The relationship between white matter hyperintensity clusters (size and location) and prospective falls in older adults across the cognitive spectrum

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Outline

1. Background
2. Aim
3. Methods
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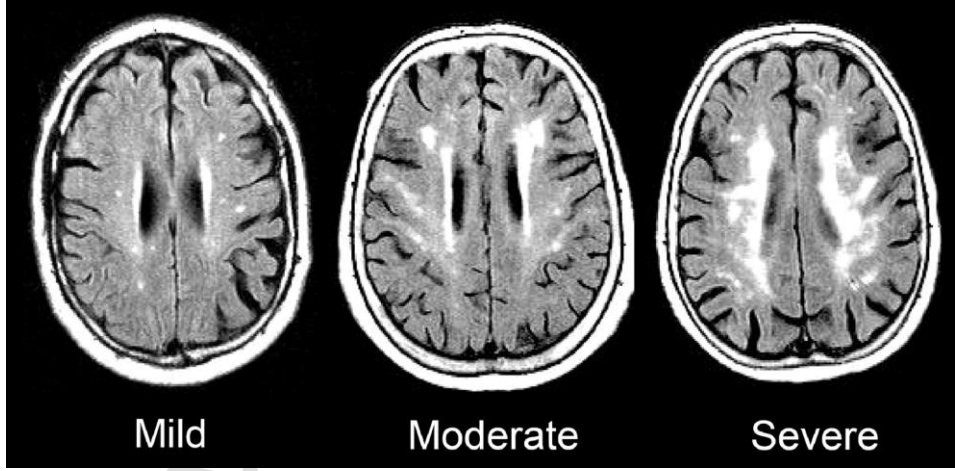
5. Conclusions

White matter hyperintensities



Inzitari 2009

- Thought to be vascular in origin (chronic ischaemia/SVD)
- Associated with incident dementia and impaired gait, balance and cognition and increased fall risk in cognitively healthy older people
- Associated with cognitive and physical function and falls in people with dementia
- Investigating WMH number of clusters (NoC; size/location) may identify differential effects in relation to WMH aetiology and, sensorimotor performance and fall risk

Inzitari, D, et al. (2009). Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS study cohort. *BMJ, 339*
Prins, N. D., & Scheltens, P. (2015). White matter hyperintensities, cognitive impairment and dementia: an update. *Nature Reviews Neurology, 11*(3)
Taylor ME, et al. (2018) White matter hyperintensities are associated with falls in older people with dementia. *Brain Imaging Behav*

Aim and Hypothesis

Aim

Investigate the relationship between WMH NoCs (whole brain/size/location) and sensorimotor function and falls in older adults spanning the cognitive spectrum

Hypothesis

The number of WMH NoCs will be associated with sensorimotor function and falls, and this relationship will be strongest in the frontal brain region

Study flow

Participants (n=168)

Cognitively normal (n=79)	Mild Cognitive Impairment (n=61)	Dementia (n=28)

Baseline Assessment

Sociodemographic Self-reported medical history	Neuropsychological function: MMSE, Trail Making Test B, Geriatric Depression Scale	Physical function: Physiological Profile Assessment	MRI: T1 + T2 FLAIR WMH volumes and NoC (size and location)

12-months follow-up (n=163)

CN n=76, MCI n=59, dementia n=28	Prospective falls

Study flow

Participants (n=168)

Cognitively normal (n=79)	Mild Cognitive Impairment (n=61)	Dementia (n=28)
Inclusion: 70-90 years, community-dwelling MCI inclusion: subjective cognitive complaint compared to 5 yrs ago, normal or min impairment in IADLs, presence of cognitive impairment (below 1.5SD) Exclusion: no dementia or MMSE <24, inability to speak and understand English, neurological, cardiovascular or major musculoskeletal condition/s that precluded walking 20 m		Inclusion: 60+ years, community-dwelling, mild to moderate dementia, PR with ≥ 3.5h contact each week Exclusion: MMSE <11, recent stroke (18 months), progressive neurodegenerative disorder, insufficient English, known end-stage illness

12-months follow-up (n=163)

CN n=76, MCI n=59, dementia n=28	Prospective falls

Methods

MRI acquisition:

- T1-weighted and T2-weighted fluid-attenuated inversion recovery (FLAIR) images were acquired from a Philips 3T Achieva Quasar Dual or a Philips 3-Tesla Intera Quasar scanner

