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A link between frontal white matter integrity and dizziness in cerebral small vessel disease

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ABSTRACT

One in three older people (>60 years) complain of dizziness which often remains unexplained despite specialist assessment. We investigated if dizziness was associated with vascular injury to white matter tracts relevant to balance or vestibular self-motion perception in sporadic cerebral small vessel disease (age-related microangiopathy). We prospectively recruited 38 vestibular clinic patients with idiopathic (unexplained) dizziness and 36 age-matched asymptomatic controls who underwent clinical, cognitive, balance, gait and vestibular assessments, and structural and diffusion brain MRI. Patients had more vascular risk factors, worse balance, worse executive cognitive function, and worse ankle vibration thresholds in association with greater white matter hyperintensity in frontal deep white matter, and lower fractional anisotropy in the genu of the corpus callosum and the right inferior longitudinal fasciculus. A large bihemispheric white matter network had less structural connectivity in patients. Reflex and perceptual vestibular function was similar in patients and controls. Our results suggest cerebral small vessel disease is involved in the genesis of dizziness through its effect on balance.

1. Introduction

One in three older people (≥60 years) complain of dizziness (Colledge et al., 1994), which contributes to a loss of independence and falls (Mueller et al., 2014). In half of older patients investigated for dizziness, vestibular and cardiovascular investigations are normal and no specific diagnosis can be made (Ahmad et al., 2015; Belal and Glorig, 1986; Bösner et al., 2018; Maarsingh et al., 2010). The clinical characteristics of such dizziness in older people are ill-defined, and its pathophysiology is not known (Colledge et al., 2002; Fife and Baloh, 1993). An association between dizziness and severe sporadic cerebral small vessel disease (SVD) raises the possibility that vascular injury to white matter tracts involved in postural balance or vestibular perception underpins such dizziness symptoms (Kaski et al., 2019).

Various terms have been used to describe otherwise unexplained dizziness in older people. These include 'presbyataxia', 'presbyvertigo' or 'primary presbyastasis' (Belal and Glorig, 1986), 'disequilibrium of unknown cause' (Fife and Baloh, 1993), and 'unexplained dizziness' (Ahmad et al., 2015). In the absence of consensus, and in recognition that the pathophysiology of this syndrome remains unclear, we use the term 'idiopathic dizziness' within this work.

SVD is very common in older people and, when severe, it is associated with impaired cognition, gait and balance performance (Wardlaw et al., 2019). Slow gait in SVD is mediated by less structural integrity in a

Abbreviations: BCI, Balance Control Index; DHI, dizziness handicap inventory; HADS, hospital anxiety and depression scale; FDR, False Discovery Rate; FESI, falls efficacy scale international; FLAIR, Fluid-Attenuated Inversion Recovery; MoCA, Montreal Cognitive Assessment; NART, National Adult Reading Test; PPPD, persistent postural-perceptual dizziness; SPPB, Short Physical Performance Battery; SVD, small vessel disease; TMT, Trail Making Test; TUG, Timed Up and Go test; vHIT, video head impulse test; VSS, vertigo symptom scale.

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large bihemispheric white matter network, with the strongest association frontally in the genu of the corpus callosum (de Laat et al., 2011). Dizziness is often co-reported with unsteadiness in older people (Fife and Baloh, 1993). While a cross-sectional and longitudinal relationship between SVD and slow gait is well established (Baloh et al., 2003; Pinter et al., 2017), the implication for dizziness symptoms is less clear. Previous work investigated white matter hyperintensities (on T2-weighted MRI as a marker of SVD) and dizziness in older people, with inconclusive results (Colledge et al., 2002; Day et al., 1990; Lorbeer et al., 2017). More sensitive neuroimaging measures of SVD progression such as fractional anisotropy in diffusion tensor imaging have however never been applied. Whether less integrity in balance-relevant white matter is associated with idiopathic dizziness is not known.

Patients with dizziness undergo caloric ear irrigation, video head-impulse tests, or rotational chair testing to quantify peripheral and brainstem vestibular functioning (Brandt and Strupp, 2005). Clinical vestibular test results are however normal in many dizzy older people (Ahmad et al., 2015; Belal and Glorig, 1986), which implies dizziness could instead arise from altered higher (thalamocortical (Lopez and Blanke, 2011)) vestibular processing. A relationship between impaired structural integrity in white matter, reduced vestibular self-motion perception and dizziness was recently defined in the context of traumatic brain injury (Calzolari et al., 2020). It is not known if vestibular self-motion perception is impaired in patients with idiopathic dizziness, and if this relates to structural integrity in cortical vestibular white matter under the influence of SVD.

Here we investigated the association between SVD and the common problem of idiopathic dizziness in older people. We prospectively recruited older patients with idiopathic dizziness and controls. We assessed clinical, cognitive, balance, gait and vestibular function. We compared these measures with white matter hyperintensity and fractional anisotropy as markers of white matter integrity to test for an association between idiopathic dizziness and SVD. We hypothesised that idiopathic dizziness is associated with vascular white matter injury in (i) frontal tracts involved in the control of postural balance and/or (ii) a cortical vestibular network relevant to vestibular self-motion perception. Additionally, we hypothesised that (iii) the combination of idiopathic dizziness and worse balance is linked to more SVD, and more widespread SVD-related functional impairment.

2. Materials and methods

2.1. Participants

Patients with idiopathic dizziness were recruited from neurology and neuro-otology clinics in London by the following criteria: (i) expert assessment found no relevant neurological or vestibular deficit, (ii) peripheral vestibular function was normal (assessed by caloric testing or video head impulse tests [vHIT], excluding presbyvestibulopathy as per Agrawal et al. (Agrawal et al., 2019)) and (iii) brain MRI identified no other neurological disease. We used dizziness here as an umbrella term meaning a sensation of disturbed or impaired spatial orientation (Bisdorff et al., 2009), with or without vertigo (defined as the sensation of self-motion when no motion is occurring (Bisdorff et al., 2009)). Thirty-eight patients meeting these criteria took part in the study (fourteen females, age >60 years, median 77, interquartile range [73–80]). No patients met diagnostic criteria for persistent postural-perceptual dizziness (PPPD) - a common cause of chronic dizziness in younger patients. Of note, our patients' symptoms were not precipitated by a pre-existing, defined vestibular disorder.

Thirty-six asymptomatic older people were recruited as controls (fourteen females, age >60 years, median 76, interquartile range [72–80] years). They were recruited from a general practice-based community register of older people interested in participating in research, and from a local older persons' group following screening to exclude significant dizziness (all had no imbalance, dizziness or spinning vertigo in the last 12 months, and no neurological disorders). Neurological and eye movement examinations were within normal limits for age. Video head impulse tests confirmed normal vestibulo-ocular reflex function (Agrawal et al 2019). Written informed consent was obtained as approved by the local ethics research committee.

2.2. Clinical assessment

2.2.1. Symptoms, history and examination

All participants had a standardised clinical assessment. A history detailed the onset, duration, description and associations of their symptoms, comorbidities, medication and vascular risk. The eye movement examination included an assessment of gaze-holding for evidence of nystagmus, horizontal and vertical saccades for their accuracy and speed, horizontal head impulse tests for vestibular reflex responses, and smooth pursuit. Hallpike manoeuvres were undertaken to screen for benign paroxysmal positional vertigo, given the high frequency of this disorder in older people. Participants were asked to rank their burden of dizziness when standing compared to sitting ('more', 'the same', 'less') as this would indicate whether their dizziness was related to posture.

