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Detecting the effects of cerebral small vessel disease on balance control using postural, kinematic and prefrontal near infra-red spectroscopy measures

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ABSTRACT

Cerebral small vessel disease (cSVD) is a common, potentially modifiable cause of poor balance control and falls in older people, but its early effects on balance control are difficult to detect. In this exploratory study, 20 older people with a broad range of cSVD on head MRI scans (median age 74.5 years, interquartile range 68–79 years) had their balance perturbed by motorised pulls at the shoulder. Body movements, ground reaction forces and prefrontal functional near-infrared spectroscopy (fNIRS) haemodynamic responses were recorded. Head MRI scans were reviewed to produce a score of cSVD burden ranging from 0 to 7 points based on lacunes (0–3), white matter hyperintensities (0–3), and cerebral microbleeds (0–1). Participants were divided into "low" (0–2 points) and "moderate" (3–7 points) cSVD burden subgroups, each of 10 participants. Moderate vs. low cSVD burden associated with worse cognitive function. Balance and gait measures (Short Physical Performance Battery test score, tandem walking, stepping responses to manual retropulsion) were similar in the two cSVD burden groups, as were pull-related body sway and resisting ground reaction forces. More cSVD associated with less pull force to induce steps, and with greater balance-related fNIRS prefrontal cortical haemodynamic responses. Prefrontal cortical activation was the most significant measure, explaining 33% of the variation in cSVD burden, while the stepping force threshold explained 17%. Our results suggest that, in addition to cognition, prefrontal cortical responses and stepping force thresholds are likely sensitive to effects of cSVD.

Background

Falls due to poor balance control are common in older people, and they are a significant cause of injury and death (Rubenstein, 2006; Gelbard et al., 2014). The prevention of falls and contributory diseases is thus a major focus of clinical research (Sleet et al., 2008; Schwenk et al., 2012). Damage to small brain blood vessels – cerebral small vessel disease (cSVD) – is a very common, potentially modifiable (Smith and Markus, 2020) cause of poor balance (Tabara et al., 2015), and falls in older people (Srikanth et al., 2009). cSVD is thus a potential treatment target to prevent falls in those at highest risk. Despite the importance of cSVD, its early effects on balance have proved difficult to reliably detect (Pinter et al., 2017).

Sporadic cerebral small vessel disease (cSVD) is the commonest acquired brain disease (Thompson and Hakim, 2009), and the burden of disease is associated with ageing, hypertension, early life, and genetic factors (Wardlaw et al., 2019). Indeed, by the age of 60 years, neuroimaging markers of cSVD are present in over 9 in 10 adults, with the prevalence increasing further with age (de Leeuw et al., 2001). Though early cSVD is often asymptomatic (Hannawi et al., 2023), advancing cSVD can lead to a broad range of symptoms and signs including: cognitive impairment and dementia (Hainsworth et al., 2024), neuropsychiatric symptoms such as apathy and depression (Tay et al., 2019; Rensma et al., 2018; Clancy et al., 2021), parkinsonism (Jacob et al.,

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2023), slow gait (Smith et al., 2015), and falls (Srikanth et al., 2009). cSVD burden has also been shown to associate with chronic dizziness and poor balance (Ibitoye et al., 2022) together with a lower threshold for taking steps when balance is challenged (Castro et al., 2024).

Distinct from an association with slower gait (Sharma et al., 2023), the effect of cSVD on balance control has less often been a focus of investigation. The largest of the studies to date have shown no significant relationship between the burden of neuroimaging markers of cSVD and body sway across 1387 people (Tabara et al., 2015), or a measure of bipedal standing balance across 678 people (Pinter et al., 2017). Some studies have reported a relationship between cSVD and an inability to stand for sustained periods on one leg (Tabara et al., 2015; Starr et al., 2003). The specificity of single leg standing to balance control is however limited, as the measure depends on other factors such as general fitness and muscle strength (Ditroilo et al., 2010; Khanal et al., 2021). Better measures are needed to detect the effects of early cSVD on balance control.

The control of balance is commonly and efficiently studied by perturbing the body in the upright position, then measuring subsequent balance-correcting responses (Nashner, 1980). Studies of the effect of ageing on balance correcting responses have shown that older people tend to have delayed lower limb muscular and movement responses (Claudino et al., 2017; Woollacott et al., 1986; Nardone et al., 1995; Allum et al., 2002; Lin and Woollacott, 2002), which are less organised with respect to timing and sequencing (Woollacott et al., 1986; Nardone et al., 1995; Allum et al., 2002; Lin and Woollacott, 2002; Manchester et al., 1989; Stelmach et al., 1989; Gu et al., 1996; Okada et al., 2001; Tokuno et al., 2010; Fujimoto et al., 2013). Furthermore, protective stepping responses which are necessary to prevent falls occur at lower levels of instability in older than younger adults (Pai et al., 1998; Jensen et al., 2001), and these steps are commonly slower (Lee et al., 2014), multiple (Luchies et al., 1994; McIlroy and Maki, 1996; Maki et al., 2000) and of shorter length (Lee et al., 2014; Luchies et al., 1994; Schulz et al., 2005). The relevance of these ageing associated changes to cSVD are currently unclear but their dependence on cortical processing (Jacobs and Horak, 2007) implies brain pathologies such as cSVD could be important.

Separate to postural measures, measures of balance control-related brain activation could also be useful in cSVD. Neuroimaging studies have shown that such activation responses are detectable in health – for example, using functional near-infrared spectroscopy (fNIRS) (Mihara et al., 2008). These cortical activations are more prominent in older people both in health (Lin et al., 2017; Teo et al., 2018; St George et al., 2021), and even more so following brain pathology such as stroke (Mihara et al., 2012). The overactivation of prefrontal and other cortices during balance with ageing (St George et al., 2021) and pathology (Mihara et al., 2012), is explainable within modern models of brain/cognitive ageing. These predict that brain pathology (such as cSVD) will lead (at least early on) to greater and more spatially widespread task-related cortical activation (Cabeza, 2002; Davis et al., 2008; Reuter-Lorenz and Cappell, 2008; Cabeza et al., 2018). Though cSVD has not been a focus of previous work applying fNIRS in balance control, the known association between cSVD and ageing implies some of the cortical overactivation seen with ageing may be secondary to cSVD.

In this exploratory study, we aimed to identify which of a set of balance-related measures are most sensitive to associations of cSVD with balance control. We applied an established paradigm involving the recovery of balance after perturbation of the body in bipedal standing (Di Giulio et al., 2016). We modified the existing protocol (Di Giulio et al., 2016) to include a measure of prefrontal brain activation using fNIRS. We tested a small, pragmatically defined population of older people who had head magnetic resonance imaging (MRI) data from which an estimate of cSVD burden could be made. We hypothesised that (i) more cSVD associates with abnormal feet-in-place postural responses to pulls – specifically a lower resisting force and a greater displacement of the centre of mass (Di Giulio et al., 2016); (ii) more cSVD associates with inefficient stepping responses to perturbation – specifically a lower threshold to step, shorter steps, lower stepping height, and a greater number of steps; and (iii) prefrontal cortical activation following pulls associates with cSVD burden on imaging.

Materials and methods

Participants

Our aim was to investigate a moderately broad range of subjects with cSVD based on existing MRI scans. A convenience sample (Etikan et al., 2016) of twenty participants were therefore recruited from existing research volunteers (known to the researchers), patients from a general neurology clinic with dizziness/balance symptoms potentially linked to cSVD (Ibitoye et al., 2022), and patients known to the stroke unit (median age 74.5 years, interquartile range 68–79 years, 5 females, Table 1). Inclusion criteria were age 60 years or more, and available previous head MRI data. Previous head MRI images had been acquired on average 10 months prior to the research visit (interquartile range 2 to 19 months). Scanners and protocols varied across settings, but at a minimum included whole brain T1-weighted, fluid-attenuated inversion recovery and gradient echo sequences at 1.5 Tesla or 3.0 Tesla field strength. Exclusion criteria were: an inability to stand or walk unaided, an established diagnosis of dementia, known peripheral neuropathy, significant visual impairment, severe hearing impairment, or known vestibular hypofunction.

We defined MRI neuroimaging markers of cSVD using white matter hyperintensities, lacunes, and cerebral microbleeds using consensus definitions (Amin Al Olama et al., 2020), as implemented within an established score – the amended small vessel disease (cSVD) score (Amin Al Olama et al., 2020). This score is suited to MRI data acquired across clinical settings. We applied this score to quantify cSVD burden (Amin Al Olama et al., 2020), based on the review of existing head MRI scans by the first author (RI) with experience in rating cSVD burden (Ibitoye et al., 2022). We refer to this as the *amended cSVD score* in the remainder of this manuscript. The score combines a numeric measure of the burden of white matter hyperintensities (0–3 points from the modified Fazekas scale (Fazekas et al., 1993)), the number of lacunes seen (0 = 0 points, 1–2 = 1 point, 3–5 = 2 points, >5 = 3 points) and the presence or absence of microbleeds on a blood sensitive sequence (absent = 0 points, presence = 1 point).

To support summary analyses of the balance associations of cSVD burden, participants were divided to produce two equal groups based on their amended cSVD scores. Scores of 0 to 2 constituted a “low” burden, and 3 or more constituted a “moderate” group. Each resulting cSVD burden group had 10 members (Table 2).

Written informed consent was obtained from all participants. Health Research Authority approval was obtained for the work (Research Ethics Committee reference 23/NW/0061). All procedures were performed in accordance with the ethical standards of the research ethics committee.

Clinical and behavioural

Each participant had a general clinical assessment undertaken by the first author before the balance assessments. Clinical head impulse tests of the horizontal semicircular canals were performed to confirm normal vestibular function (supplemented by a video head impulse test to verify normal peripheral vestibular function – defined as both horizontal canal gains $\geq$ 0.8; Interacoustics ® EyeSeeCam). Current (state) anxiety, and general (trait) anxiety levels were estimated using the State-Trait Anxiety Inventory (STAI), which has state (STAI-S) and trait (STAI-T) components (Spielberger et al., 1983). Premorbid cognition was assessed using the National Adult Reading Test (Nelson, 1982). Global cognition was measured using the Montreal Cognitive Assessment (MoCA, English, version 7.1) (Nasreddine et al., 2005). Executive function was assessed using the Trail Making Test (Strauss et al., 2006).

Table 1

Participant characteristics. SPPB = Short Physical Performance Battery (Guralnik et al., 1994); SPPB (Balance) = the standing balance component of the SPPB; MoCA = Montreal Cognitive Assessment (Nasreddine et al., 2005); TMT B-A = Trail Making Test part B time minus part A time; STAI = State Trait Anxiety Inventory (with T for 'trait', and S for 'state') (Spielberger et al., 1983); WMH = white matter hyperintensity burden as per modified Fazekas scale (Amin Al Olama et al., 2020; Fazekas et al., 1993); Lacunes = number of lacunes (cSVD score points in brackets); Microbleeds = number of microbleeds (cSVD score in brackets); cSVD score = amended small vessel disease score (Amin Al Olama et al., 2020); biothesiometer vibration thresholds at the knees and ankles are reported.