- WMH volumes and NoCs were calculated with a fully automated toolbox for extracting WMH (UBO Detector; https://cheba.unsw.edu.au/group/neuroimaging-pipeline)

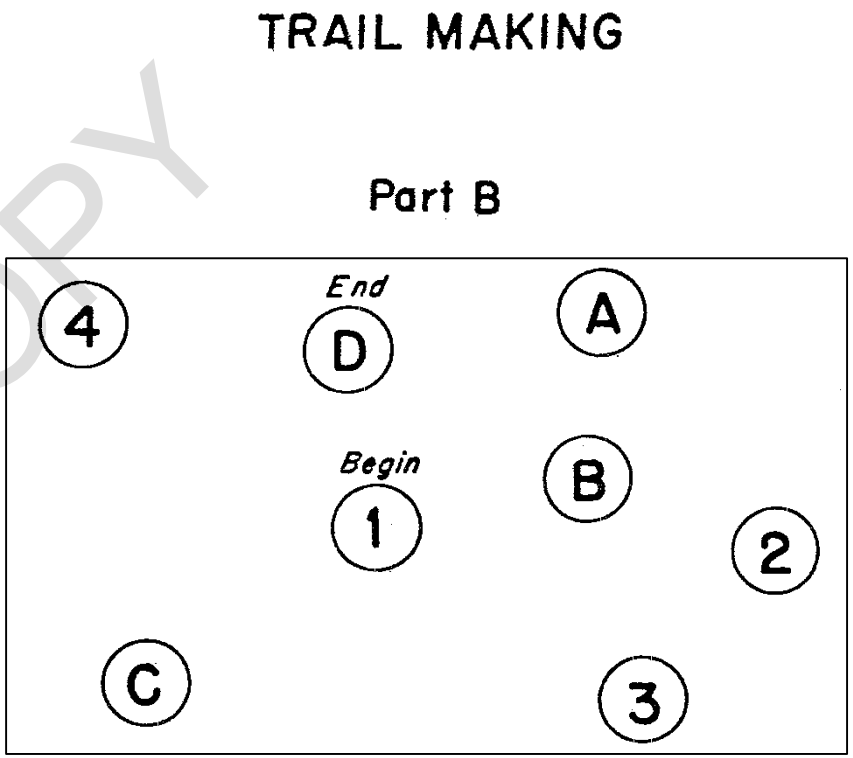
Neuropsychological function:

Mini-Mental State Examination (MMSE)

Patient's Name:_____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

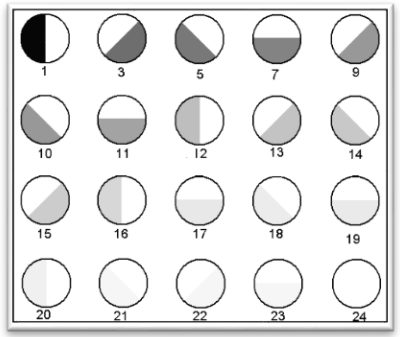


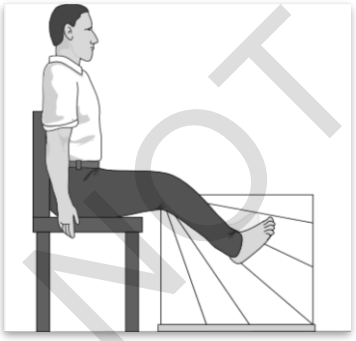
Geriatric Depression Scale (GDS) – 15-item

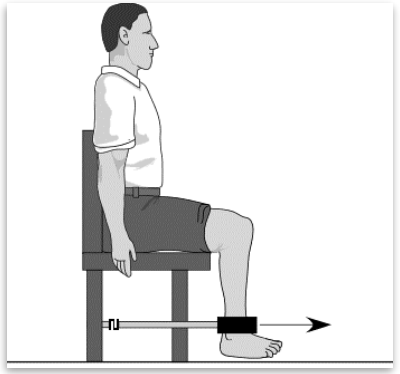
Are you basically satisfied with your life?	Y/N
Do you feel your life is empty?	Y/N
Are you afraid something bad is going to happen to you?	Y/N