The Hospital Anxiety and Dizziness Scale quantified anxiety (HADS-A) and depression (HADS-D) symptoms (Zigmond and Snaith, 1983). The frequency and functional consequences of dizziness and vertigo were measured by the Vertigo Symptom Scale (with vertigo [VSS-V] and autonomic/anxiety [VSS-A] subscales (Yardley et al., 1992)) and the Dizziness Handicap Inventory (DHI (Jacobson and Newman, 1990)) respectively. Fear of falling was assessed by the Falls Efficacy Scale International (FESI (Tinetti et al., 1990)). Established diagnoses of hypertension (NICE, 2019) and diabetes (NICE, 2015), treated hypercholesterolaemia (defined as taking a cholesterol lowering agent), obesity (body mass index >30 kg/m^2), smoking (>20 pack years) and previous transient ischaemic attack were documented. All patients with hypertension or diabetes were on suitable treatments, and blood pressure and blood glucose were appropriately controlled. An aggregate vascular risk score was determined by scoring one for each vascular risk factor (Ahmad et al., 2015). In order to exclude orthostatic hypotension, a common cause of dizziness in older people (Freeman, 2008), blood pressure and heart rate were assessed while supine, immediately on standing and after 3 min of standing; the mean change between supine and standing measurements was the measure of orthostatic blood pressure change (Freeman et al., 2011).

2.2.2. Balance, gait, vestibular and somatosensory function

Heel-toe (tandem) walking, postural reactions to retropulsion and a three-metre timed up-and-go task quantified balance and gait speed. Heel-toe (tandem) walking was assessed over 10 steps; the maximum number of contiguous steps across three trials was recorded. Postural reactions to retropulsion were assessed; the best of three responses (fewest steps) was recorded. A 'fall' was recorded if the subject failed to produce an adequate step and the examiner had to support the patient to prevent a fall to the ground. Falls were excluded from further analyses. The Short Physical Performance Battery (SPPB) - a combined measure of gait speed, standing balance and repeated chair stands - summarised lower limb performance (Guralnik et al., 1995).

Postural sway was measured during 30 s of eyes closed standing with shoes on, and with feet shoulder width apart; a Fastrak electromagnetic sensor (Vermont, USA) placed at the level of the C7 vertebra recorded anteroposterior movements. Data was recorded at 250 Hz. The recording offset was eliminated; a zero-phase low-pass fourth order 10 Hz Butterworth filter was then applied. Following Fast Fourier Transform, total power between 3.5 Hz and 8 Hz was calculated to look for group differences in high frequency sway (Krafczyk et al., 1999).

Balance was further assessed using a sensitive, validated clinical test battery of standing balance and gait, performed while wearing a SwayStar® truncal sensor (Supplementary Material (Allum et al., 2006)). Each task lasted up to 20 s and the best of three performances

was selected. Participants stood without shoes, with their feet hip width apart in each of four conditions represented by two factors: surface - firm or foam, eyes - open or closed. They then stood on one leg (of their preference) with eyes open. Three metre tandem walks were undertaken with eyes open on a firm surface, and separately on foam. Further three metre walks were undertaken with eyes closed, with eyes open while turning the head side-to-side, and additionally with eyes open while looking up then down with each step. Data from these measures were combined within SwayStar® software to produce a summary measure of balance performance in an automated way - the Balance Control Index (BCI (Allum et al., 2006)).

Vestibulo-ocular reflex and perceptual thresholds to rotation about the vertical axis were measured using an established technique (Supplementary Material; (Cutfield et al., 2011)). Ankle sensory thresholds to vibration (64 Hz) were recorded using a quantitative Rydel-Seiffer tuning fork (Bergin et al., 1995).

2.2.3. Cognition

Premorbid intelligence was estimated by the National Adult Reading Test (NART (Nelson, 1982)). The Montreal Cognitive Assessment (MoCA) summarised global cognition (Nasreddine et al., 2005). The Cogstate® Brief Battery - a computerised cognitive assessment - was administered (Maruff et al., 2009); this included decision and identification tasks as tests of processing speed, one card learning and a one back task as tests of working memory and visual learning. Executive function was assessed by the Trail Making Test (TMT) and the Delis-Kaplan Executive Function System Colour-Word Interference (Stroop) test (Delis et al., 2001). Raw cognitive scores were used for analyses.

2.2.4. MRI acquisition

Structural, FLAIR and diffusion weighted MRI data were acquired on a Siemens 3-T Verio scanner (Siemens® Healthcare) using standard methods (Supplementary Material). Images were reviewed routinely by a clinical neuroradiologist to exclude additional pathology.

2.3. MRI analysis

2.3.1. White matter hyperintensities

Voxel-wise white matter hyperintensity probabilities were determined by the Lesion Prediction Algorithm, a MATLAB® toolbox which was applied to FLAIR images (Fig. 1A and Supplementary Material (Schmidt et al., 2012)). This pre-trained classifier has been shown to perform well in older people with SVD (Guerrero et al., 2018). White matter hyperintensity masks were inspected and checked for accuracy by a neurologist.

2.3.2. Diffusion weighted imaging

Diffusion weighted imaging data were pre-processed using standard methods (Kinnunen et al., 2011). Default settings were used unless otherwise stated. Diffeomorphic (tensor-based) registration was then applied using DTI-TK (Zhang et al., 2006) using an approach reported in previous work (Jolly et al., 2020; Scott et al., 2018). This involved bootstrapping participant image volumes to an IXI aging template to define a population-specific study template using affine and non-linear diffeomorphic transformations (Zhang et al., 2007). The study specific template was registered to MNI space by an affine transformation within FSL software. Participant images were transformed to MNI space by combining participant to group template, and group template to MNI