Participant	Group	Source	Age/ years	Sex	Weight/ kg	Height/ m	Contiguous Tandem Steps	Retropulsion Steps	SPPB	SPPB (Balance)	Vibration (Knee)/ µm	Vibration (Ankle)/ µm	MoCA	TMT/ s	ABC	STAI-S	STAI-T	WMH score	Lacunes (score)	Microbleeds (score)	cSVD Score
1	Low	Stroke	68	Male	89	1.75	10	1	11	4	18.5	16	30	78.7	157	20	24	2	0 (0)	0 (0)	2
2	Low	Control	80	Male	67	1.68	4	2	12	4	19.5	12	27	49.3	157	22	34	1	1 (1)	0 (0)	2
3	Low	Control	74	Male	82	1.75	10	1	12	4	31	17	29	57.3	159	23	31	1	0 (0)	0 (0)	1
4	Low	Control	75	Female	72	1.67	3	2	10	4	13	14	28	18.0	129	42	45	1	1 (1)	0 (0)	2
5	Low	Control	79	Male	77	1.75	8	1	11	4	24	28	22	49.4	113	28	20	2	0 (0)	0 (0)	2
6	Low	General	66	Female	94	1.68	3	1	9	4	25	20	27	53.6	94	36	46	2	0 (0)	0 (0)	2
7	Low	General	77	Female	54	1.6	6	2	12	4	19	20	22	39.9	88	40	44	1	0 (0)	0 (0)	1
8	Low	General	79	Male	118	1.8	3	2	5	4	60	60	27	95.2	107	30	34	2	0 (0)	0 (0)	2
9	Low	Stroke	60	Male	79	1.73	10	1	12	4	15	18	28	11.2	160	26	21	1	0 (0)	0 (0)	1
10	Low	General	76	Male	84	1.71	10	2	11	4	27.5	30	27	19.4	130	20	28	1	0 (0)	0 (0)	1
11	Moderate	General	80	Male	91	1.65	2	2	10	4	19.5	36	22	63.1	142	31	46	2	0 (0)	1 (1)	3
12	Moderate	Stroke	71	Male	123	1.83	3	1	10	4	40	50	22	103.3	144	20	53	1	5 (2)	5 (1)	4
13	Moderate	Stroke	61	Male	80	1.78	10	2	11	4	14	21	22	118.9	151	30	32	2	6 (3)	5 (1)	6
14	Moderate	General	82	Female	59	1.63	4	3	11	4	14	21	24	74.3	119	51	53	2	0 (0)	1 (1)	3
15	Moderate	Stroke	63	Male	80	1.71	0	2	10	3	27.5	22.5	21	104.6	35	57	68	2	2 (1)	0 (0)	3
16	Moderate	General	73	Male	88	1.73	0	4	4	0	50	48	22	77.0	34	46	49	2	1 (1)	0 (0)	3
17	Moderate	General	80	Male	70	1.85	0	2	6	2	30	55	19	107.3	81	33	52	2	0 (0)	2 (1)	3
18	Moderate	Stroke	76	Female	74	1.57	2	2	8	4	30	33	25	60.8	151	35	26	2	0 (0)	1 (1)	3
19	Moderate	Stroke	68	Male	79	1.78	10	1	12	4	10	13.5	27	27.0	151	22	37	2	1 (1)	1 (1)	4
20	Moderate	Stroke	70	Male	94	1.8	5	1	12	4	19	17	25	93.4	117	22	29	2	1 (1)	3 (1)	4

Table 2

Low and moderate cerebral small vessel disease burden participant group characteristics. Median and interquartile range (IQR) data is shown, as well as two-tailed Mann-Whitney *U* test p-values. ABC = activities specific balance confidence scale; (Powell and Myers, 1995) SPPB = short physical performance battery; (Guralnik et al., 1994) STAI = State Trait Anxiety Inventory; (Spielberger et al., 1983) MoCA = Montreal Cognitive Assessment; TMT = trail making test; WMH = white matter hyperintensity burden (0 to 3, as per the modified Fazekas scale score (Amin Al Olama et al., 2020; Fazekas et al., 1993)).

	Low median (IQR)	Moderate median (IQR)	Rank sum	p
Age/years	75.5 (68–79)	72 (68–80)	107	0.94
Height/m	1.72 (1.68–1.75)	1.75 (1.65–1.8)	96	0.49
Weight/kg	80.7 (71.7–88.8)	80.4 (74.4–90.7)	100	0.73
ABC	130 (107–157)	130 (81–151)	117	0.38
Contiguous Tandem Steps	7 (3–10)	2.5 (0–5)	130	0.06
Retropulsion Steps	1.5 (1–2)	2 (1–2)	90	0.22
SPPB	11 (10–12)	10 (8–11)	121	0.24
SPPB (Balance)	4 (4–4)	4 (3–4)	120	0.08
Vibration Threshold – Knee/µm	21.8 (18.5–27.5)	23.5 (14–30)	103.5	0.94
Vibration Threshold – Ankle/µm	19 (16–28)	27.8 (21–48)	84.5	0.13
State Anxiety (STAI)	27 (22–36)	32 (22–46)	92	0.32
Trait Anxiety (STAI)	32.5 (24–44)	47.5 (32–53)	77	**0.034**
MoCA	27 (27–28)	22 (22–25)	141	**0.006**
TMT B-A	49.3 (19.4–57.3)	85.2 (63.1–105)	71	**0.011**
WMH	1 (1–2)	2 (2–2)	80	**0.025**

Vibration thresholds were measured using a biothesiometer (using ascending levels of vibration) at the lateral malleoli (ankles) and tibial tuberosities (knees); an average of left and right thresholds is reported at the knee and ankle. A general neurological examination of cranial nerve, upper and lower limb function (tone, power, reflexes, coordination and sensation) was undertaken to look for any focal neurological deficits.

General measures of balance (and gait) were then undertaken. Heel-toe (tandem) walking was assessed over 10 steps, repeated three times. The maximum number of contiguous steps across the trials was recorded. Postural reactions to manual retropulsion at the shoulder were assessed. The number of steps taken (up to 3) was recorded; where more than 3 steps were taken, participants were supported (to prevent a fall) and a value of "4″ was recorded; the best of three responses (smallest number of steps) was recorded. The Short Physical Performance Battery (SPPB) – a combined measure of gait speed, standing balance and repeated chair stands was undertaken as a summary measure of lower limb performance (Guralnik et al., 1994). Balance confidence was assessed using the Activities-specific Balance Confidence scale questionnaire (ABC) (Powell and Myers, 1995). Lower limb psychomotor speed was assessed using a foot-lift task (see Supplementary Methods).

Pull experiment

General set-up and data recording

An experimental setup for delivering pulls at the shoulder and measuring postural responses was implemented based on previous work in the laboratory (Fig. 1, see Supplementary Methods) (Di Giulio et al., 2016). Pull force delivery and the recording of kinematic and force data were done by previously published methods (Di Giulio et al., 2016) (see Supplementary Methods). The original pull experiment set-up (Di Giulio et al., 2016) was adapted to include the recording of prefrontal responses by fNIRS using an Oxymon Mk III system (Artinis Medical Systems, see below and Supplementary Methods).

Functional near-infrared spectroscopy

Functional near-infrared spectroscopy (fNIRS) is a non-invasive

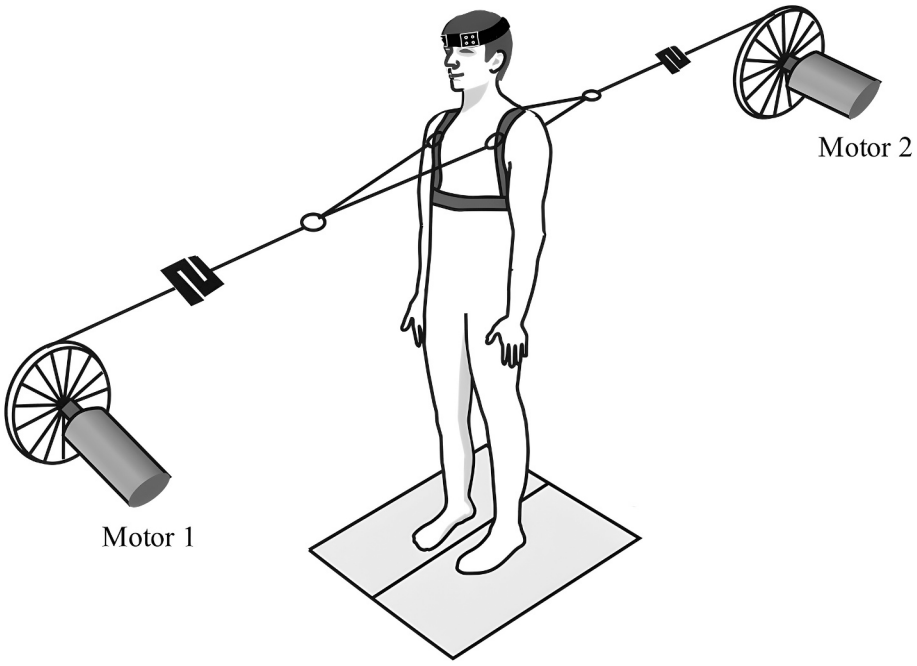

Fig. 1. Study setup. Participants stood on two force platforms. They were attached at shoulder level to two motors which delivered pull stimuli either forwards or backwards (motor 1, 2). A headband was worn over the forehead including optode holders over prefrontal areas. The image is adapted from Di Giulio et al. 2016 (Di Giulio et al., 2016).

brain imaging method which estimates changes in cortical oxyhaemoglobin and deoxyhaemoglobin from the absorption of two different wavelengths of light. A custom, non-elastic, headband was applied; this included two 2 × 2 arrays of fNIRS optode holders overlying the forehead. Any hair was moved out of the way to ensure good contact between optodes and the skin. Source and detector fibre-optic cables were connected such that each array held two source and two detector optodes, spaced 3.5 cm apart (see Supplementary Fig. 1). The inner optodes of each array were 8 cm apart and the midpoints of the arrays lay 4 cm above the nasion; this positioning resulted in the centre of the left and right arrays being situated approximately over areas F7 and F8 (in the 10–20 electroencephalography system), areas commonly sampled in fNIRS work on the prefrontal cortex (Moriguchi and Hiraki, 2013; Al-Yahya et al., 2016). With the optodes in place, the headband was further secured using a disposable net cap (Tenocom ®, China) to minimise movement during the study. fNIRS cables were secured using custom trunking, and taped to a harness to further minimise movement.

The fNIRS system delivered two continuous wavelengths of light at 760 and 850 nm. fNIRS data were synchronised with the control computer and motion capture system via an analogue channel, using a 250 ms boxcar signal at the start of each pull trial. fNIRS data were sampled at 10 Hz continuously throughout the experimental session (30–40 min). Eight fNIRS channels were defined by source-detector pairings (Supplementary Table 1). Traces were inspected to ensure good recovery of physiological (pulse-related) signals prior to experimental recordings.

Experimental protocol

The experiment involved multiple trials wherein pulls of fixed and variable force were delivered at the level of the shoulder. The design was of 64 trials delivered as eight sets of 8 pull trials, each followed by a short rest break. Data collection took 35–40 min. The trial count was selected on the basis of pilot work assessing feasibility and tolerability, to avoid fatigue, or discomfort from prolonged wearing of the headband. This count (64) was less than the 80 trials used in previous work not involving fNIRS (Di Giulio et al., 2016).

Fixed forces of 10 N and 20 N were selected as they have previously been shown to be tolerable, and sufficient to produce robust feet-in-place balance-correcting responses in older people (Di Giulio et al., 2016). The selection of pull force amplitude and direction, and the initiation of trials was as per published methods (described below) (Di Giulio et al., 2016).

Before the first trial, foot positioning was marked with chalk to ensure a consistent starting stance across the experiment. A brief tone (250 ms, 250 Hz) was delivered as a "get ready" signal. This tone was accompanied by a tightening of the kite stings linking the shoulder to the motors (sustained 0.18 N force). After 5 to 15 s of random delay (to reduce the risk of anticipatory responses), the recording of motion capture and force data commenced. Two seconds into the onset of the recording, a pull was delivered by a motor – consisting of a 100 ms ramp to the required force (see below), followed by a 1-second sustained pull. Motion and force data were recorded for a total of 7 s per trial. The fNIRS system recorded continuously.

Within each set of 8 pulls, half the trials were of a fixed force and direction: 10 N forward, 10 N backward, 20 N forward or 20 N backward; the other four trials were of variable force with two in the forward and two in the backward direction. The order of trials within each set was randomised. After each pull trial, the experimenter situated near the participant made note of whether a step was taken and this data was entered into custom control software. A predefined algorithm in custom-built LabVIEW software varied the non-fixed pull forces with the goal of defining a threshold whereby steps occurred in 50% of trials (with a target of up to 8 steps per direction) (Di Giulio et al., 2016). Where the automated process failed to produce reliable stepping responses, estimated thresholds were manually input to the software and up to 8 additional trials were undertaken (Di Giulio et al., 2016).

Preprocessing and analysis

Dedicated software and code were used to process kinematic, force and fNIRS data. Analyses were undertaken within a custom MATLAB® (version 2022b, Mathworks) script. Statistical significance was defined as a p-value of less than 0.05 (or, $q < 0.05$ for analyses corrected for multiple comparisons by false discovery rate). Mixed-effects linear regression was done using the *fitlme* MATLAB function. For regression

models, categorical variables were encoded using dummy coding.

Kinematic and force data

Kinematic and force data were pre-processed using previously described methods (Di Giulio et al., 2016) to determine centre of mass displacement, and resisting force at the level of the force plates (see Supplementary Methods). We investigated for a possible linear relationship between resisting force and pull force using simple linear regression (Wilkinson notation (Wilkinson and Rogers, 1973): *ResistingForce PullForce* + 1).

Tests of effects of participant group on force and kinematic measures were done by mixed-effects linear regression. Resisting force or centre of mass displacement were the *response variable*. Participant *group* was the predictor of interest. Age was included as a covariate of no interest, given our interest in isolating the effects of cSVD. A random intercept model was used with the average response allowed to vary randomly by participant (*ResponseVariable Group* + *Age* + (1|*Participant*)). Tests of interaction between pull force and cSVD burden group in predicting resisting force were done by linear mixed-effects regression using a random intercept model (*ResistingForce PullForce* : *Group* + *Group* + *Force* + *Age* + (1|*Participant*)).