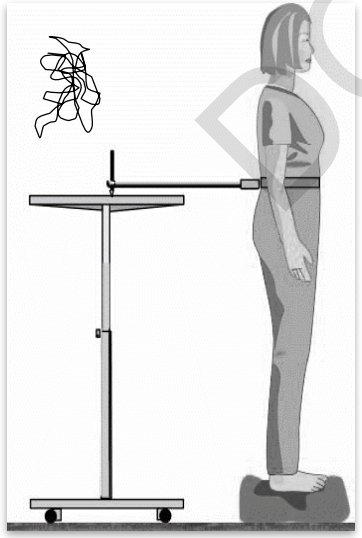
Methods

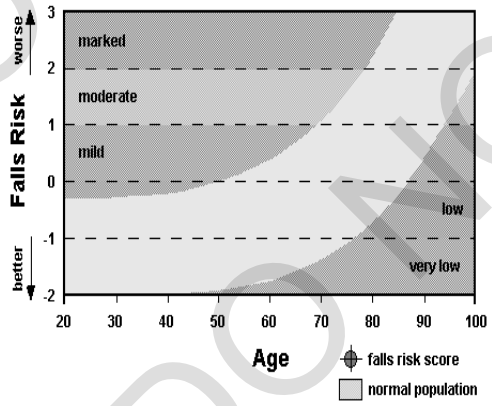
Sensorimotor function: Physiological Profile Assessment