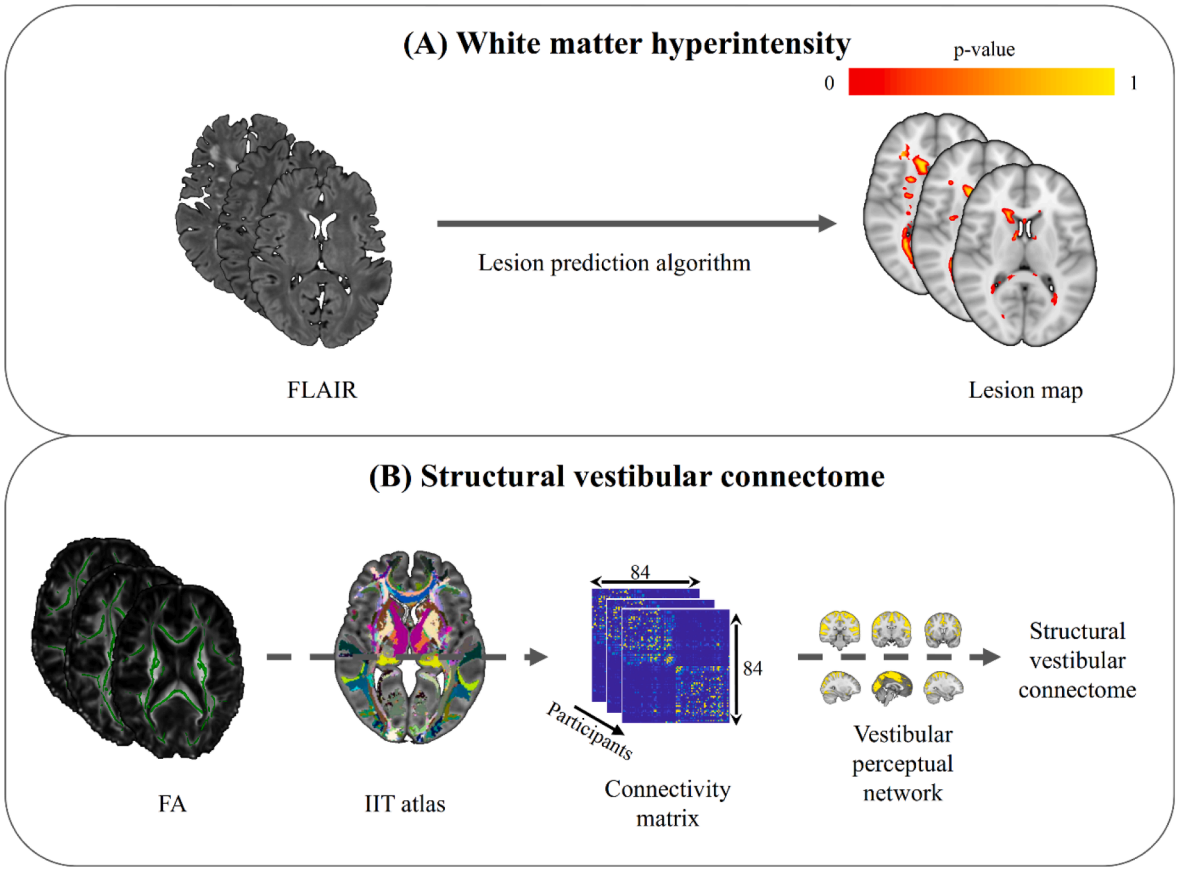

Fig. 1. Imaging methods. (A) Voxel-wise probabilities for white matter hyperintensity were determined by applying the lesion prediction algorithm to FLAIR images. (B) Skeletonised fractional anisotropy images were intersected with the Illinois institute of technology (IIT) white matter atlas (of 84 by 84 grey matter nodes; image adapted from Qi & Arfanakis(Qi and Arfanakis, 2021) to produce participant-specific connectivity matrices. Connectivity matrices were intersected with a vestibular network (Ibitoye et al., 2022) to produce a structural vestibular connectome. Dashed arrows denote intersection.

transformations. Images were visually inspected to ensure there was no major misalignment during registration.

Fractional anisotropy data was produced from participant diffusion imaging data within FSL software, as described in previous work (Jolly et al., 2020). Tensor fitting was done by DTIFIT using a weighted least squares approach. Individual fractional anisotropy maps were registered to MNI space by tract based spatial statistics (Smith et al., 2006), using the FMRIB 1 mm fractional anisotropy atlas. Group fractional anisotropy maps were skeletonized at a threshold of 0.2 to sample the core of tracts, thus reducing variability due to partial volume effects. Within white matter tracts, lower fractional anisotropy values generally reflect less white matter structural integrity. Fractional anisotropy was chosen as a common diffusion measure of white mater axonal integrity (Kochunov et al., 2012), and as a basis for estimating structural connectivity using established methods (Fagerholm et al., 2015).

2.3.3. Structural connectivity

We defined a whole brain structural connectome for each participant by combining fractional anisotropy data with tractography using methods described in previous work (Fig. 1B) (Fagerholm et al., 2015; Jolly et al., 2020). To avoid known limitations of probabilistic tractography in patients with reduced white matter integrity (Squarcina et al., 2012) (such as in SVD), we instead mapped fractional anisotropy data to a predefined high-quality tractography atlas derived from healthy controls using an established method (Supplementary Material).

In previous work we had defined a vestibular network involved in vestibular self-motion perception on the basis of functional connectivity with a posterior subregion of right OP2 (Ibitoye et al., 2022), an area previously identified in *meta*-analysis studies as being core to cortical vestibular function (Lopez et al., 2012; zu Eulenburg et al., 2012). We intersected the grey matter connectivity of this subregion with the structural connectome of each participant to produce a structural vestibular connectome (Fig. 1B and Supplementary Material). Between-group differences in whole brain or vestibular structural connectivity were then tested using Network Based Statistics (Zalesky et al., 2010).

2.3.4. Network based statistics

Functional deficits in SVD are mediated by impaired connectivity in brain networks. Network Based Statistics combines general linear models with permutation tests to test hypotheses in network space (Zalesky et al., 2010). Patients and controls were compared to determine network differences in connectivity. In the first step of Network Based Statistics, connections exceeding a threshold ($p < 0.01$) were selected. In the second step, significant networks ($p < 0.05$) which differed between groups were determined by comparing the 'intensity' of connectivity (defined as the sum of suprathreshold connections) against a null distribution created by permutation.

2.3.5. Statistics

Two-group independent sample tests for normally distributed data were done by Student t-tests. Tests in non-normally distributed data were undertaken by the Wilcoxon Rank Sum Test (W = rank sum test statistic). Voxel-wise tests on white matter hyperintensity probability and fractional anisotropy were undertaken by non-parametric permutation using randomise (within FSL, 10,000 permutations). Corrections for multiple comparisons were done by the False Discovery Rate (FDR, $p < 0.05$). Significant results are two-tailed throughout unless specified.

Linear trend analyses, and two-group comparisons with nuisance variates were undertaken using multiple linear regression. Trend analysis is an established way of testing for a relationship between a continuous dependent variable and an ordinal categorical predictor within a linear model. A variable coding strategy is chosen in linear regression, such that category weights vary in a manner which preserves the proposed ordinal relationship (e.g. in a three-level category, −1 for the lowest, 0 for the next group, and 1 for highest group).

The Kolmogorov-Smirnov test was applied as a test of normality for regression residuals ($p < 0.05$). Where residuals were not normally distributed, p-values were determined by permutation testing (by randomly sampling over 10,0000 iterations) (Winkler et al., 2014). Permutation methods are accurate in circumstances where normality assumptions of parametric statistics are violated (Nichols and Holmes, 2002). Under the null hypothesis of exchangeability, regression models were permuted using the Freedman-Lane algorithm (Freedman and Lane, 1983). The statistic of interest from the unpermuted model was then compared to its distribution under the null hypothesis to derive p-values. Analyses were undertaken using custom scripts in MATLAB® (R2019a, Natick, Massachusetts: The MathWorks Inc.).

Canonical correlation analysis was applied to test for a relationship between dizziness and vertigo measures, and other variables (Supplementary Material).

3. Results

3.1. Clinical and behavioural

All patients reported an insidious rather than acute onset of dizziness (mean symptoms duration 6 ± 5 [standard deviation] years). They all reported more dizziness when standing compared to sitting. When asked to describe their dizziness, 87% (33) reported a feeling or a sense of unsteadiness, 61% (23) reported an illusion of self motion, 21% (8) reported light-headedness. Patients had more vestibular (DHI, VSS-V) and psychological symptoms (HADS-A, HADS-D and FESI) than controls ($p < 0.05$, Table 1). One patient, and one control were taking antidepressant medication. No participants were on sedatives such as benzodiazepines or opioids. Symptom scores correlated with each other (DHI, VSS-V, VSS-A, HADS-A, HADS-D and FESI, Table 2). Factor analysis showed one factor (eigenvalue 3.72) explained 53% of symptom score variance, loading mainly onto dizziness handicap, anxiety and depression scores (Supplementary Table 1). Ideal factorisation was 1 by the latent root criterion, suggesting dizziness and psychological symptoms were best explained by a single underlying factor. No alternative clinical diagnosis emerged during a minimum of 6 months of follow-up.