Characteristics of the initial posture in the period before pulls were calculated using previously described methods (Di Giulio et al., 2016). Body segment characteristic were first estimated from kinematic data (see Supplementary Methods). The time period of interest was defined as between 1 and 0.5 s before pull onset (thus *after* kite strings had tightened, but before a pull). Mean lower, upper, and overall body configurations were measured to define the following variables: anterior position of the centre of mass relative to the ankle joint centre, ankle joint flexion angle, hip flexion angle and torso sagittal plane angle.

Stepping thresholds

Thresholds for taking a step were estimated from stepping responses to pulls using a previously published method (Fig. 4 and Supplementary Methods (Di Giulio et al., 2016)). Group differences (effects) in stepping thresholds were determined by linear mixed-effects regressions using a random intercept model (*Threshold Group* + *Age* + (1|*Participant*)), weighted by the reliability of threshold estimates (1/*Variance*).

Step characteristics

To enable the characteristics of individual steps to be accurately quantified, force and kinematic data were processed offline. For this purpose, step characteristics were detected algorithmically using a method similar to that described in previous work (Di Giulio et al., 2016) (see Supplementary Methods). Step variables were: step number/count, length, height, duration and onset time (see Supplementary Methods). Group differences (effects) were determined by linear mixed-effects regressions using a random intercept model (*Stepvariable Group* + *Age* + (1|*Participant*)).

Sway

The path length of anteroposterior sway of the centre of mass during the initial pre-pull period (0 s to 2 s) was calculated as a postural measure relevant to static balance. A standard formula was applied ($p = \sum_{i}^{n-1}(x_{i+1} - x_i)$, where p is the path length of sway and x is the anteroposterior component of centre of mass displacement at the i'th sample of data in a total of n data samples (Hufschmidt et al., 1980)). Group differences (effects) were determined by linear mixed-effects regressions using a random intercept model (*Sway Group* + *Age* + (1|*Participant*)).

Functional near-infrared spectroscopy

fNIRS data were pre-processed then analysed within the Near Infrared Spectroscopy (NIRS) Brain AnalyzIR Toolbox (Santosa et al., 2018) using standard methods (see Supplementary Methods). The average inter-pull interval was 42 s, giving an average trial frequency of 0.02 Hz which is above the low frequency filter (0.01 Hz) used for preprocessing (see Supplementary Methods). Across most analyses in this work, deoxygenated haemoglobin responses were non-significant. For clarity, only oxyhaemoglobin responses are reported.

To detect pull-related cortical activation responses, response data for in-place fixed-force pull trials were modelled using general linear convolution (Friston et al., 1998), within the NIRS Brain AnalyzIR toolbox (Santosa et al., 2018). Convolution has better statistical power than block averaging methods as it makes use of information from the full fNIRS time series (Pinti et al., 2019) as well as existing knowledge of the haemodynamic response at the cortex. Estimated oxyhaemoglobin concentrations were inputs to linear models. The first level analysis included all conditions of interest (i.e. from 10 N or 20 N, forward or backward pull trials) and was run for each participant separately. The observed fNIRS data were fitted to an expected response produced by convolving the stimuli (pulls) with a canonical haemodynamic response function (double-gamma function as implemented in the toolbox (Santosa et al., 2018)).

For the second level analysis, the predictor estimates for each experimental condition and each participant were input to a weighted mixed effects model within the NIRS Brain AnalyzIR toolbox (Santosa et al., 2018), estimating a fixed intercept for each experimental condition and a random intercept for each participant to attain the best overall fit to the data. The summary oxyhaemoglobin (oxyHb) response across participants was determined using a linear mixed-effects regression model (*oxyHb Condition* + (1|*Participant*) −1). *Condition* was a variable encoding the force and direction of pull (i.e. 10 N Forward, 20 N Forward, 10 N Backward or 20 N Backward); *Group* was a variable encoding Moderate, or Low cSVD burden. Correlation between balance variables (*Balance*) and the oxyhaemoglobin response was tested via regression (*oxyHb Condition* + *Condition* : *Balance* + (1|*Participant*) −1). The effect of cSVD burden was estimated with a model including age as a covariate of no interest (*oxyHb Condition* : *Age* + *Condition* : *Grouping_Variable* + (1|*Participant*) −1). cSVD burden group, amended cSVD Score and white matter hyperintensity burden score (0–3, as per the modified Fazekas scale score (Amin Al Olama et al., 2020; Fazekas et al., 1993)) were the grouping variables.

Student t-tests of the predictor co-efficient estimates for each condition (e.g. 10 N forward), or contrasts (e.g. 20 N minus 10 N) are reported. Channel results were considered significant where $p < 0.05$ after adjustment for false discovery rate across all 8 channels for that condition (reported as $q < 0.05$ in the text).

Hierarchical partitioning

To investigate the relative strengths of association of each balance-related measure with cSVD burden, we applied multiple linear regression and combined this with hierarchical partitioning. Hierarchical partitioning allows calculation of the individual contribution of many predictors to the total explained variance of a regression model (Chevan and Sutherland, 1991). The dependent variable for the model was amended cSVD score (which was treated as an interval variable for the purpose of this exploratory analysis). Balance-relevant measures (as listed in the results) were the independent variables. Age was included as a covariate in this analysis as age is known to associate with cSVD burden. Our focus was on the relative importance of balance-related measures in their sensitivity to cSVD. To improve the efficiency of the hierarchical partitioning analysis, measures with a multiplicity of variables were first reduced to a smaller number of variates by principal component analysis (Abdi and Williams, 2010) as implemented by the MATLAB's *pca* function. We used a recent implementation of the hierarchical partitioning algorithm as defined in the *glmm.hp* R package (Lai et al., 2022), within a custom R script (R version 4.3.1).

General statistical analyses

Common statistical methods were used for comparing data across the two cSVD burden groups. Participant characteristics (e.g. demographics,

balance measures, cognitive measures, see Table 2) were compared using the Mann-Whitney-*U* test (as implemented via the equivalent Rank Sum test [*ranksum* function] in MATLAB). The frequencies of stepping by group, and pull condition were compared using the Chi squared test (χ^2, for independence of two categorical variables). P-values are reported for two-tail tests. Where multiple statistical tests were performed within the same dataset (e.g. effect of participant group in predicting many stepping characteristics/variables), corrections for multiple comparisons were undertaken by false discovery rate, as implemented in the MATLAB *mafdr* function, using the Benjamin-Hochberg method.

Multichannel fNIRS data are reported corrected for multiple comparisons by the false discovery rate (Genovese et al., 2002), as implemented in the NIRS Brain AnalyzIR Toolbox (Santosa et al., 2018).

Data availability

Raw data which support these results and derived data supporting the findings in this study are available from the corresponding authors upon reasonable request.

Results

Participant characteristics

Participants were divided into two equal groups based on their amended cSVD scores (Table 2). The moderate cSVD burden group had worse global cognition (Montreal Cognitive Assessment, $p = 0.006$, Table 2) and worse executive function (Trail Making Test, $p = 0.011$), than the low cSVD burden group. General (trait) anxiety levels were also higher in the moderate burden cSVD group (STAI-T, $p = 0.034$, Table 2). General balance measures were the number of contiguous tandem steps taken, steps following manual retropulsion (a backward pull at the shoulder) and short physical performance battery scores (SPPB, including specifically the balance subcomponent); these measures did not differ significantly between the two groups ($p > 0.05$, Table 2). Vibration thresholds at the ankles and knees did not differ significantly between the two groups ($p > 0.05$, Table 2). Participant age, height and weight also did not differ significantly between the two cSVD burden groups ($p > 0.05$, Table 2). The moderate cSVD group tended to be *younger* than the low cSVD burden group (median 72 years vs 76 years respectively; Table 2). Foot lift reaction times (as a measure of lower limb psychomotor speed) did not differ significantly between the two cSVD burden groups (mean [S.D.]|Low: 0.597 [0.107] s, Moderate: 0.554 [0.0972] s; Group $\beta = -0.0488$ s, $p = 0.17$).

Participant characteristics, including demographics, performance on general balance measures, cognitive performance and summary neuroimaging measures of cSVD burden are summarised in Table 1. Clinical features are summarised in Supplementary Table 2 (comorbidities, medication, and general neurological examination findings and – for previous stroke patients – stroke syndrome and examination findings).

In-place balance-correcting postural responses to pulls

First, we examined postural responses during feet-in-place fixed force pull trials (10 N or 20 N). An in-place response was defined as maintaining balance such that there were no steps taken following the pull. Five hundred and twenty-two trials were included in this analysis (one or more steps were taken in 63 of the 585 trials and thus excluded, Table 3).

It is useful to briefly summarise the associations of stepping, and thus the data excluded from this analysis. Taking a step (stepping) was more likely with 20 N than 10 N pulls in the backward direction in low cSVD burden participants ($\chi^2 = 22.9$, $p < 0.001$). Stepping was also more likely for pulls in both forward and backward directions in moderate cSVD burden participants compared to the low cSVD burden group (Forward $\chi^2 = 15.6$, $p < 0.001$; Backward $\chi^2 = 18.9$, $p < 0.001$; Table 3). Due to consistent stepping, three participants contributed no trial data from 20 N backward pulls to these analyses (two in the moderate cSVD burden group, 1 in the low cSVD burden group).

In-place pull trials produced stereotyped behavioural responses. At the onset of the pull, the body initially swayed in the direction of the pull (Fig. 2; additional data in Supplementary Fig. 2 and Supplementary Fig. 3). Around 150 ms later, the ground reaction force reversed in direction due to a *resisting force* which opposed the pull. The average resisting force was approximately equal to the delivered pull force (mean [SD]|10 N pull: 9.53 [2.17] N; 20 N pull: 20.1 [3.46] N; Supplementary Fig. 4). Average displacement of the centre of mass by pulls was more for 20 N than 10 N pulls (mean [SD]|10 N pull: 10.8 [8.65] mm; 20 N pull: 15.6 [12.4] mm; Supplementary Fig. 4).

Postural responses for in-place trials are similar across small vessel disease groups

We compared resisting force and centre of mass responses between the two cSVD burden groups. For in-place pull trials, resisting force did not differ significantly between the two cSVD burden groups, for forward or backward pull directions at either 10 N or 20 N (10 N Forward Group $\beta = 0.422$ [95% C.I. −1.06 to 0.218] N, $F[1,156] = 1.69$, $p = 0.20$; 10 N Backward Group $\beta = 0.405$ [95% C.I. −0.251 to 1.06] N, $F[1,160] = 1.49$, $p = 0.22$; 20 N Forward Group $\beta = 0.355$ [95% C.I. −1.37 to 0.657] N, $F[1,143] = 0.481$, $p = 0.49$; 20 N Backward Group $\beta = 0.473$ [95% C.I. −1.42 to 2.37] N, $F[1,114] = 0.244$, $p = 0.62$; Supplementary Fig. 4). Centre of mass displacement also did not differ significantly between the two groups for 10 N or 20 N trials (10 N Forward Group $\beta = 5.64$ [95% C.I. −1.27 to 12.5] mm, $F[1,156] = 2.6$, $p = 0.11$; 10 N Backward Group $\beta = 2.11$ [95% C.I. −10.3 to 6.07] mm, $F[1,160] = 0.26$, $p = 0.61$; 20 N Forward Group $\beta = 4.99$ [95% C.I. −5.71 to 15.7] mm, $F[1,143] = 0.849$, $p = 0.36$; 20 N Backward Group $\beta = 0.496$ [95% C.I. −11.1 to 12.1] mm, $F[1,114] = 0.00722$, $p = 0.93$; see Supplementary Fig. 4).

A scatterplot showed a linear relationship between resisting force

Table 3
Stepping in pull trials. Stepping data is shown for Low and Moderate cerebral small vessel disease (cSVD) burden groups. The number of trials in each shoulder pull direction (*Forward*, *Backward*), or combined (*Any* direction) are shown. *Step* means one or more steps occurred, and *No Step* means no steps were taken following the pull. χ^2 statistics for independence of cSVD burden group and stepping are shown for 10 N and 20 N data, and relatedly for force (10 or 20 N) and stepping (step/no step) for each cSVD burden group.

