with lower PR (conditional effect = 0.12, SE = 0.04, t = 3.03, $p = 0.01$, LLCI = 0.04, ULCI = 0.21). (**B**) Interaction between Intranetwork FPN Connectivity and White Matter Hyperintensity Volume on Postural Balance. Foam Sway = postural balance on foam surface, units in mm; White matter hyperintensity volume units in mm^3. Compared with individuals with higher intranetwork FPN connectivity (conditional effect = 0.06, SE = 0.01, t = 6.45, $p < 0.01$, LLCI = 0.04, ULCI = 0.08), those with lower intranetwork FPN connectivity was able to maintain postural balance at high WMH load (conditional effect = − 0.01, SE = 0.01, t = − 1.16, $p = 0.26$, LLCI = − 0.03, ULCI = 0.01).

Default mode network configuration with physical reserve

We found that those with lower PR demonstrated greater connectivity between DMN-paracingulate gyrus, and DMN-inferior temporal gyrus. Conversely, individuals with higher PR demonstrated greater connectivity between DMN-frontal medial cortex, DMN-precentral gyrus, and DMN-orbitofrontal cortex. The paracingulate and inferior temporal gyrus are regions found within the DMN, whereas the precentral gyrus and orbitofrontal cortex are considered to be areas within the sensorimotor network and attentional networks. Given the well-established anti-correlation relationship between DMN and goal-oriented networks[44], our findings that participants with higher PR displayed an increased connectivity between DMN and regions within other goal-oriented networks suggest a more complex interplay between these large-scale brain systems may be involved. Emerging evidence suggest functional involvement of the DMN extends beyond that of the default (i.e., resting) state, where the DMN also contribute to goal-oriented behaviours[45]. Critically, among healthy younger adults (mean age = 28.5 years), increased DMN connectivity to major task-relevant brain regions such as the insula, inferior frontal lobe, and frontal medial cortex was observed during tasks related to autobiographical memory, emotion, inhibitory control, working memory, and language[45]. Aligning with these findings, recent study found that canonical representation of DMN functional mapping may be oversimplified[46]. It is more plausible that functional parcellation of the DMN can be dynamically decomposed into different subsystems, where true functional maps of the DMN could vary (i.e., areas functionally connected to the DMN) depending on the task orientation. This suggests that as opposed to a static dichotomous behaviour (i.e., "on" vs "off" during rest vs task states), DMN architecture may be more flexible and adaptive. Therefore, we postulate that our observed attenuation of DMN anti-correlation among those with higher PR may be a depiction of a more adaptive and efficient brain state exhibited by these individuals.

Overall functional network architecture with physical reserve

Recent systematic review concluded that there is an aging-related increase in long range inter-network connections wherein cognitive impairments were attributed to this increased integration of physically distant brain networks[47]. However, current reserve framework suggests that functional reorganization of brain network may be a plausible mechanism of action for reserve-related maintenance of function despite presence of atrophy[48,49]. For instance, a cross-sectional study involving adults 50 years or older found a significant interaction between cognitive reserve, WMH, and connectivity patterns of the FPN[49]. Compared with individuals with lower cognitive reserve, those with high cognitive reserve displayed greater inter-FPN connectivity. However, it is important to note that all of the studies included in this review quantified reserve via a self-report proxy measurement (e.g., derived from education, or other questionnaires), and did not compute a direct measurement of reserve.

The overall network connectivity configuration we observed in individuals with high PR supports the notion of a successful pathology-driven compensatory neural processes proposed in the seminal work by Cabeza and colleagues[50], and importantly, the capacity to flexibly allocate neural resource is a crucial component of reserve and resiliency.

Strength and limitations

The strength of the present study is the novelty in mapping function neural networks of PR through resting-state fMRI. By elucidating the underpinning networks relevant to PR, we can gain better understanding of the relationship between PR, and aging- or disease-related brain pathology. There are several limitations for this cross-sectional study. First, a significant portion of the MRI data did not pass quality control, future studies investigating older adults with SIVCI will need to take this into consideration. Currently, it is unknown whether there is a universal PR construct and there is no consensus regarding standard measures that should be used to quantifying physical reserve. We used one single measure of mobility—the TUG—to derive PR. Thus, our results may not generalize to other measures or aspects of mobility. However, the protective effects of residual-derived PR across different studies using gait speed[21], the Short Physical Performance Battery[22], and TUG (herein) suggest potential clinical utility to PR that extends beyond a specific mobility measure. Further, our data should be cautiously interpreted as the sample size is small and cross sectional by design. Due to the small sample, we were also unable to examine potential sex-differences, which is an important topic as evidence demonstrated the influence of sex hormones on the brain[51]. An age-matched control group without SIVCI was not included in this study. The inclusion of a control group may provide further support for the premise of the current study. Lastly, as stated in the Resiliency and Reserve Framework[10], longitudinal studies are required for investigating the core features of reserve; therefore, future study with larger sample size and longitudinal design will be needed to confirm and replicate our findings.

Data availability

All data used in the study are available upon reasonable request to the corresponding author CLH.

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Author contributions

CLH contributed to data collection, fMRI data analysis, statistical analyses, interpretation of findings, and writing of the manuscript. CLH, RH, and TLA contributed to conceptualization and design of the study. RCT and WaK contributed to quantification of white matter hyperintensities. RH, RCT, WaK, and TLA contributed to review and editing of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to C.L.H.