Hypertension and treated hypercholesterolaemia were more common in patients with idiopathic dizziness than controls ($p < 0.05$, Table 1). Patients were overall more likely to have impaired balance (Short Physical Performance Battery score < 10, $p < 0.001$, odds ratio = 0.130, Fisher test), but vestibular function did not differ (vHIT horizontal gains, and vestibular perceptual delay - perceptual threshold velocity as a proportion of the nystagmus threshold velocity, Table 1). Patients completed fewer accurate tandem steps (median 4.5 vs. 10), took more steps to regain balance following retropulsion (median 2 vs. 1), took longer to complete the timed up and go assessment (12.4 vs. 9.5 s), and had higher (worse) Balance Control Index scores ($p < 0.05$, Table 2). Patients were more likely to report a fall in the preceding 12 months (43% vs 11%, $p = 0.009$, odds ratio = 6.48, Fisher test). High frequency sway at 3.5–8 Hz did not differ between groups (Total Sway Power, Table 1).

Orthostatic blood pressure change did not differ between groups (Table 1). Two patients and one control however had a single recorded orthostatic drop in systolic blood pressure (≥20 mmHg); excluding these participants did not affect significant results. Ankle sensory threshold scores were lower (worse) in patients ($p < 0.05$, Table 1), but knee threshold scores did not significantly differ ($p = 0.07$, Table 1). We investigated the difference of ankle and knee thresholds as a surrogate for the length-dependent peripheral (nerve) contribution to vibration thresholds. The difference of ankle and knee thresholds did not differ significantly between groups ($p = 0.19$, Table 1). To understand the potential implications of differing ankle vibration sensory thresholds, we undertook a subsidiary analysis of the data after excluding six patients with low (zero) ankle sensory threshold scores; findings which differed in this subsidiary analysis are detailed at the end of the results section.

Table 1
Clinical characteristics. Ankle vibration thresholds were measured using a quantitative tuning fork (0–8, lower is worse). Values are shown as median (lower quartile – upper quartile). Counts are prefixed by #. (a) = Wilcoxon Rank Sum Test; (b) = Fisher exact test. ǂ = significant after correction for multiple comparisons ($p < 0.05$). HADS-D = hospital anxiety and depression scale; depression subscale; HADS-A = anxiety subscale of HADS; DHI = dizziness handicap inventory; VSS-V = vertigo symptom scale, vertigo subscale; VSS-A = vertigo symptom scale, autonomic-anxiety subscale; FESI = falls efficacy scale international; WMH = white matter hyperintensity; FA = fractional anisotropy.

	Non-dizzy	Dizzy	W	p
Aggregate vascular risk	1.00 (0–1.00)	2.00 (1.00–3.00)	898	<0.001 (a) ǂ
Heart Disease	# 4	# 8		0.34 (b)
Hypertension	# 9	# 24		<0.001 (b)
Diabetes	# 3	# 7		0.31 (b)
Treated Hypercholesterolaemia	# 6	# 22		<0.001 (b)
Obesity	# 0	# 5		0.05 (b)
Smoking > 20 pack year	# 6	# 7		1 (b)
Previous TIA	# 1	# 2		1 (b)
Visual acuity (LogMAR)	0.176 (0.176–0.342)	0.176 (0.0458–0.342)	640	0.73 (a)
Knee vibration thresholds (arb. units)	5.50 (4.68–6.03)	5.00 (4.00–5.62)	1289	0.07 (a)
Ankle vibration thresholds (arb. units)	5.25 (3.78–6.03)	3.87 (1.71–4.84)	1361	0.006 (a)ǂ
Knee minus ankle vibration thresholds (arb. units)	0.250 (0–1.15)	0.687 (0.0625–1.43)	1046	0.19 (a)
Video head impulse test horizontal gain	1.02 (0.915–1.14)	1.02 (0.942–1.07)	536	0.94 (a)
Vestibulo-ocular reflex threshold / °s-1	3.64 (3.31–4.47)	4.25 (3.48–5.25)	859	0.12 (a)
Vestibular perceptual threshold / °s-1 (Cutfield et al., 2011)	9.46 (6.61–13.3)	9.68 (7.54–16.5)	938	0.35 (a)
Vestibular Perceptual Delay (perceptual threshold velocity as a proportion of the nystagmus threshold velocity)	4.78 (2.07–6.01)	4.44 (3.29–7.22)	933	0.72 (a)
Supine Systolic / mmHg	154 (136–161)	154 (139–165)	1058	0.43 (a)
Supine Diastolic / mmHg	75.0 (68.7–81.5)	78.0 (71.0–83.0)	1049	0.36 (a)
Immediate Standing Mean Increase / mmHg	−0.320 (-5.96–2.98)	−0.930 (-9.64–3.70)	1252	0.60 (a)
3 min Standing Mean Increase / mmHg	−0.610 (-6.60–4.80)	1.90 (-5.38–11.0)	1124	0.34 (a)
Total Sway Power 3.5 Hz to 8 Hz / mm^2	350 (300–400)	350 (300–350)	746	0.41 (a)
HADS-D	1.00 (0–4.00)	6.00 (4.00–9.00)	790	<0.001 (a) ǂ
HADS-A	2.00 (0.750–4.00)	6.00 (3.00–9.00)	808	<0.001 (a) ǂ
DHI	0 (0–0)	33.0 (22.0–46.0)	562	<0.001 (a) ǂ
VSS-V	0 (0–0)	9.50 (6.00–13.0)	579	<0.001 (a) ǂ
VSS-A	0 (0–1.00)	5.00 (2.00–8.00)	713	<0.001 (a) ǂ
FESI	7.00 (7.00–8.00)	13.0 (11.0–16.0)	647	<0.001 (a) ǂ
WMH volume/ml	4.79 (2.65–12.6)	8.16 (4.02–24.2)	1136	0.08
Mean FA	0.438 (0.427–0.458)	0.430 (0.417–0.447)	1426	0.06

Table 2
Balance and gait. Values are shown as median (lower quartile – upper quartile). (a) = Wilcoxon Rank Sum Test; (b) = Fisher exact test; # = count. ǂ = significant after correction for multiple comparisons ($p < 0.05$).

	Non-dizzy	Dizzy	W	p
Accurate Tandem Steps (max. 10)	10 (10–10)	5 (2–10)	1073	<0.001 (a)ǂ
Retropulsion Steps (discounting falls)	1 (1–1.25)	2 (2–3)	832	<0.001 (a)ǂ
Retropulsion (Falls)	# 0	# 4	–	0.12 (b)
3 m timed up and go / s	9.5 (8.5–10.7)	12.4 (10.7–15.7)	777	<0.001 (a)ǂ
Short Physical Performance Battery (max. 12)	12 (11–12)	10 (8–11)	1142	<0.001 (a)ǂ
Balance Control Index / arbitrary (Allum et al., 2006)	298 (273–318)	380 (340–454)	124	<0.001 (a)ǂ

3.2. Lower frontal white matter integrity and less structural connectivity in dizzy patients

Although dizziness and white matter integrity (total white matter hyperintensity volume and mean FA) did not correlate (first mode canonical correlation coefficient $r = 0.190$, $p = 0.73$), there was a trend for total white matter hyperintensity volume to be higher (one-tailed $p = 0.04$, Table 1) and for mean white matter fractional anisotropy to be lower (one-tailed $p = 0.03$, Table 1) in patients with idiopathic dizziness than in controls. Patients had more white matter hyperintensity in the right superior longitudinal fasciculus, anterior thalamic radiations bilaterally, and the right posterior thalamic radiation ($p < 0.05$, Fig. 2A).