		Low		Moderate		Chi square findings			
		10 N	20 N	10 N	20 N	10 N χ^2, p-value	20 N χ^2, p-value	Low χ^2, p-value	Moderate χ^2, p-value
Forward	Step	0	0	1	17	$\chi^2 = 1.0063, p = 0.32$.	$\chi^2 = 18.748, p < 0.001$.	N/A	$\chi^2 = 15.561, p < 0.001$.
	No Step	80	81	79	65				
Backward	Step	0	19	3	23	$\chi^2 = 3.1297, p = 0.08$.	$\chi^2 = 0.4516, p = 0.50$.	$\chi^2 = 22.8681, p < 0.001$.	$\chi^2 = 18.9216, p < 0.001$.
	No Step	84	60	79	57				
Any Direction	Step	0	19	4	40				
	No Step	164	141	158	122				

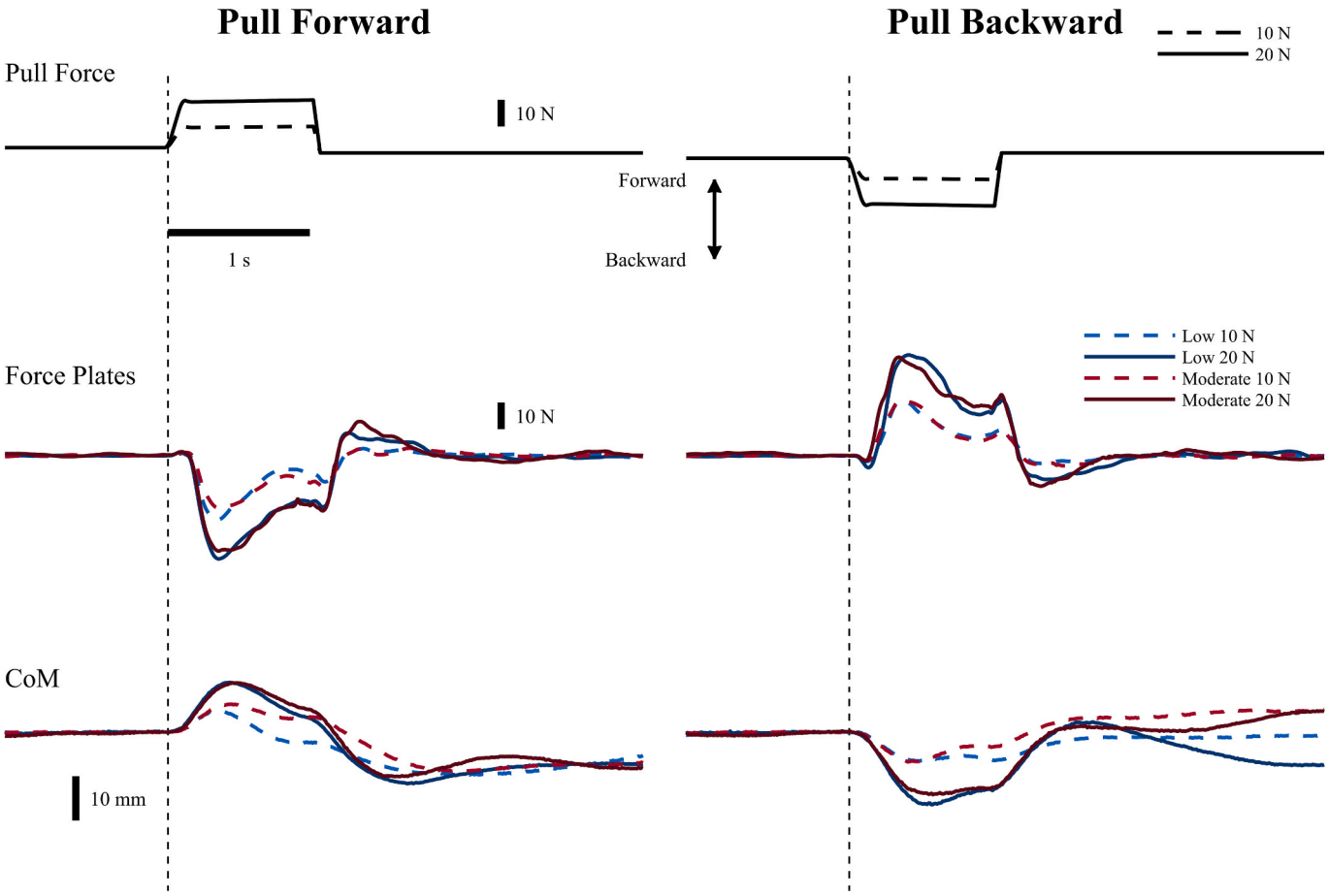

Fig. 2. Postural responses to fixed force pulls. Postural responses to pulls at the shoulder are summarised. Plots of pull force, mean anteroposterior force plate measurements, and mean centre of mass displacement (CoM) are shown for feet-in-place pull responses. Both forward and backward directions are show, for 10 N and 20 N pulls. The line plots show the average for each of the two small vessel disease burden groups (cSVD: Low, Moderate). The plots have been aligned to the onset of the pull (vertical dashed line). Note the similarity between the shape of the force place force, and displacement measures across pull conditions, and the scaling of these responses with pull force.

and pull force (Low cSVD burden: Force $\beta = 0.876$ [95% C.I. 0.835 to 0.916] N/N, $F[1,258] = 1820$, $p < 0.001$; Moderate cSVD burden: Force $\beta = 0.911$ [95% C.I. 0.864 to 0.959] N/N, $F[1,256] = 1420$, $p < 0.001$; Fig. 3). We investigated whether the scaling (slope) between resisting

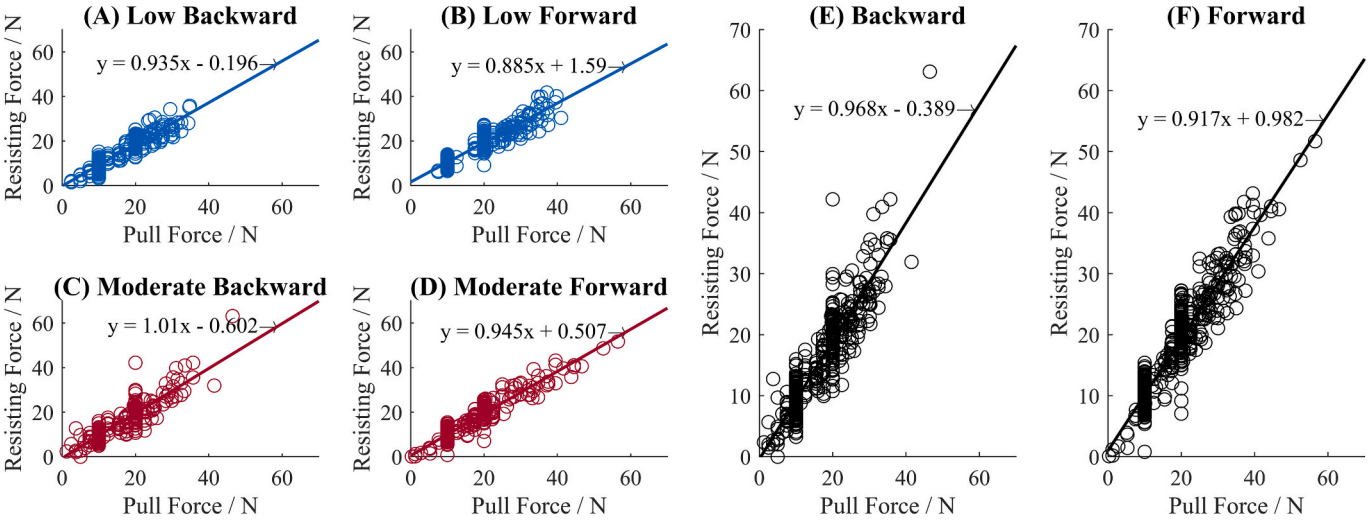

Fig. 3. Linearity of the relationship between resisting force and pull force. For all feet-in-place responses to shoulder pulls, scatter plots of pull force and resisting force are shown by pull direction (Forward or Backward) and group (Low or Moderate cerebral small vessel disease [cSVD] burden). Each data point (circle) represents a pull trial. Low cSVD burden group participant data is shown in blue, moderate cSVD burden data is in red, and pooled data (across all participants) is in black. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

force and pull force was influenced by cSVD burden group across all in-place pull trials (including both fixed and variable pull forces); this analysis included 1299 trials (Table 3). There was no significant interaction between pull force and cSVD burden group in predicting average resisting force for either backward, or forward pulls (BACKWARD Interaction $\beta = \beta = 0.0108$ [95% C.I. −0.133 to 0.111] N/N, F[1,489] = 0.0301, p = 0.86; FORWARD Interaction $\beta = 0.0541$ [95% C.I. −0.131 to 0.0227] N/N, F[1,512] = 1.91, p = 0.17). The scaling of resisting force with pull force in in-place trials thus did not differ significantly between the two groups.

Small vessel disease associates with lower thresholds for stepping

Stepping force thresholds varied by cSVD burden group and pull direction (Fig. 4 and see Supplementary Table 3). We investigated the effect of cSVD burden on the stepping threshold, adjusted for linear effects of age. There was significant interaction between pull direction and participant group in predicting stepping force thresholds (Interaction $\beta = 0.144$ [95% C.I. 0.0975 to 0.191] N/kg; F[1,35] = 39.1, p < 0.001), consistent with a stronger association between greater cSVD burden and lower stepping force thresholds for backward compared to forward pulls. For both forward and backward pulls, the moderate cSVD burden group had significantly lower stepping thresholds than the low cSVD burden group (BACKWARD mean [S.D.]|Low: 0.429 [0.0591] N/kg, Moderate: 0.283 [0.0999] N/kg; $\beta = -0.179$ [95% C.I. −0.244 to −0.114] N/kg; F[1,17] = 33.9, p < 0.001; FORWARD mean [S.D.]|Low: 0.396 [0.0953] N/kg, Moderate: 0.432 [0.119] N/kg; $\beta = 0.088$ [95% C.I. 0.000877 to 0.175] N/kg; F[1,17] = 4.54, p = 0.048). Stepping force thresholds did not correlate with state or trait anxiety, for either backward or forward stepping (Forward: State Anxiety (STAI-S) r = −0.127, p = 0.59, Trait Anxiety (STAI-T) r = 0.0540, p = 0.82; Backward: State Anxiety (STAI-S) r = −0.442. p = 0.05, Trait Anxiety (STAI-T) r = −0.164, p = 0.49).

Next, we assessed the characteristics of stepping responses to pulls (number/count, length, height, duration and onset time). Examples of stepping responses with one, and more than one step, are illustrated in Fig. 4A. These measures did not differ significantly between the two cSVD burden groups in either the backward or forward directions when