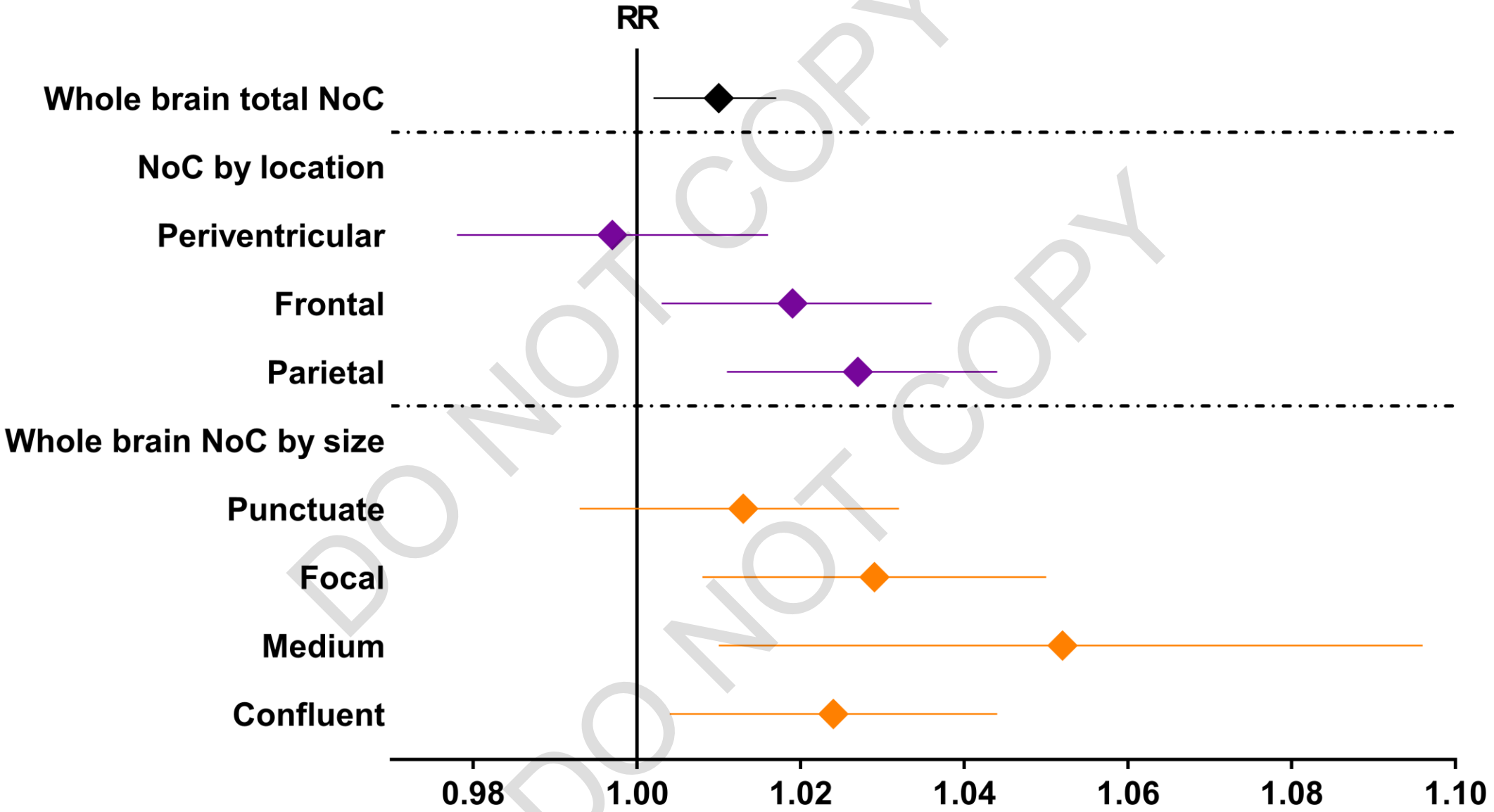


Falls follow-up

Characteristic, mean ± SD, median [IQR] or n(%)	Non-faller (n=77)	Faller (n=86)
Demographic		
Age, years	78.8 ± 5.4	78.4 ± 5.6
Female	40 (52)	47 (55)
Years of education	10 [9 – 14]	11 [9 – 14]
Previous falls	15 (20)	43 (51)***
Self-reported medical history		
TIA	6 (8)	8 (10)
Stroke	1 (1)	3 (4)
Hypertension	40 (53)	52 (61)
Heart problem	25 (33)	30 (35)
Diabetes	7 (9)	17 (20)
Cholesterol	44 (57)	46 (54)
Depression	9 (12)	22 (27)*
Cognitive status		
Intact	40 (52)	36 (42)
Amnestic MCI	19 (25)	15 (17)
Non-amnestic MCI	11 (14)	14 (16)
Dementia	7 (9)	21 (24)

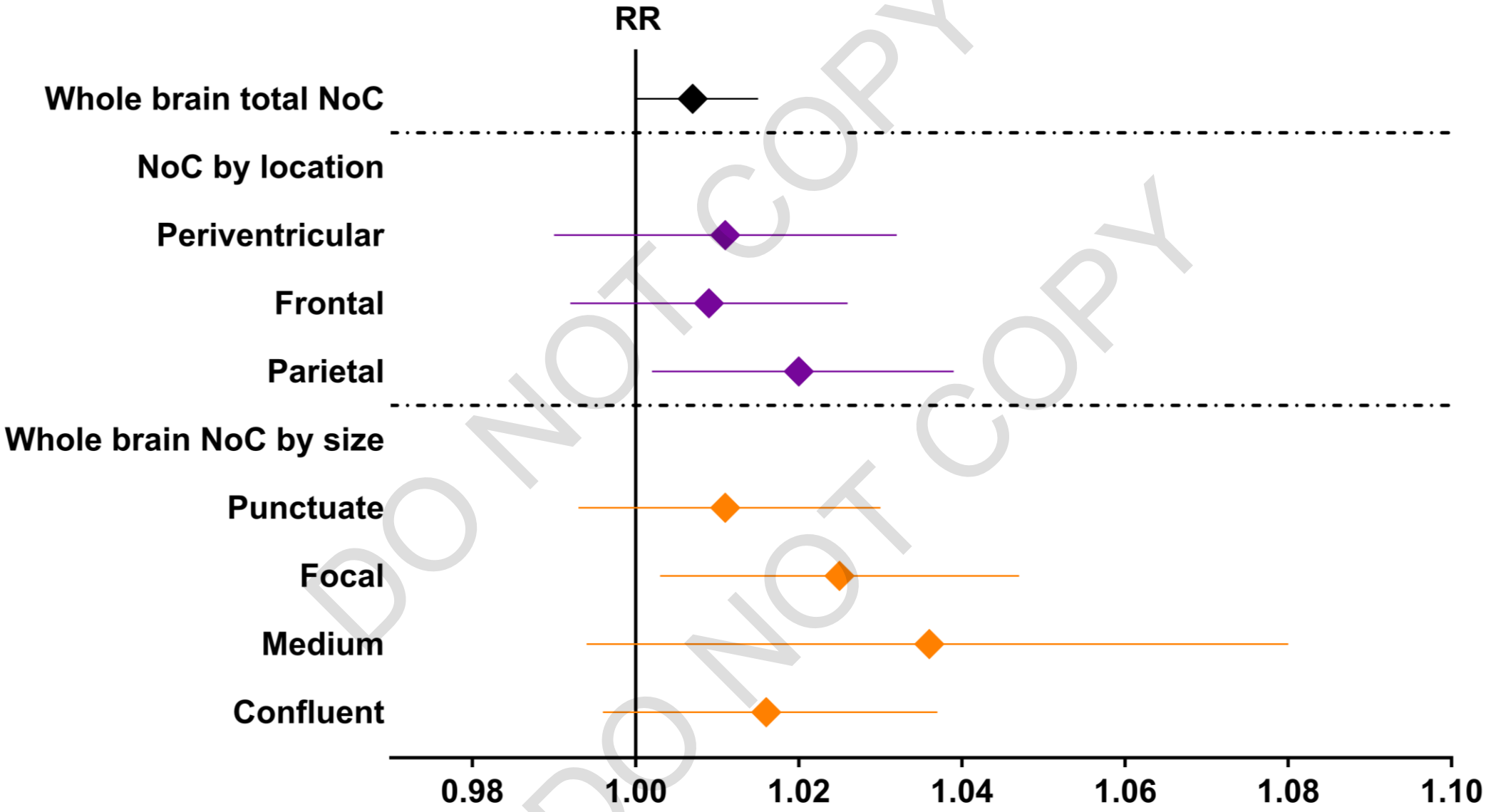
Characteristic, mean ± SD, median [IQR] or n(%)	Non-faller (n=77)	Faller (n=86)	RR (95% CI)
Neuropsychological performance			
MMSE	28 [27 – 29]	28 [26 – 29]	0.95 (0.91, 0.99)**
TMT B, seconds	105 [86 – 146]	120 [92 – 205]	1.00 (1.00, 1.00)**
GDS	2 [1 – 3]	3 [1 – 4]	1.11 (1.07, 1.16) ***
Sensorimotor performance			
PPA score	0.39 [-0.05 – 1.00]	0.77 [0.28 – 1.75]	1.27 (1.12, 1.44)***
WMH volumes, cm^3			
Total WMH	9.8 [5.4 – 15.1]	15.1 [6.7 – 30.0]	1.01 (1.00, 1.02)*
PV WMH	7.3 [3.8 – 11.8]	10.5 [5.1 – 20.1]	1.02 (1.00, 1.03)*
Deep WMH tertiles			
Lowest	36 (47)	29 (34)	Ref
Middle	24 (31)	19 (22)	0.96 (0.61, 1.49)
Highest	17 (22)	38 (44)	1.54 (1.09, 2.18)*