Fractional anisotropy was lower in the genu of the corpus callosum and the right inferior longitudinal fasciculus in patients ($p < 0.05$, Fig. 2B). Across all participants, lower SPPB (worse gait/balance) correlated with lower fractional anisotropy in the genu and body of the corpus callosum, the right anterior thalamic radiation and the right and left inferior longitudinal fasciculi ($p < 0.05$, Fig. 2B). Lower white matter integrity in the genu of the corpus callosum was thus associated with both poorer balance, and idiopathic dizziness ($p < 0.05$, Fig. 2B).

Across the whole brain structural connectome, a large bihemispheric white matter network identified by Network Based Statistics had less structural connectivity in patients than controls ($p = 0.021$, 750 of 6972 possible connections, Fig. 3A). Structural connectivity in the vestibular connectome was also lower in patients ($p = 0.007$, 308 of 1681 possible connections, Fig. 3B), however, after adjusting for the average burden of white matter injury in each participant using mean fractional anisotropy as covariate of no interest, there was no network of differing

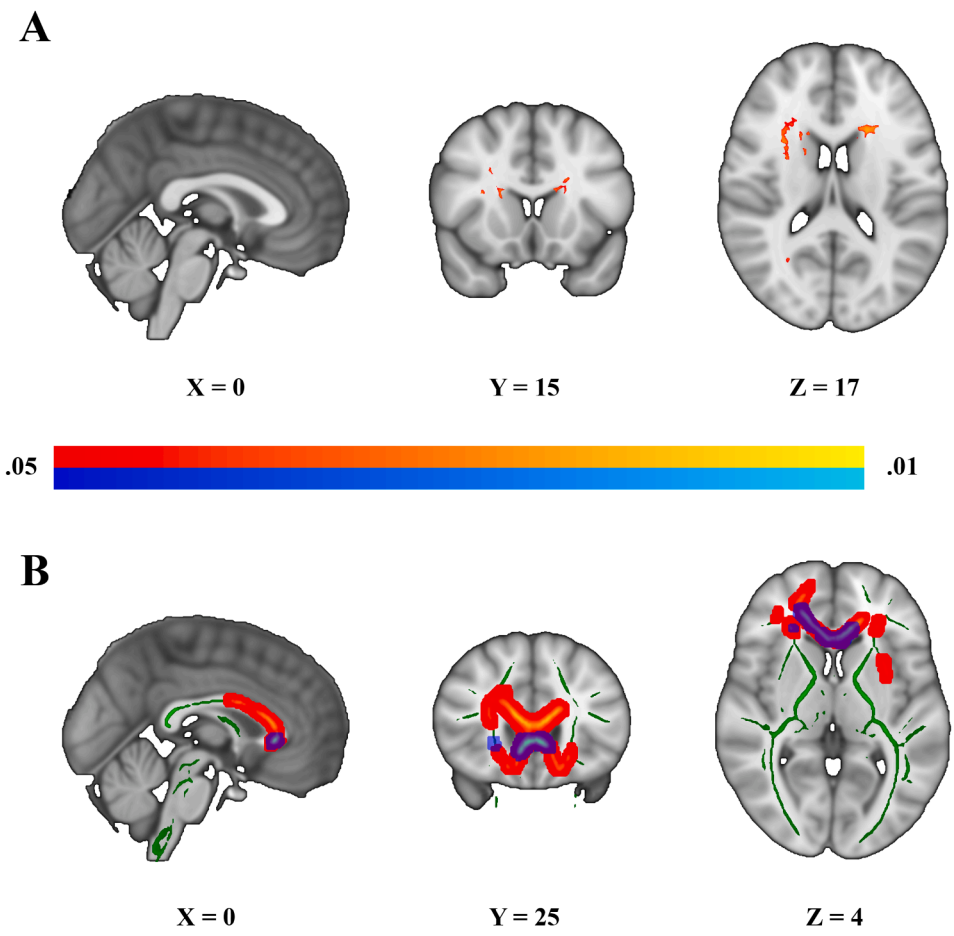

Fig. 2. Lower frontal white matter integrity in patients with idiopathic dizziness. (A) Significant areas where the probability of white matter hyperintensity was higher in patients than controls are illustrated in red-yellow. (B) Tracts of lower fractional anisotropy in patients than controls are illustrated in blue, overlaid upon tracts where lower fractional anisotropy correlated with poorer balance (lower Short Performance Physical Battery score) across all participants in red-yellow. White matter skeleton is illustrated in green.

connectivity. Thus, the lower structural connectivity found in patients was not specific to the vestibular network.

Given known associations of small vessel disease with psychological symptoms (Clancy et al., 2021), we investigated for correlation between markers of SVD burden (white matter hyperintensity volume, mean fractional anisotropy) and anxiety and depression (HADS-A and HADS-D questionnaire scores). In patients with idiopathic dizziness, canonical correlation identified one significant mode with correlation coefficient 0.567 (null distribution mean r = 0.293, p = 0.005). This relationship was driven by correlation between the anxiety subscale of the Hospital Anxiety and Depression inventory (HADS-A) and lower mean fractional anisotropy values (normalised coefficients: HADS-A = 1.29, HADS-D = 0.741, white matter hyperintensity volume = 0.221, mean fractional anisotropy = −0.825). No relationship was found for controls, or across all participants. An association between anxiety and depression symptoms, and small vessel disease burden was therefore found only in patients.

3.3. Correlation between more symptoms and poorer balance

Dizziness correlated with balance performance. Canonical correlation identified one significant mode with correlation coefficient of 0.603 (null distribution mean r = 0.400, p = 0.040) between dizziness (DHI and VSS-V scores) and balance (SPPB, TUG, accurate tandem steps and retropulsion steps). This relationship was driven by correlation between higher DHI scores and lower SPPB scores (normalised coefficients: SPPB = 1.49, TUG = 0.946, accurate tandem steps = −0.0279, retropulsion steps = −0.0154, VSS-V = 0.884, DHI = −1.13). More dizziness therefore correlated with poorer balance in the patient group.

3.4. Poor balance in dizzy patients is associated with more SVD and worse cognition

An association between idiopathic dizziness, balance and SVD burden predicts a trend where SVD burden is lowest in controls (C+), higher in dizzy patients with good balance (D+), and highest in patients with both dizziness and poor balance (D-, see Fig. 2). Poor balance was defined as SPPB < 10 on the basis of this score being associated with worse functional outcomes (Guralnik et al., 1995). Age correlated with more dizziness and balance-related impairment (p = 0.017, Fig. 5A). Age was thus included as a nuisance covariate in subsequent tests. Greater total white matter hyperintensity volume and lower mean fractional anisotropy correlated with greater dizziness and balance-related impairment (white matter hyperintensity p = 0.039, fractional anisotropy p = 0.025, FDR-p < 0.05 for both, Fig. 5C). Lower fractional anisotropy in frontal and right-hemispheric white matter tracts was associated with greater dizziness and balance-related impairment (p < 0.05, Fig. 2C). Significant voxels were in the genu, body and central splenium of the corpus callosum, the inferior longitudinal fasciculus bilaterally and the right superior longitudinal fasciculus.