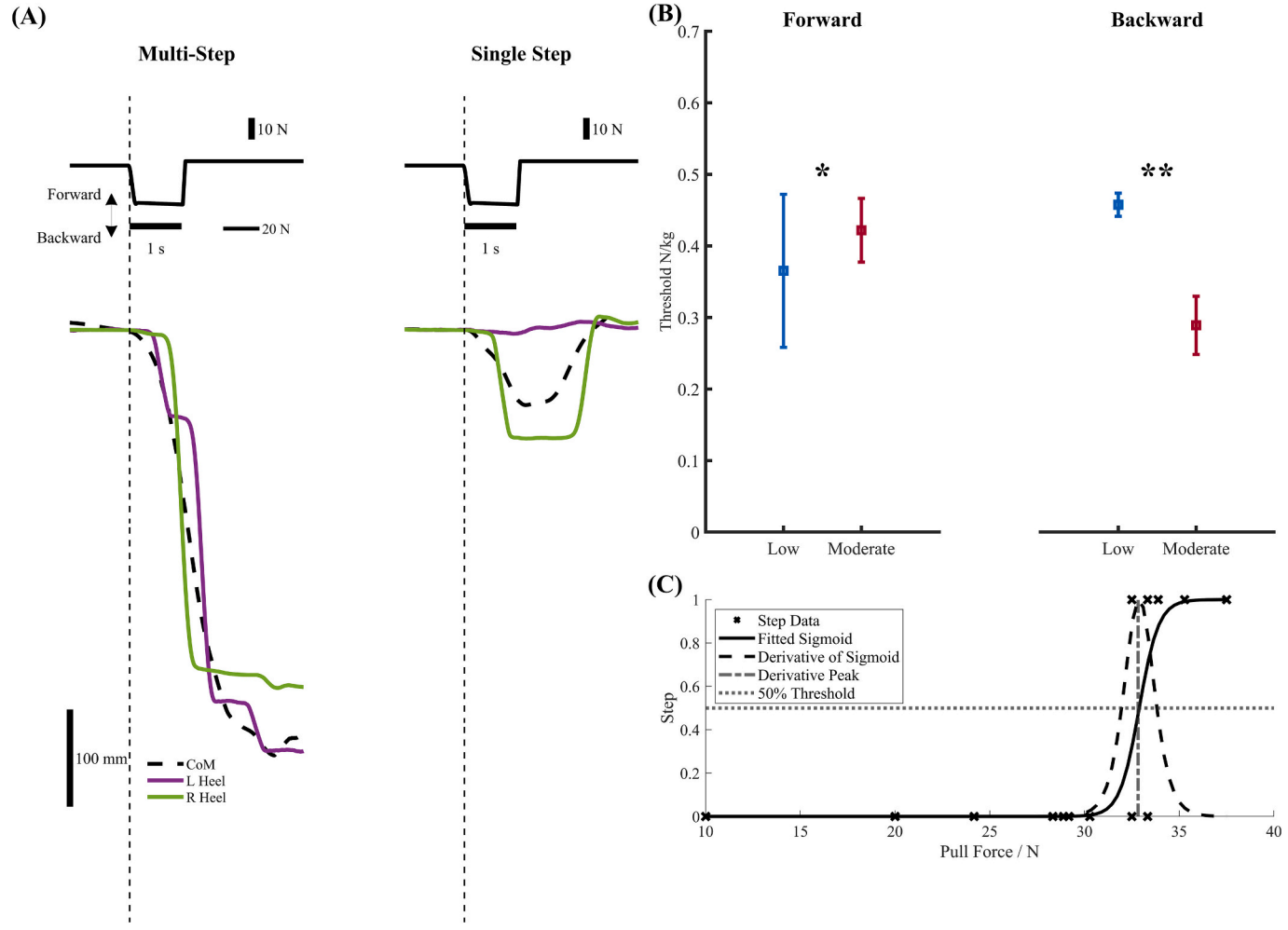

Fig. 4. Stepping characteristics and force thresholds. (A) Single trial plots of a 20 N backward shoulder pull showing foot position and centre of mass in two participants, selected to illustrate a multi-step, and a single step response. The multi-step plot shows multiple backward steps following the pull; the single step plot shows a single backward step. Green = right heel; purple = left heel; dashed black line = centre of mass. (B) Stepping force threshold estimates for each cerebral small vessel disease (cSVD) burden group are shown; blue represents low cSVD burden, and red represents moderate cSVD burden. Error bars represent 95% standard error of the mean. Thresholds were normalised (pull force divided by participant weight). Significant effects of participant *group* in a linear mixed effects model with age as a covariate of no interest are shown (* is p < 0.05; ** is p < 0.001); for visualisation purposes, the numerical data is presented after adjustment for age. (C) The process of stepping threshold estimation is shown for an example participant. Data points (x) represent pull trials with no step (y-axis value = 0), or one or more steps (y-axis value = 1). A sigmoid curve is fitted (solid line), then differentiated (dashed line). The stepping force threshold is the pull force at the peak of the fit sigmoid function, and the width of the differentiated curve reflects the variability of the estimate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

adjusted for multiple comparisons (false discovery rate $q > 0.05$; Forward: count $F(1,650) = 0.312$, $p = 0.58$, height $F(1,253) = 0.0447$, $p = 0.83$; length $F(1,253) = 0.0962$, $p = 0.76$; onset $F(1,133) = 1.28$, $p = 0.26$; Backward: count $F(1,642) = 0.00165$, $p = 0.97$, $q = 0.97$, height $F(1,328) = 0.105$, $p = 0.75$, $q = 0.97$; length $F(1,328) = 4.1$, $p = 0.044$, $q = 0.088$; onset $F(1,148) = 5.31$, $p = 0.023$, $q = 0.088$; length, height, duration and onset are shown in Supplementary Fig. 5).

We investigated posture during the initial pre-pull period (Supplementary Fig. 6). The anterior position of the centre of mass relative to the ankle joint centre, ankle joint flexion angle, hip flexion angle and torso sagittal plane angle were compared at 150 ms before pulls (Supplementary Fig. 6). None of the initial posture measures differed significantly between the two cSVD burden groups (anterior position of centre of mass relative to ankle joint centre mean [S.D.]|Low: 98 [23.6] mm, Moderate: 104 [25] mm; $F[1,1296] = 0.398$, $p = 0.53$; ankle flexion angle mean [S.D.]|Low: 82.9 [5.01] degrees, Moderate: 82.4 [4.64] degrees; $F[1,1296] = 0.092$, $p = 0.76$; hip flexion angle mean [S.D.]|

Low: 12.5 [6.37] degrees, Moderate: 10.6 [6.39] degrees; $F[1,1296] = 0.647$, $p = 0.42$; torso sagittal plane angle mean [S.D.]|Low: 8.64 [4.57] degrees, Moderate: 4.9 [5.53] degrees; $F[1,1296] = 4.52$, $p = 0.034$, $q = 0.14$).

Next, we compared postural sway during quiet standing (the two-second period before pull onset). The path length of sway was not significantly different between the two cSVD burden groups (Mean [S.D.]|Low: 92.8 [36.6] mm, Moderate: 97 [24.8] mm, Group $\beta = 4.06$ [95% C.I. −14.1 to 22.2] mm, $F[1,1295] = 0.192$, $p = 0.66$; Supplementary Fig. 7).

Prefrontal activation is influenced by pull force and direction

To investigate the recovery of pull-related prefrontal cortical activity, we summarised fNIRS pull responses across all in-place pull trials using data from all participants (Fig. 5). Oxyhaemoglobin levels peaked at 5 s following pull onset in all channels (Response Peak mean [S.D.]|0.185 [0.0765] HbO2/μM; Response Peak Time mean [S.D.]|5.03 [0.773] s, Fig. 5A), similar to the canonical haemodynamic response function (Friston et al., 1998; Lindquist et al., 2009) – a model for cortical activation responses to stimuli (Fig. 5B). Prefrontal activity therefore significantly increased in the period following a pull.

To investigate the effects of pull force and direction on brain responses, we estimated prefrontal activity following fixed force (10 N and 20 N) pulls. No significant increase in prefrontal oxyhaemoglobin levels (prefrontal activation) occurred for 10 N pulls in either direction ($q > 0.05$, Fig. 6A). For 20 N forward pulls, there was significant activation over the right middle frontal area (D = detector, S = source; D2S2: $t(73) = 3.35$, $q = 0.021$). For 20 N backward pulls there was significant bilateral activation over most of the prefrontal channels (7 channels, D2S1: $t(73) = 6.94$, $q < 0.001$; D1S2: $t(73) = 12.2$, $q < 0.001$; D2S2: $t(73) = 9.18$, $q < 0.001$; D3S3: $t(73) = 3.79$, $q < 0.001$; D4S3: $t(73) = 5.92$, $q < 0.001$; D4S4: $t(73) = 5.38$, $q < 0.001$; D1S2: $t(73) = -3.26$, $q = 0.004$).

Prefrontal activation was greater for 20 N than 10 N pulls in four channels overlying right and left dorsolateral prefrontal areas (D2S1: $\beta = 33.8$ μmol/l, $t(73) = 5.47$, $q < 0.001$; D1S2: $\beta = 40$ μmol/l, $t(73) = 5.83$, $q < 0.001$; D2S2: $\beta = 32.4$ μmol/l, $t(73) = 5.93$, $q < 0.001$; D4S3: $\beta = 21.5$ μmol/l, $t(73) = 3.98$, $q < 0.001$; Fig. 6B). Prefrontal activation was also greater for backward compared to forward pulls in 5 channels overlying the right dorsolateral prefrontal, left dorsolateral prefrontal and left ventromedial prefrontal areas (D1S2: $\beta = 51.4$ μmol/l, $t(73) = 7.52$, $q < 0.001$; D2S2: $\beta = 20.3$ μmol/, $t(73) = 3.73$, $q = 0.003$; D4S3: $\beta = 17.9$ μmol/l, $t(73) = 3.44$, $q = 0.005$; D4S4: $\beta = 22.4$ μmol/l, $t(73) = 3.2$, $q = 0.008$; D3S3: $\beta = 8.46$ μmol/l HbO2, $t(73) = 2.63$, $q = 0.034$; Fig. 6B). There was significant interaction between pull force and pull direction in the prediction of prefrontal activation across most prefrontal channels, in keeping with disproportionally greater activation in response to backward 20 N pulls (5 channels: D2S1: $\beta = 20.9$ μmol/l, $t(73) = 3.39$, $q = 0.006$; D1S2: $\beta = 42.3$ μmol/l, $t(73) = 6.19$, $q < 0.001$; D2S2: $\beta = 21.6$ μmol/l, $t(73) = 3.98$, $q = 0.001$; D4S3: $\beta = 15.2$ μmol/l, $t(73) = 2.92$, $q = 0.019$; D4S4: $\beta = 17.5$ μmol/l, $t(73) = 2.5$, $q = 0.047$; Fig. 6B).

Prefrontal activation correlates with balance performance

To investigate the relevance of brain responses to balance control, we correlated prefrontal activation responses with general measures of balance performance (Fig. 7). More steps on manual retropulsion (worse balance performance) correlated with more prefrontal activation (Fig. 7A). In the 10 N forward condition, significant correlation was observed over the left middle frontal area (D3S3: $t(69) = 3.28$, $q = 0.026$). In the 20 N forward and 20 N backward conditions, significant correlation occurred across most prefrontal areas (FORWARD: 5 channels; D2S1: $t(69) = 3.27$, $q = 0.005$; D2S2: $t(69) = 2.69$, $q = 0.024$; D3S3: $t(69) = 6.83$, $q < 0.001$; D4S3: $t(69) = 4.06$, $q = 0.001$; D3S4: $t(69) = 3.46$, $q = 0.005$; BACKWARD: 6 channels; D2S1: $t(69) = 6.67$, $q < 0.001$; D1S2: $t(69) = 7.51$, $q < 0.001$; D2S2: $t(69) = 5.45$, $q < 0.001$;

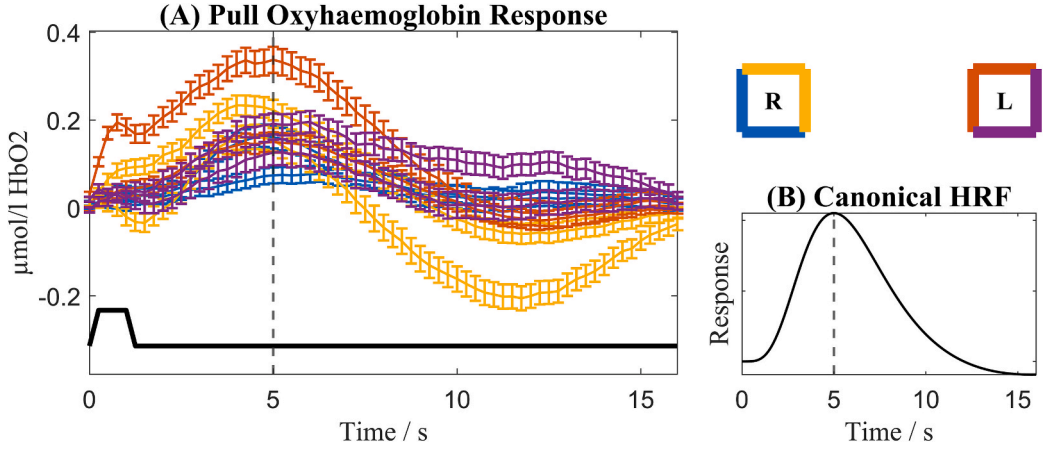

Fig. 5. Deconvolved pull-related prefrontal oxyhaemoglobin responses. (A) Oxyhaemoglobin response data to shoulder pulls is shown across functional near infrared spectroscopy channels. Oxyhaemoglobin concentration data from all feet-in-place pull trials across all participants was deconvolved using a finite impulse response model with responses proportional to pull force. Mean and standard errors of the response (error bars +/− 1.96 S.D.) are shown. The dashed line is average time at the peak of the response curves. Detector (D1-4) and source (S1-4) configurations over the right (R) and left (L) prefrontal areas are shown on the right. (B) A model synthetic canonical haemodynamic response function (HRF) is shown, (Friston et al., 1998) with a peak at 5 s (dashed line).