WMH NoCs and falls – minimally adjusted



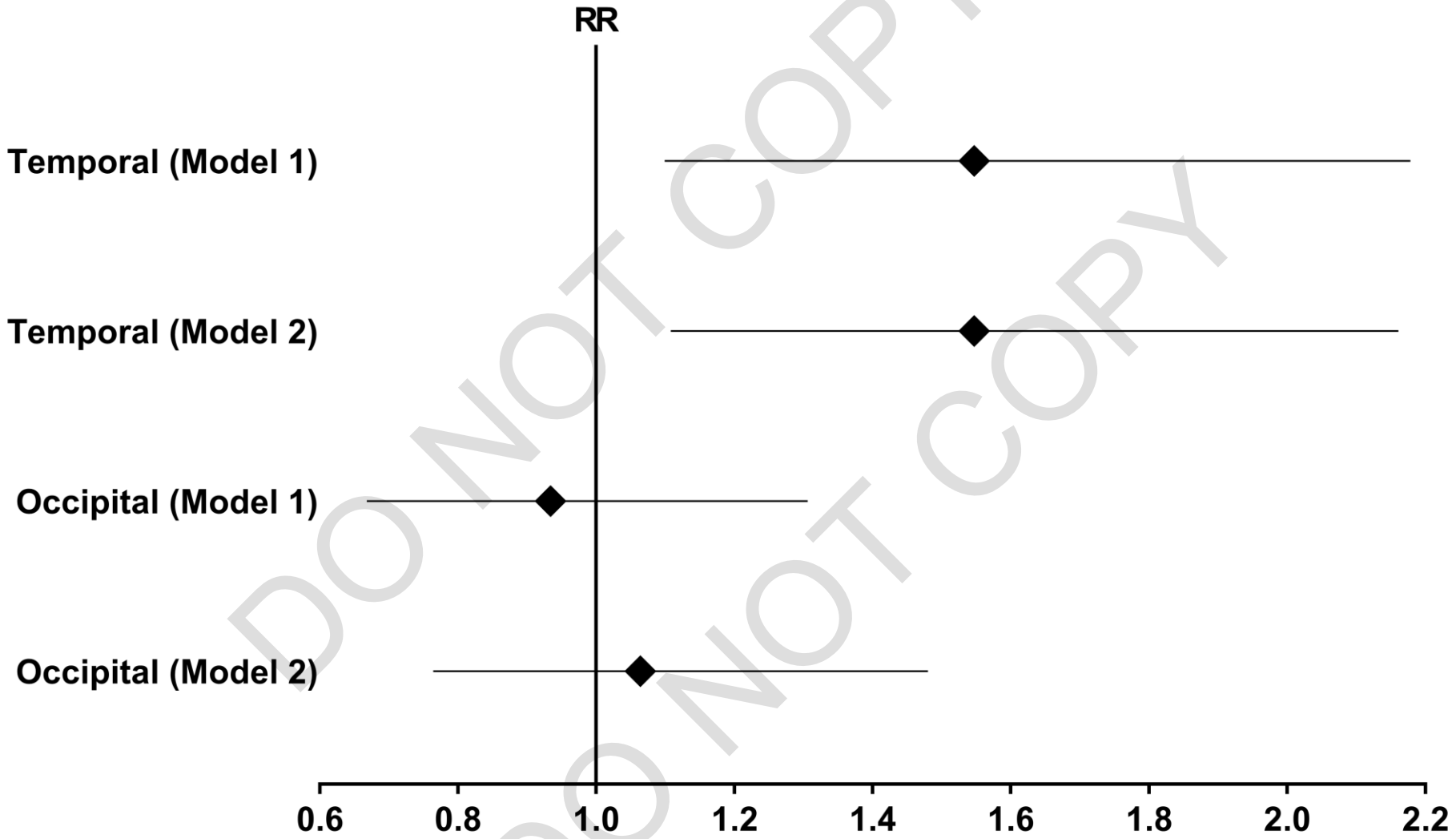
Minimally adjusted models: age, sex, education, MMSE, vascular risk (0, 1-2, 3+) and scanner