More aggregate vascular risk (p < 0.001), less premorbid intelligence (NART p = 0.001), and poorer summary and executive cognitive function correlated with more dizziness and balance-related impairment (Fig. 5A). Lower (worse) MoCA scores and longer trail making and Stroop task times correlated with more dizziness and balance-related impairment (MoCA p < 0.001; TMT p = 0.007; Stroop p = 0.003, Fig. 5B). Slower processing speed correlated with more dizziness and balance-related impairment (identification p = 0.028, detection p = 0.05) but neither result was significant after correcting for multiple comparisons (FDR-p > 0.05 in Fig. 5B). Adding NART as a covariate of

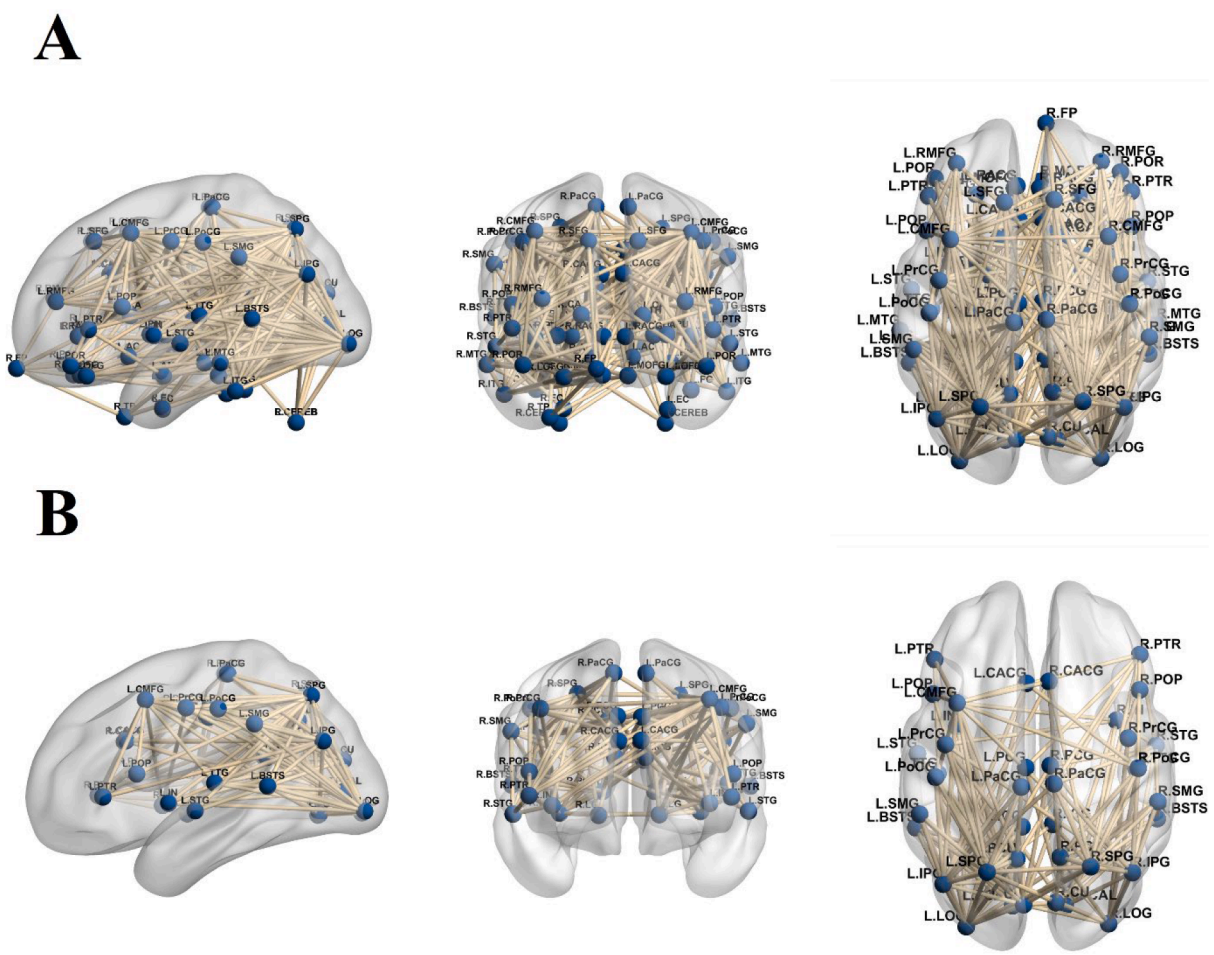

Fig. 3. Structural vestibular connectome in idiopathic dizziness. (A) Network based statistics within the whole brain structural connectome found a network with lower connectivity in patients with idiopathic dizziness compared to controls. Nodes (blue) represent grey matter areas, labelled as per the Illinois Institute of Technology atlas (Desikan et al., 2006). Lines (brown) represent the undirected strength of white matter connections, weighted by their relative strength. (B) Network based statistics within the structural vestibular connectome identifies a network wherein connectivity is lower in patients with idiopathic dizziness than controls. The labels for nodes are as defined in the Illinois institute of technology atlas (Desikan et al., 2006).

no interest abolished the trend relationship between cognition and dizziness and balance-related impairment. Premorbid intelligence may thus be a mediating or confounding factor in the relationship between cognition and dizziness and balance-related impairment.

We compared patients (D+) and controls (C+) with good balance to better isolate the effect of idiopathic dizziness. Patients had lower mean fractional anisotropy ($p < 0.001$, Fig. 5C), a higher aggregate vascular risk ($p = 0.004$, Fig. 5A), less premorbid intelligence (NART $p < 0.001$, Fig. 5B), and worse cognitive performance (MoCA $p = 0.001$, Stroop $p = 0.002$, detection $p \leq 0.001$, identification $p \leq 0.001$, one back task $p \leq 0.001$, Fig. 5B) than controls, confirming the trend effects were not entirely attributable to the balance-impaired patient group.

3.5. Ankle vibration sensory thresholds

There were six patients with idiopathic dizziness with very poor (zero) ankle threshold vibration scores. We investigated the effect of excluding these patients from our analyses. As all six patients fell into the patient subgroup with poor balance, reported differences in vascular risk, mean fractional anisotropy and cognition between patients and controls with good balance were unaffected. Other results were changed in the subsidiary analysis. Voxel-wise differences in white-matter hyperintensity between patients and controls were no longer significant. Voxel-wise correlation between less fractional anisotropy and more dizziness and balance-related impairment was also no longer significant. In patients with idiopathic dizziness, dizziness symptoms no longer correlated with balance measures. In trend analyses, the relationship between more white matter hyperintensity and more dizziness and balance-related impairment was also no longer significant. Worse ankle vibration scores correlated with higher total white matter hyperintensity volume across all participants (Spearman $r = -0.274$, one-tailed $p = 0.013$), suggesting a relationship between SVD burden (under the influence of vascular risk factors) and sensory function.