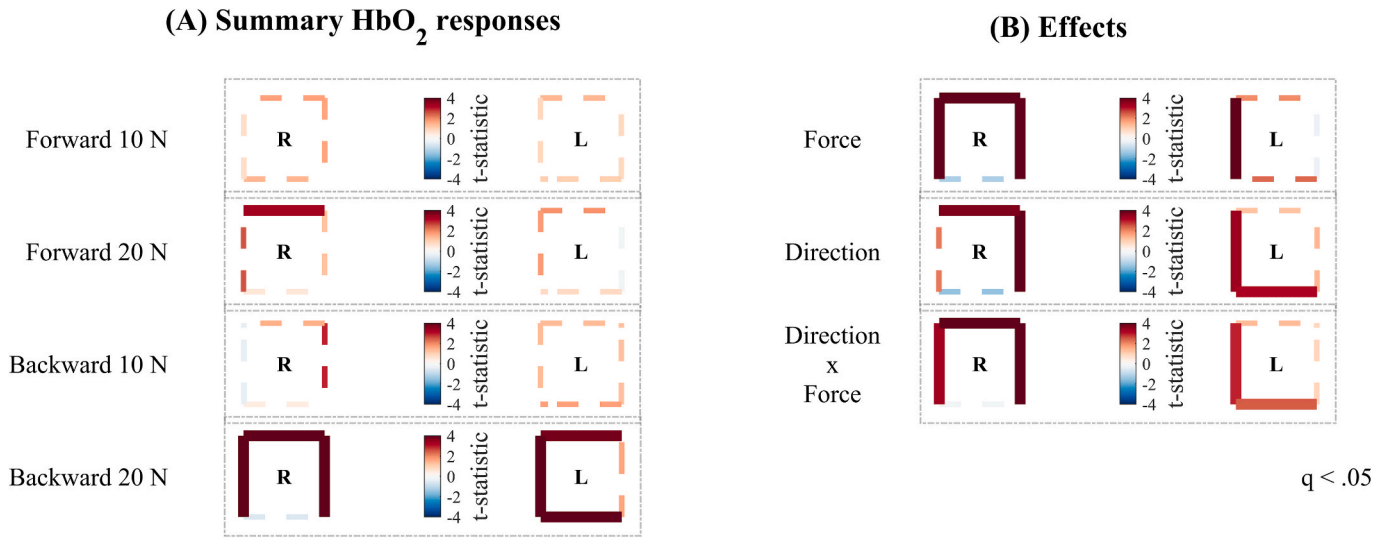

Fig. 6. Prefrontal activation by pull force and direction. (A) Summary oxyhaemoblogin responses to shoulder pulls are shown in channels overlying the right and left prefrontal cortical areas using data from all participants, separated by the force (10 N or 20 N) and direction (forward or backward) of pulls. Red lines represent cortical "activation" (increased blood flow), and blue lines represent deactivation. Thick lines represent statistical significance after correction for multiple comparisons across all 8 channels by false discovery rate ($q < 0.05$). (B) Effects of pull force, pull direction (backward > forward) and the interaction of pull force and direction are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

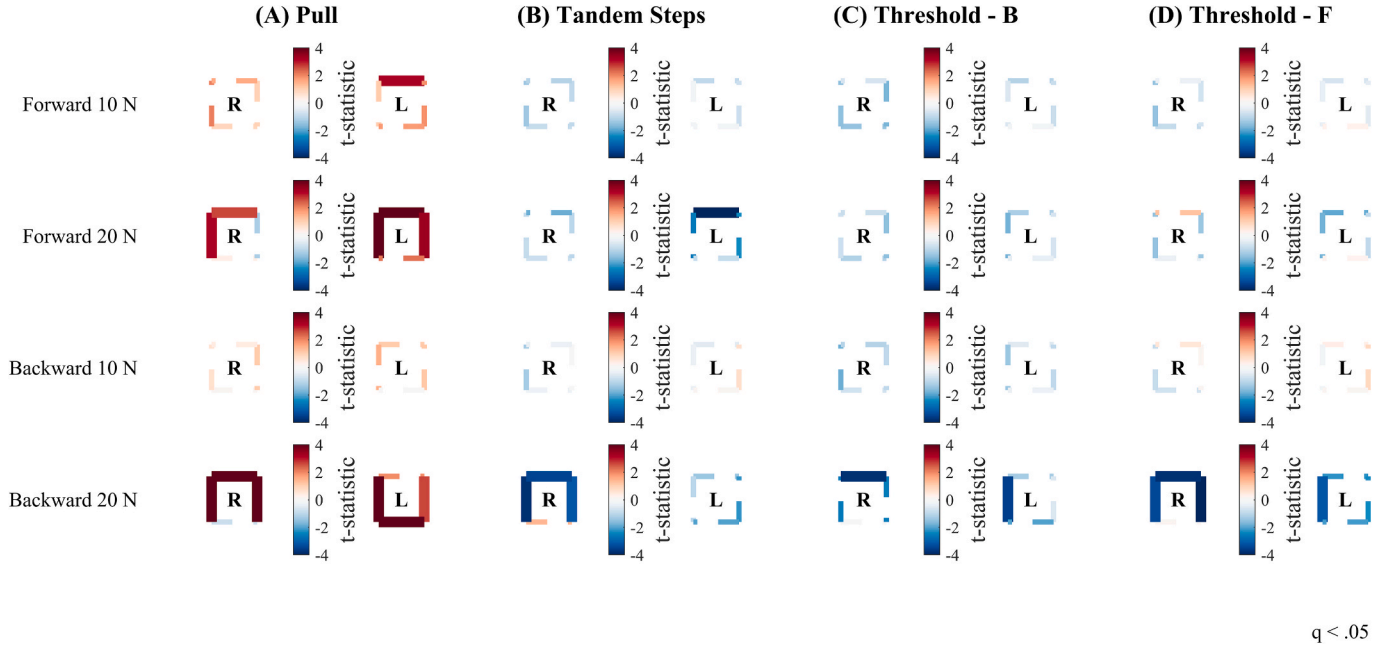

Fig. 7. Correlation between general measures of balance and pull-related prefrontal activation. Data from all in-place fixed force shoulder pull trials (10 N or 20 N, forward or backward) were used. Functional near infrared oxyhaemoglobin activation responses were correlated against general balance measures. (A) Pull = steps taken following manual retropulsion (more is worse balance performance); (B) Tandem Steps = number of good contiguous tandem steps out of 10 (more is better balance performance); (C) Threshold – B = force threshold for backward stepping (higher is worse balance performance); (D) Threshold – F = force threshold for forward stepping (higher is worse balance performance). For plots (A) to (D): red lines represent cortical "activation" (increased blood flow), and blue lines represent deactivation. Thick lines represent statistical significance after correction for multiple comparisons across all 8 channels by false discovery rate ($q < 0.05$). Note the correlation between more prefrontal cortical activation and worse balance performance (more retropulsion steps, fewer good tandem steps, lower backward and forward stepping force thresholds). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

D4S3: $t(69) = 4.12$, $q < 0.001$; D3S4: $t(69) = 2.66$, $q = 0.017$; D4S4: $t(69) = 5.82$, $q < 0.001$).

More contiguous steps on tandem walking (better balance performance) correlated with less prefrontal activation (Fig. 7B). In the 20 N forward condition negative correlation occurred over the left middle frontal area (D3S3: $t(69) = -4.21$, $q = 0.001$). In the 20 N backward condition, negative correlation occurred over right prefrontal areas (3 channels: D2S1: $t(69) = -3.83$, $q = 0.004$; D1S2: $t(69) = -3.19$, $q = 0.011$; D2S2: $t(69) = -3.48$, $q = 0.007$). Greater stepping force thresholds correlated with less prefrontal activation (Fig. 7C and D). For backward pulls, stepping force thresholds correlated with less activation in the 20 N backward condition over the right and left middle frontal areas (D2S2: $t(69) = -3.84$, $q = 0.004$; D4S3: $t(69) = -3.54$, $q = 0.006$). Similarly, for forward pulls, stepping force thresholds correlated with

less prefrontal activation in the 20 N backward condition over right superior frontal, right and left middle frontal areas (D2S1: t(69) = −3.43, q = 0.005; D1S2: t(69) = −4.35, q < 0.001; D2S2: t(69) = −3.81, q = 0.002; D4S3: t(69) = −3.21, q = 0.008). Prefrontal activation did not correlate significantly with either lower limb performance (SPPB), or balance confidence (ABC). In summary, more steps following retropulsion, poorer tandem walking, and lower stepping force thresholds correlated with more prefrontal activation for in-place pull trials.

Small vessel disease burden correlates with prefrontal activation

Next, we looked at pull-related prefrontal activation by cSVD burden group for fixed pull forces (10 N and 20 N) and both forward and backward pull directions (Fig. 8). In the moderate cSVD burden group, there was significant activation for 20 N pull conditions (q < 0.05, Fig. 8B). For 20 N forward pulls there was significant activation over right and left middle frontal areas (D2S1: t(65) = 3.05, q = 0.013; D2S2: t(65) = 4.35, q < 0.001; D3S3: t(65) = 5.5, q < 0.001; D4S3: t(65) = 3.12, q = 0.013). For backward pulls, 10 N pull force associated with significant activation over the right superior frontal area (D1S2: t(65) = 3.12, q = 0.043) and for 20 N pull force, activation was significant in most channels (D2S1: t(65) = 6.78, q < 0.001; D1S2: t(65) = 10.7, q < 0.001; D2S2: t(65) = 9.46, q < 0.001; D4S3: t(65) = 4.92, q < 0.001; D4S4: t(65) = 4.87, q < 0.001). In the low cSVD burden group, there was no significant prefrontal activation in any of the pull conditions (q > 0.05, Fig. 8A).

SVD burden influenced prefrontal activation (Fig. 8C). For 20 N forward pulls, the moderate cSVD burden group had more prefrontal activation than the low burden group over left middle and inferior frontal areas (D3S3: t(65) = 4.85, q < 0.001; D3S4: t(65) = 3.12, q = 0.022). For 20 N backward pulls, the moderate cSVD burden group showed greater activation than the low burden group bilaterally in most prefrontal areas (D2S1: t(65) = 6.58, q < 0.001; D1S2: t(65) = 5.49, q < 0.001; D2S2: t(65) = 6.07, q < 0.001; D4S3: t(65) = 3.08, q = 0.01; D3S4: t(65) = 2.48, q = 0.042; D4S4: t(65) = 4.29, q < 0.001). More cSVD therefore associated with greater prefrontal activation in response to 20 N pulls.

We conducted further analyses across all participants to test for correlation (rather than association) of fNIRS response with cSVD burden. We used the white matter hyperintensity score, and the amended cSVD score as alternative measures of cSVD burden (Fig. 9). Greater amended cSVD score correlated with more prefrontal activation for 20 N pulls (Fig. 9A). For 20 N forward pulls correlation was significant over the left inferior and middle frontal areas (D3S3: t(65) = 3.42, q = 0.009; D3S4: t(65) = 3.42, q = 0.009). For 20 N backward pull, correlation was significant over most areas (D2S1: t(65) = 4.81, q < 0.001; D1S2: t(65) = 4.3, q < 0.001; D2S2: t(65) = 2.79, q = 0.018; D4S3: t(65) = 3.05, q = 0.011; D3S4: t(65) = 3.46, q = 0.005; D4S4: t(65) = 3.03, q = 0.011). Results for greater white matter hyperintensity score were similar to those for amended cSVD score (Fig. 9B). WMH score correlated with prefrontal activation for 20 N forward, and 20 N backward pulls (Forward: D3S3: t(65) = 3.54, q = 0.012; D3S4: t(65) = 3.1, q = 0.023; Backward: D2S1: t(65) = 4, q < 0.001; D1S2: t(65) = 4.63, q < 0.001; D2S2: t(65) = 4.12, q < 0.001; D4S3: t(65) = 4.49, q < 0.001; D3S4: t(65) = 3.78, q = 0.001; D4S4: t(65) = 3.14, q = 0.007).

Pull-related prefrontal activation is an important predictor of small vessel disease burden

Next, we investigated the relative importance of individual balance-related measures in the relationship with cSVD burden. Amended cSVD score was the measure of cSVD burden. Balance-related measures included general balance measures, posturography data, and functional near infrared data. General balance measures were: steps following manual retropulsion, contiguous tandem steps, short physical performance battery score and activity related balance confidence scale score. Posturography measures were the scaling (slope) of resisting force to pull force, centre of mass displacement from in-place fixed force pull trials, stepping force thresholds (backward and forward), and the path length of sway during quiet standing. Functional near infrared prefrontal activation data from in-place fixed force pulls were included. The number of variables was reduced by principal component analysis; for prefrontal activation data, 6 components accounted for 92% of the variance of the original data; for centre of mass displacement data 3 components accounted for 96% of the variance in the original data. Hierarchical partitioning was applied to estimate the individual contribution of each variable to the explainable variability of cSVD burden. Age was included as a predictor given its potential to explain cSVD burden. The hierarchical partitioning model including all predictor variables had an adjusted R^2 value of 1.