WMH NoCs and falls – maximally adjusted

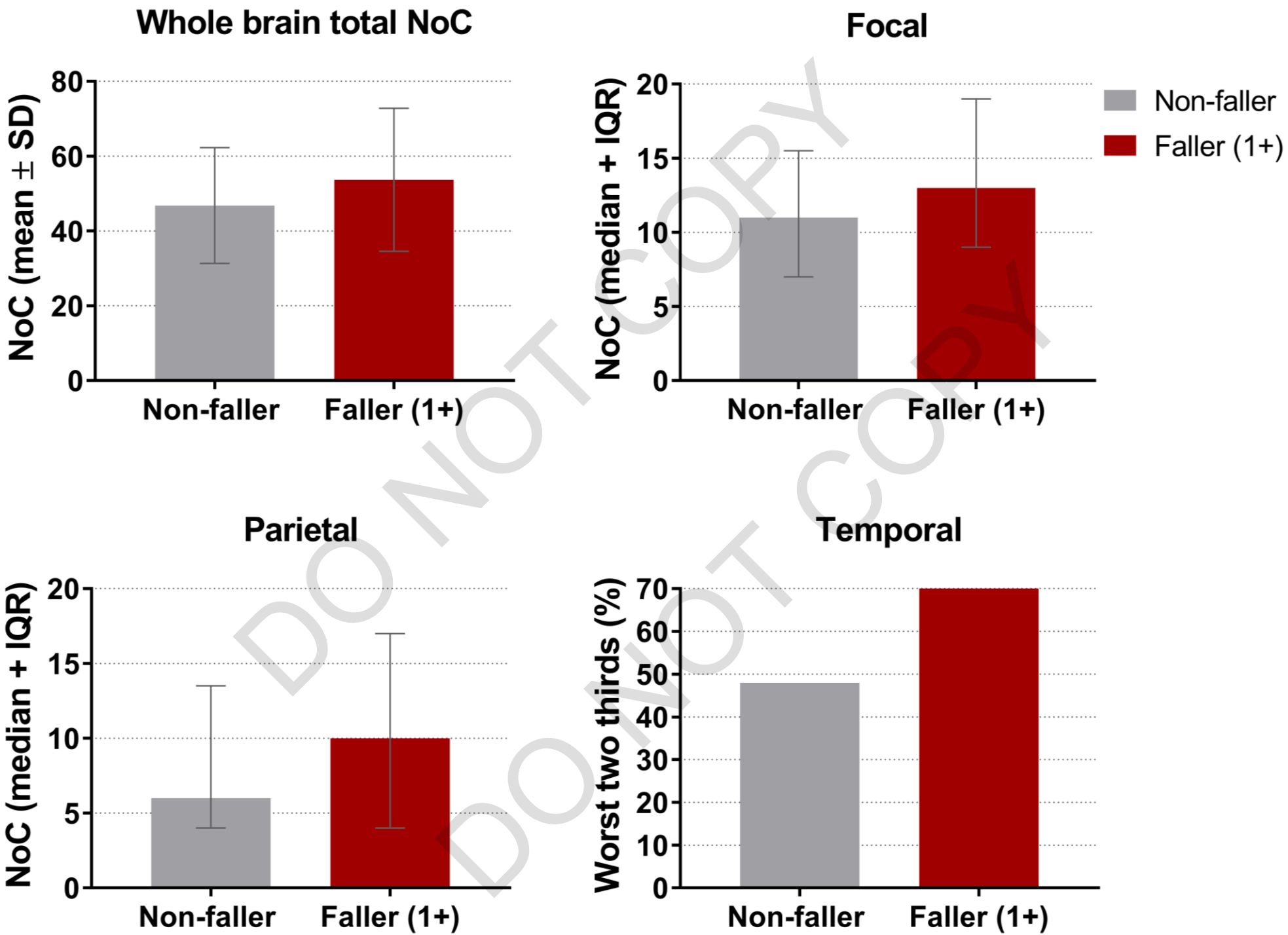


Maximally adjusted models: age, sex, education, MMSE, vascular risk (0, 1-2, 3+), scanner, total WMH volume, PPA score, TMT B and GDS

WMH NoCs and falls – minimally and maximally adjusted



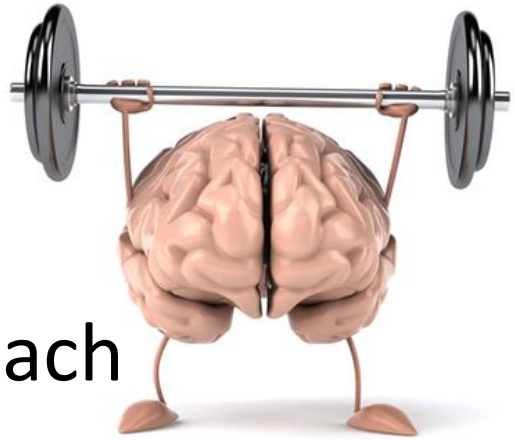
Model 1: minimally adjusted for age, sex, education, MMSE, vascular risk (0, 1-2, 3+) and scanner
Model 2: maximally adjusted for age, sex, education, MMSE, vascular risk (0, 1-2, 3+), scanner, total WMH volume, PPA score, TMT B and GDS



WMH NoCs and Sensorimotor function

WMH NoC	Multivariate model (adjusted for age, sex, education, MMSE, vascular risk (0, 1-2, 3+) and scanner)	
	B (95% CI)	*p*-value
Whole Brain NoC by size		
Focal (lowest/best tertile=ref group)	0.312 (0.014, 0.611)	0.040
Medium	0.044 (-0.001, 0.089)	0.054
NoC by location		
Frontal (lowest/best tertile=ref group)	0.371 (0.096, 0.647)	0.008
Parietal	0.021 (0.002, 0.039)	0.028

Conclusions



- Total, focal, parietal and temporal WMH NoCs were each independently associated with falls
- The strength of the association between frontal NoCs and falls was affected by mood, sensorimotor and executive function
  - which may be secondary to the known relationships between fronto-executive circuits and sensorimotor function and/or apathy
- WMH clusters present as a novel fall risk factor in this study
  - these findings need validating in future studies

Conclusions

- Sensorimotor function was associated with similar cluster locations and size to falls (except temporal lobe)
  - suggesting sensorimotor function may play a mediating role in the relationship between NoCs and falls
- Future research
  - could examine potential mechanistic relationship between temporal NoC and falls
    - ? shared cognitive pathway
    - ? complex visual processing
  - could examine impact of individual mediators (PPA, GDS and TMT B) on the relationship between WMH NoCs and falls
  - does management of vascular risk impact NoCs, and sensorimotor function and falls

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