We characterised the 6 patients with very poor ankle proprioceptive scores by comparison to the remaining patients (Supplementary Table 2). The subgroup with poorer ankle vibration thresholds took fewer accurate tandem steps ($p < 0.001$, Supplementary Table 2), took longer to complete the timed up and go task ($p = 0.021$, Supplementary Table 2), and had poorer lower limb performance (SPPB, $p = 0.014$, Supplementary Table 2) in keeping with worse balance. Average white matter hyperintensity volume was higher (median 18.3 vs 8.16 ml), and mean FA lower (median 0.427 vs 0.433) but neither was statistically significant. They did not differ in cognitive performance, anxiety and depression symptoms, dizziness symptoms, or reported falls (Supplementary Table 2).

4. Discussion

Dizziness in older people is a challenging biological and clinical problem, particularly when vestibular, neurological, cardiovascular and

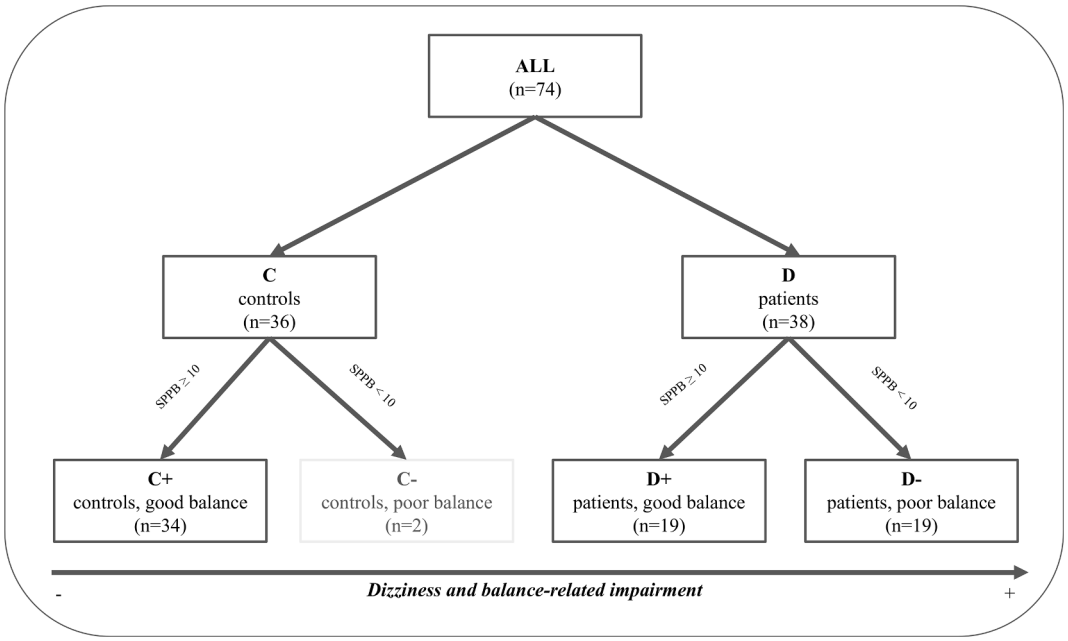

Fig. 4. Idiopathic dizziness and balance across participants. Participants were split into subgroups on the basis of dizziness (C = asymptomatic control, D = idiopathic dizziness) and balance performance (+ = Short Performance Physical Battery [SPPB] ≥ 10, - = SPPB < 10) (Guralnik et al., 1995). The arrow schematically denotes increased dizziness and balance-related impairments, as presented in Fig. 5. Group C- is greyed as there are insufficient members to support meaningful inferences. n = number of participants in the subgroup.

brain imaging examinations are normal for age (Ahmad et al., 2015) – hence the unsatisfactory label of unexplained, idiopathic or presbivestibulopathy given to these patients. Despite being common (Ahmad et al., 2015; Belal and Glorig, 1986), the pathophysiology of this syndrome has remained elusive. We found patients with idiopathic dizziness reported dizziness when upright in addition to elevated anxiety, depression and fear of falling. They had lower fractional anisotropy in the genu of the corpus callosum, the integrity of which is important to postural control (Massa et al., 2019). Lower frontal white matter integrity occurred on a background of excess vascular risk, more hyperintensity in deep frontal white matter, poorer structural connectivity in a large bihemispheric white matter network, worse executive function, and poorer balance as known associations of SVD (Wardlaw et al., 2019). The results therefore support the hypothesis that idiopathic dizziness arises from deleterious effects of SVD on the control of balance.

Brain structure and early life factors (e.g. premorbid intelligence) influence functional outcomes in SVD (Backhouse et al., 2017). These reserve factors combine with vascular risk to determine the burden and clinical expression of SVD. We found lower premorbid intelligence and more vascular risk in dizzy patients than in controls, consistent with both factors being modifiers of the emergence of idiopathic dizziness in SVD. Though a cross-sectional relationship between dizziness in older people and vascular risk is well established (Colledge et al., 1994; Maarsingh et al., 2010), less is known on the influence of cognitive reserve. One previous study in a general practice setting reported an association between lower educational attainment and dizziness, consistent with a role for cognitive reserve in the genesis of dizziness symptoms (Maarsingh et al., 2010). Future work should include early life factors such as educational attainment and premorbid intelligence as a potential predictor of dizziness in older populations.

Impaired vestibular self-motion perception has been suggested to produce dizziness symptoms in older people (Chiarovano et al., 2016). A relationship between vestibular self-motion perception and clinical symptoms was recently shown in a study of traumatic brain injured patients where less integrity in the right inferior longitudinal fasciculus associated with less vestibular self-motion perception (Calzolari et al., 2020). We found less connectivity within a structural vestibular network in patients with idiopathic dizziness but this finding was not network-specific, occurring in the context of diffusely impaired connectivity across white matter tracts. Diffusely impaired structural connectivity in idiopathic dizziness is consistent with previous work showing small vessel disease impairs function through network effects in widespread white matter tracts (Lawrence et al., 2014). We found an association between SVD in frontal white matter and idiopathic dizziness and poorer balance (Fig. 2), but contrastingly no relationship was found between dizziness and SVD burden, and vestibular self-motion perception was not impaired in patients. Our results overall suggest impaired balance rather than impaired vestibular self-motion perception underpins symptoms in idiopathic dizziness. This view is in accord with recent EEG evidence showing cortical activity and connectivity involved in postural control is disrupted in idiopathic dizziness under the influence of small vessel disease (Ibitoye et al., 2021).