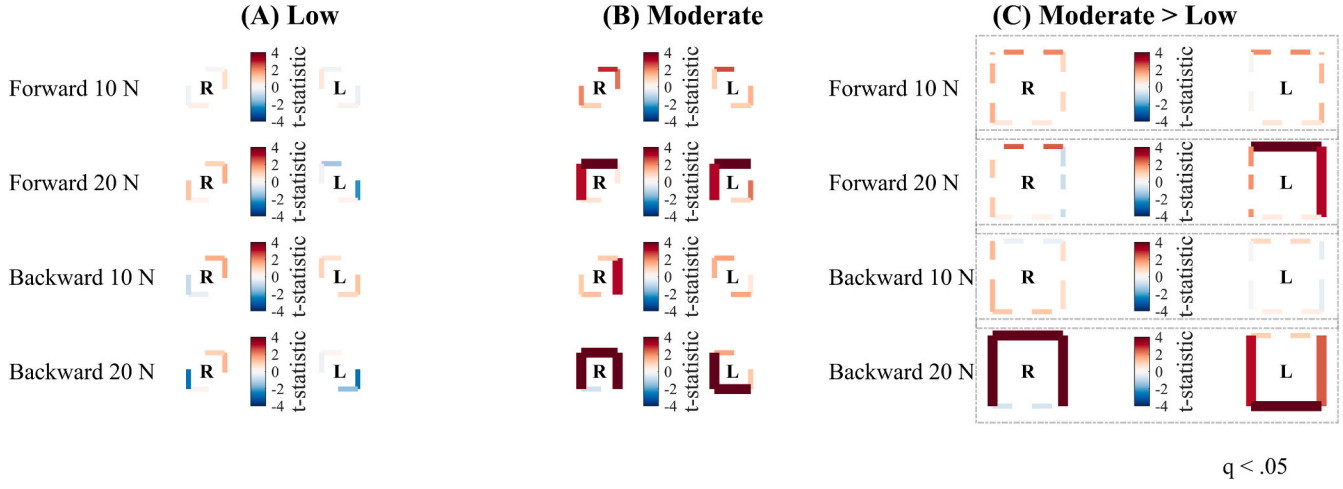

Fig. 8. Small vessel disease burden and pull-related prefrontal activation. Data from all in-place fixed force shoulder pull trials (10 N or 20 N, forward or backward) were used. (A) Summary activation in channels overlying the right and left prefrontal cortex is shown for four pull conditions for low and moderate small vessel disease burden groups. Red lines show activations, and blue lines show deactivation. (B) The effect of small vessel disease burden group on responses is shown – with positive values representing more prefrontal cortical activation in the moderate compared to low cerebral small vessel disease group. For (A) and (B): red lines represent cortical "activation" (increased blood flow), and blue lines represent deactivation. Thick lines represent statistical significance after correction for multiple comparisons across all 8 channels by false discovery rate (q < 0.05). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

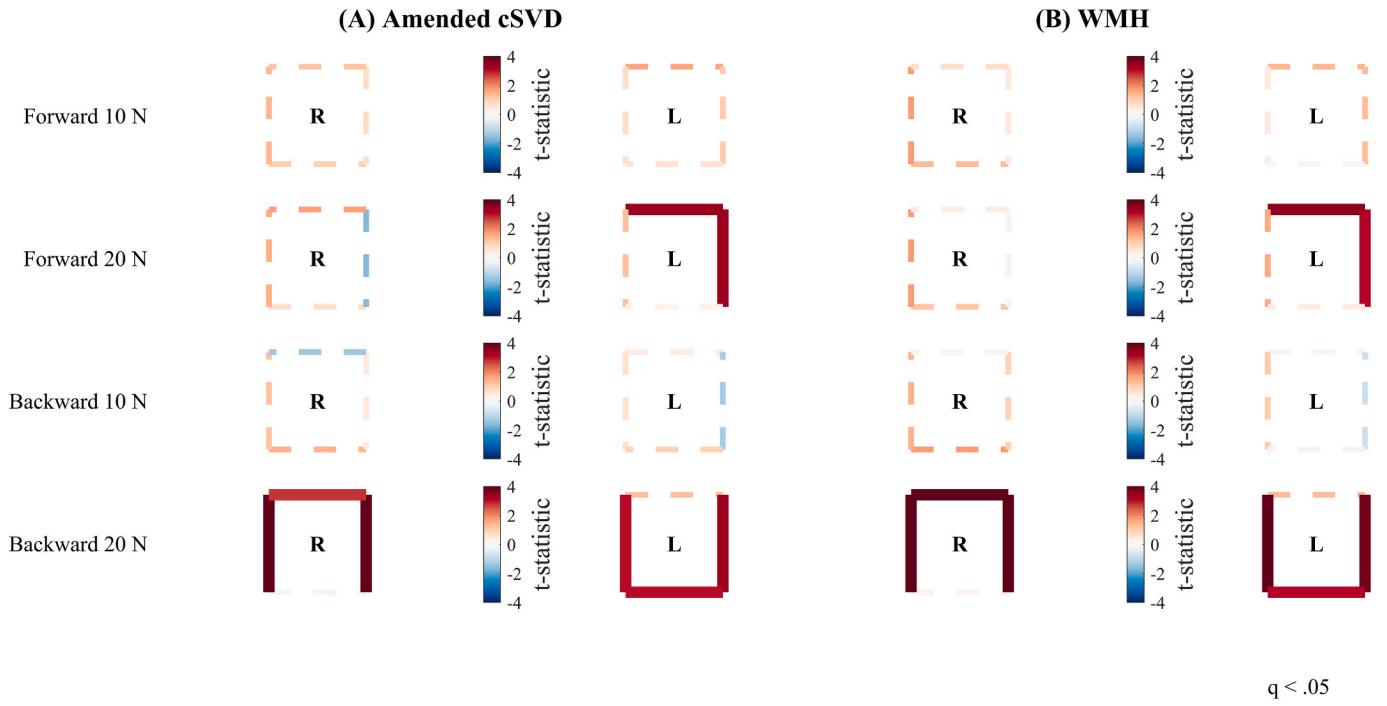

Fig. 9. Correlation between cerebral small vessel disease burden and pull-related prefrontal activation. Data from all in-place fixed force shoulder pull trials (10 N or 20 N, forward or backward) was used. Functional near infrared oxyhaemoglobin activation responses were correlated against two measures of cerebral small vessel disease (cSVD) burden. (A) Amended cSVD = amended cSVD score (0 to 7, higher is more cSVD) (Amin Al Olama et al., 2020); (B) WMH = white matter hyperintensity score (0 to 3, higher is more cSVD (Amin Al Olama et al., 2020; Fazekas et al., 1993)). For (A) and (B): red lines represent cortical "activation" (increased blood flow), and blue lines represent deactivation. Thick lines represent statistical significance after correction for multiple comparisons across all 8 channels by false discovery rate ($q < 0.05$).Note the correlation between more prefrontal activation and more cSVD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Functional near-infrared measures accounted for 33% of the explained variability in cSVD burden, and were the most important predictor (Fig. 10). Backward stepping force threshold accounted for 17%, and centre of mass displacement for 15% of the explained variability in cSVD burden (Fig. 10). Measures of least importance in the estimation of cSVD burden were short physical performance battery score (2.2% of explained variability), sway during quiet standing (2.6%) and the resisting force during in-place pull trials (2.9%).

The relative importance of our cognitive measures and anxiety in predicting the amended SVD score were separately assessed (Fig. 11). In this analysis, Trail Making Test, Montreal Cognitive Assessment and premorbid intelligence measures accounted for 20%, 15% and 9% of the explained variability in cSVD respectively. Trait and state anxiety (STAI-T and STAI-S) levels accounted for 2.6 and 1.1% respectively. Cognitive measures thus contributed more than anxiety to explained variability in cSVD burden.

Discussion

Cerebral small vessel disease impairs the control of balance, but its early effects have proved difficult to reliably detect. In this exploratory study, we assessed the sensitivity of a range of balance-related measures to the burden of cSVD as estimated from neuroimaging. When perturbing standing balance with motorised pulls at the shoulder, we found an association between a higher burden of cSVD and lower force thresholds for stepping, particularly backwards. Using functional near infrared spectroscopy, we found a greater small vessel disease burden correlated with more balance-related prefrontal cortical activation. Across a range of balance-related measures, prefrontal cortical activation and force thresholds for backward stepping accounted for most of the explained variability in cSVD burden. There was no significant relationship between cSVD burden and general measures of balance (tandem walking, steps on manual retropulsion and lower limb performance), or self-reported balance confidence. Age was similar in the two cSVD burden groups. We found an association between cSVD burden and worse cognition – consistent with known associations of cSVD. Our results show there is marked variability between balance-related measures in their relationship to cSVD burden, and they suggest (within the limits of the small sample size) that force thresholds for stepping and balance-related prefrontal cortical activation measures could be sensitive to early deficits in balance control.

General balance measures

cSVD is proposed to contribute to a risk of falls through damage to deep frontal and periventricular white matter tracts/networks involved in gait and balance (Blahak et al., 2009). A recent study applied a measure of standing balance and detailed quantification of imaging markers of cSVD burden in 673 older people (Pinter et al., 2017). Surprisingly, the authors found no significant relationship between bipedal standing balance (a component of the SPPB, measuring the ability to stand in tandem) and any neuroimaging measures of cSVD burden. This negative finding occurred despite significant association between a higher cSVD burden and slower gait (itself associated with a higher risk of falls due to impaired balance control (Espy et al., 2010; Kyrdalen et al., 2019)). The authors suggested the absence of a relationship between cSVD and standing balance could represent a limitation of the qualitative measure used and the good health of the population studied (Pinter et al., 2017).

In the present work, we found no significant association between cSVD burden and any of our general measures of balance (such as the SPPB, the quality of tandem walking or manual retropulsion responses). We did however find cSVD burden associated with a greater propensity to take a step, and lower force thresholds for backward stepping. Our

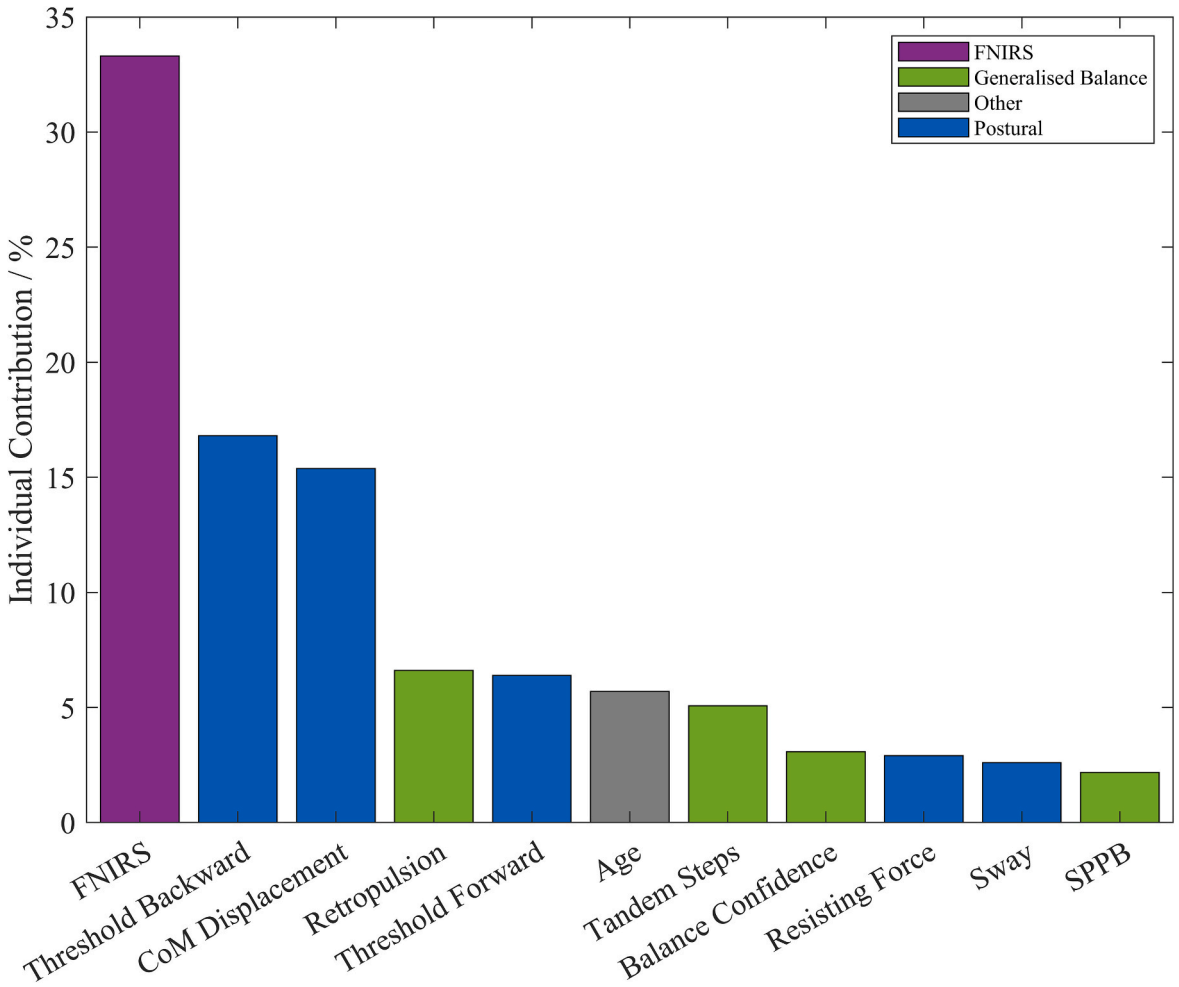

Fig. 10. Relative importance of balance variables in estimating small vessel disease burden. The individual contribution of each variable as defined by hierarchical partitioning in linear regression predicting cerebral small vessel disease burden from other measures is shown (higher is more important). FNIRS = functional near infrared spectroscopy over prefrontal cortical areas. CoM = centre of mass. SPPB = short physical performance battery.

results support the view that limitations in the sensitivity of general measures of balance (e.g. in static standing) in cSVD can be improved upon through the use of quantitative, dynamic assessments of balance.

Balance-correcting responses

We found that more cSVD associated with lower stepping force thresholds particularly for backward pulls. Backward displacements of the body, when compared to forward displacements are more likely to induce a stepping response (Rogers et al., 1996), and they associate with a higher risk of falls (Hsiao and Robinovitch, 1998) and serious injury (Kadono and Pavol, 2013; Smeesters et al., 2001). For these reasons, it has been suggested that earlier activation of backward stepping responses may protect against falls in those with otherwise impaired balance control (Lee et al., 2014). Our result could – in principle – be explainable on this basis, but more data would be needed to explore the relationship of stepping thresholds and the risk of falls.

Recent work in older people with dizziness and unsteadiness linked to cSVD has provided additional insights into associations between cSVD burden and stepping responses (Castro et al., 2024). Using a task involving a forward and backward-oscillating platform (on which participants stood), the authors found lower platform velocity thresholds for taking a step in a population with cSVD-associated idiopathic dizziness (Ibitoye et al., 2022) when compared to age-matched controls (Castro et al., 2024). The directionality of their threshold finding was not provided, precluding a direct comparison with our results. Though we have studied a different population, our results support the proposition that cSVD burden associates with poorer balance and a greater propensity to step following postural perturbation.

We found higher general (trait) anxiety levels in the moderate compared to low cSVD burden group, of potential relevance to balance. Postural (task-related) anxiety has indeed been shown to result in a conscious and hypervigilant balance strategy (Ellmers et al., 2021). Task-associated (state) anxiety, however, did not differ in our two cSVD burden groups. Furthermore, we found no association or correlation between anxiety and cSVD burden in our data, and no correlation between stepping thresholds and anxiety. These results provide no support for a link between anxiety and balance performance in our data. We are mindful however that our sample size is small, and so our study may be underpowered to detect relationships between balance and anxiety. We suggest our finding of association with general anxiety is plausibly explained by the known link between cSVD burden and general neuropsychiatric symptoms such as depression (Rensma et al., 2018; Clancy et al., 2021) which associates with anxiety (Kalin, 2020), as we reported in previous work (Ibitoye et al., 2022). Larger studies would be needed to clarify such relationships.

Pull-related cortical activation

We found pull-related oxyhaemoglobin haemodynamic responses were detectable in the explored (frontal) areas, consistent with previous fNIRS studies of perturbed balance (Mihara et al., 2008; Mihara et al.,

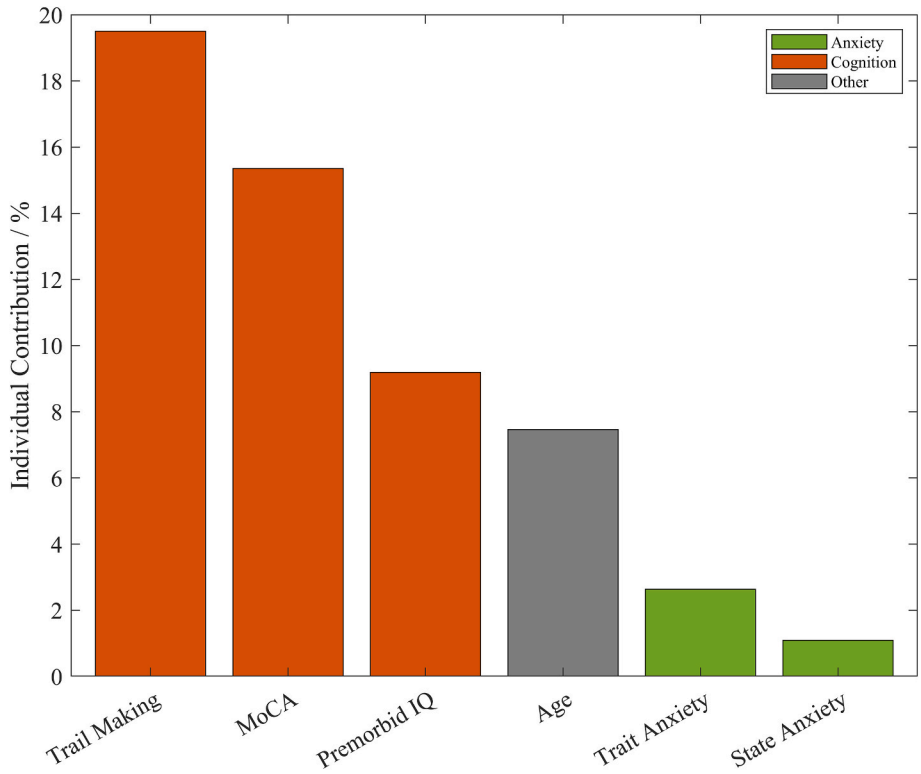

Fig. 11. Relative importance of cognitive and anxiety variables in estimating small vessel disease burden. The individual contribution of each variable as defined by hierarchical partitioning predicting cerebral small vessel disease burden from cognitive, age and anxiety measures is shown (higher is more important). Trail Making = trail making test, MoCA = Montreal Cognitive Assessment, Premorbid IQ = Premorbid intelligence quotient as estimated by National Adult Reading Test, Trait Anxiety = general anxiety levels as per the State-Trait Anxiety Inventory (Spielberger et al., 1983), State Anxiety = current anxiety levels as per the State-Trait Anxiety Inventory (Spielberger et al., 1983).

2012; Mihara et al., 2010; Fujimoto et al., 2014). Our prefrontal activation responses were also greater for more destabilising pulls (greater force and/or backward direction), similar to results from previous studies of fNIRS prefrontal activation during balance control (Lin et al., 2017; Teo et al., 2018; St George et al., 2021), in keeping with successful recovery of balance control-related brain activation.

Ageing and pathology-associated overactivation of prefrontal brain areas has been consistently reported across a wide range of tasks (Cabeza et al., 2018). We found a higher burden of cSVD associated with more pull-related prefrontal activation. Though numerous studies have detailed the associations of ageing with increased prefrontal brain activity during standing balance (Lehmann et al., 2022; Lin et al., 2017; St George et al., 2021; Teo et al., 2018), to our knowledge none have assessed for the contribution of cSVD. A relationship between cSVD burden and changes in balance-related brain activation was reported in a previous study applying electroencephalography (EEG) (Ibitoye et al., 2021). The authors found correlation between sway-related low (delta) frequency EEG power spectrum density and white matter hyperintensity volume in older adult controls, consistent with an effect of cSVD burden on neural processing in balance control (Ibitoye et al., 2021). The reported scalp EEG findings were not localisable to specific cortical sources, and the sway measure lacked specificity to balance control. Our results in the present study advance our understanding of potential effects of cSVD as they show an association with greater balance control-related activation in prefrontal cortical areas.

Potential explanations for increased task-related activation with brain ageing include both inefficiency (such that activation does not produce performance benefits) (Morcom and Henson, 2018), and recruitment of additional resources to compensate for deficits, and thus optimise performance (Reuter-Lorenz and Cappell, 2008; Cabeza et al., 2018). These mechanisms for overactivation likely co-exist (Taube and Lauber, 2026). Our study was not designed to address mechanistic questions on the effect of cSVD-related brain activation on balance performance, but we suggest that a reason for symptoms being commonly absent in early – "covert" (Hannawi et al., 2023) – cSVD, may be because of compensatory increases in cortical activation.

Sensitivity of balance-related measures to cSVD

Our regression results show fNIRS-derived measures of pull-related prefrontal activation were the most important balance-related measures when predicting cSVD burden, accounting for one third of the explained variability in cSVD burden. fNIRS measures were nearly twice as important as the next most relevant variable – force thresholds for backward stepping. Our results are therefore consistent with accumulating evidence of an increased role for prefrontal overactivation in the context of brain ageing (for which cSVD is an expected contributing pathology) (Lin et al., 2017; Teo et al., 2018; St George et al., 2021). Our results suggest that prefrontal activation measures provide unique information independent of conventional postural measures of standing balance or sway in the context of cSVD. Indeed, we reflect that sway and lower limb performance (short physical performance battery, SPPB) – as used in previous studies of balance in cSVD (Tabara et al., 2015; Pinter et al., 2017) – were two of the least important variables predicting cSVD burden in our data. Poor sensitivity to balance control may therefore explain why sway and lower limb balance performance measures have not been found to correlate with cSVD burden in previous large population studies (Tabara et al., 2015; Pinter et al., 2017).

Limitations

Our study has several limitations. First and foremost, our work is

exploratory (rather than definitive) in scope. Our use of convenience sampling, and a small (pragmatic) sample size precluded matching or adjustment for the full range of relevant potential confounders (such as whole brain volume (Pinter et al., 2017)). As this is the first study to report on the relative importance of a wide range of balance-related measures (including prefrontal activation) with cSVD, we nonetheless believe our work provides new information helpful to the design of future, definitive studies of cSVD and balance control. Second, our small sample size means some statistical tests may have been underpowered to detect real differences attributable to cSVD. Third, we conducted many analyses work which increases the risk of false discovery. Though we endeavoured to reduce this risk wherever practicable through statistical adjustments for multiple comparisons, we recognise this limitation is inherent to exploratory work. Fourth, as we used existing brain imaging data acquired using clinical protocols for this work, we were limited to a simple summary measure of cSVD. We were thus unable to leverage the full potential of MRI, such as diffusion-weighted imaging and network statistics to quantify cSVD burden (Zeestraten et al., 2016). On the other hand our work was effective in identifying an association between balance measures and a simple visual cSVD score derived from routinely available clinical MRI data. Our use of pre-existing scan data additionally means cSVD burden progression is a potential source of variability. As cSVD burden increases only very slowly over time (0.23–1.33 cm^3 /year (Schmidt et al., 2016)), and we have used a summary measure of burden, we are optimistic that such unmeasured variability is unlikely to be significant with respect to our results. Fifth, we found significant fNIRS responses in the oxyhaemoglobin fNIRS data but not in deoxyhaemoglobin data. Other studies have similarly reported oxyhaemoglobin measures are more sensitive than deoxyhaemoglobin to task effects (Mihara et al., 2008; Lin et al., 2017), likely as a result of a superior signal-to-noise ratio (Homae et al., 2007; Hoshi, 2003).

Summary

Our results suggest that behavioural and prefrontal cortical activation responses to perturbed balance vary with cSVD burden. If validated in larger populations, these findings would support the development of biomarkers of the early effects of cSVD on balance, relevant to clinical trials. The relationship between our balance measures and real-world outcomes, such as functional mobility and disability should be explored. Furthermore, as balance-relevant brain networks also deteriorate in many other common neurological diseases (e.g. multiple sclerosis and Parkinson's disease), our approach and measures may provide new insights into the earliest effects of brain disease on balance control.

In summary, our results suggest that prefrontal cortical responses and stepping force thresholds are sensitive to effects of cSVD on balance control. We suggest these measures should be a focus of future work understanding the earliest effects of brain pathology on balance.

CRediT authorship contribution statement

Richard Tolulope Ibitoye: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Matthew James Bancroft:** . **Antonia Hamilton:** Writing – review & editing, Methodology. **Adolfo Miguel Bronstein:** Writing – review & editing. **David J. Werring:** Writing – review & editing, Resources, Conceptualization. **Diego Kaski:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroscience.2026.05.039.

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