SVD has been associated with an increasing range of problems in older people in addition to its more established association with postural instability and slow gait (Clancy et al., 2021; Rensma et al., 2018). We found dizzy symptoms co-occurred with fear of falling, anxiety and depression. We also found correlation between anxiety and depression, and SVD burden in patients. These findings are consistent with previous work which found dizzy older people with objectively impaired balance reported more depressive symptoms and more falls-related anxiety (Fife and Baloh, 1993). Our results are also in accord with the recently established association of SVD with depression (Rensma et al., 2018), fatigue, delirium and apathy (Clancy et al., 2021). Whether SVD is associated with dizziness has been a focus of research (Ahmad et al., 2015; Colledge et al., 2002; Day et al., 1990; Lorbeer et al., 2017). Limited clinical characterisation (and thus the potential inclusion of participants with well-defined vestibular disorders) (Colledge et al., 2002), the use of qualitative (rather than quantitative) measures of SVD burden (Ahmad et al., 2015), and the application of clinical structural neuroimaging methods (rather than more sensitive approaches like diffusion tensor imaging) is likely to have limited the sensitivity of previous work (Ahmad et al., 2015; Colledge et al., 2002; Day et al., 1990; Lorbeer et al., 2017). We found a significant trend such that patients with idiopathic dizziness and good balance were intermediate

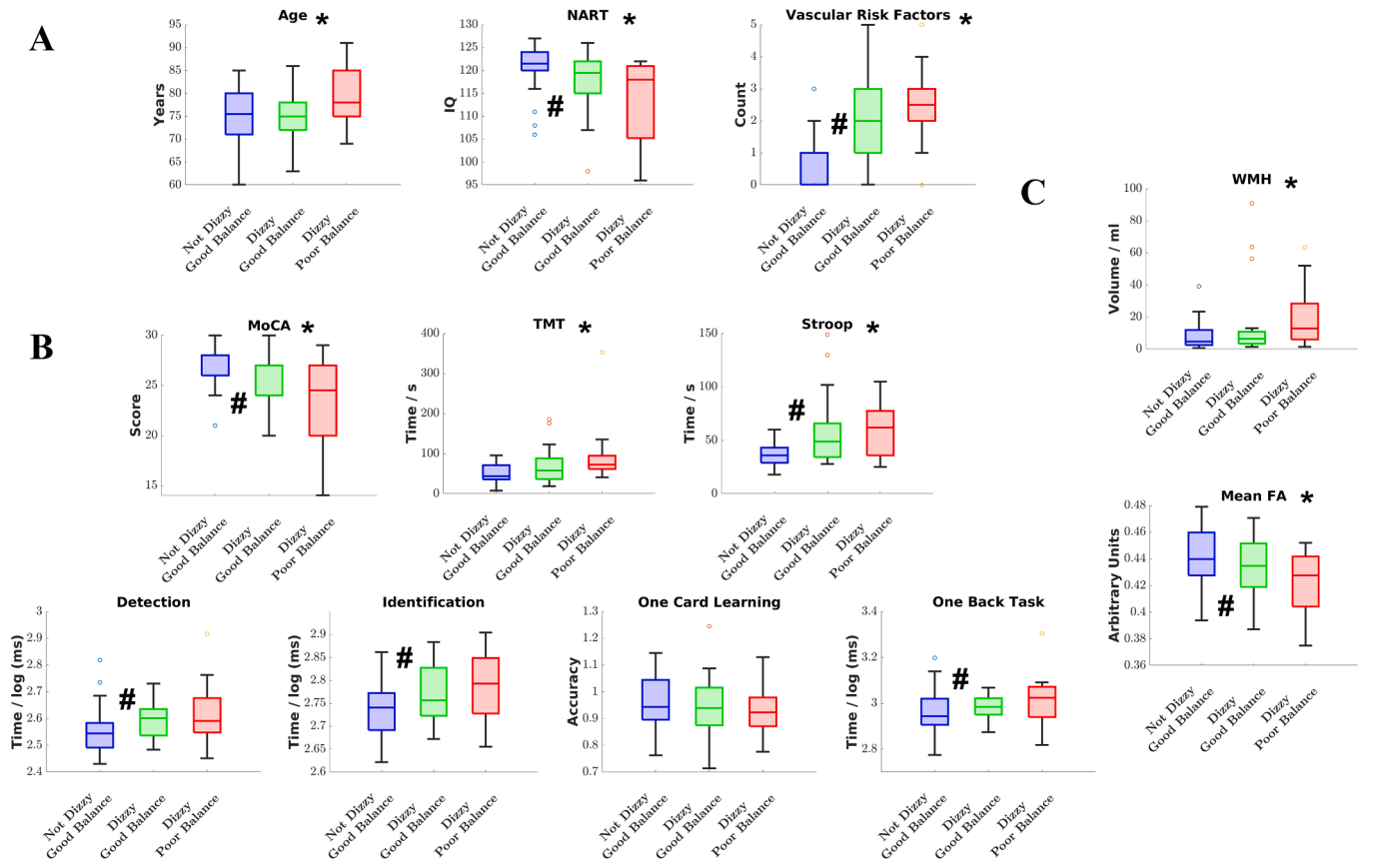

Fig. 5. Dizziness and balance-related impairment. Boxplots illustrate measures across groups, such that dizziness and balance-related impairment increases from left (Not Dizzy Good Balance) to right (Dizzy Poor Balance). The box extent represents 25th to 75th percentiles; whiskers extend below the lower and higher quartiles by 1.5 × the interquartile range. (A) Age, National Adult Reading Test (NART) estimated premorbid intelligence quotient (IQ), and aggregate vascular risk. (B) Cognitive tests: MoCA = Montreal Cognitive Assessment score; TMT = Trail Making Test time in task B minus time in task A; Stroop = time in colour-word task minus time in word task. (C) Summary white matter integrity measures: WMH = total white matter hyperintensity volume; FA = mean fractional anisotropy in white matter skeleton. * = significant linear trend with impairment in a linear regression including age as nuisance covariate, false discovery rate-corrected $p < 0.05$. # = significant difference between non-dizzy good balance, and dizzy good balance subgroup, $p < 0.05$.

between controls and dizzy patients with poor balance - with respect to SVD burden and cognitive functioning (Fig. 5). This trend suggests idiopathic dizziness is associated with SVD, even in those whose balance is objectively good. Idiopathic dizziness may therefore be an early symptom of declining balance function in small vessel disease. Whether idiopathic dizziness is a precursor or predictor of frank balance and gait impairment, and/or cognitive decline requires further research.

We defined our patient cohort as elderly patients with dizziness but an absence of a diagnostic explanation for their vestibular symptoms. Though we suggest SVD is pathophysiologically relevant, other mechanisms could also account for symptoms. For example, functional or psychogenic dizziness as operationalised in persistent postural-perceptual dizziness (PPPD) could be an alternative basis to otherwise unexplained vestibular symptoms in older people (Staab et al., 2017). Functional dizziness was, however, unlikely to have been important in our study. First, all patients were assessed by experienced clinicians with expertise in neuro-otology and their presentation was not considered to be compatible with PPPD. Second, no patients with idiopathic dizziness met research criteria for PPPD. Third, PPPD is most prevalent in mid-life, with a mean age of 46 years (standard deviation 14 years), declining beyond 60 years (Habs et al., 2020; Powell et al., 2020). This contrasts an increasing community prevalence of persistent dizziness with age beyond 60 years (Colledge et al., 1994; Gassmann et al., 2009; Sloane et al., 1989). Fourth, our patients did not show greater high frequency sway (3.5 Hz to 8 Hz), as previously reported in PPPD (Krafczyk et al., 1999). Fifth, our patients were followed up for a minimum of 6 months, within which alternative diagnoses such as PPPD did not emerge. Other well-characterised causes of neurodegeneration are also unlikely to have featured in our patients as symptoms had been present for 6 years on average prior to entering the study. This lead-in time precludes rapidly progressive neurological disorders, and signs of these were not present in our patients. The data therefore do not provide support for functional dizziness (PPPD) or neurodegenerative diseases as major contributors to dizziness in our sample.

We found worse ankle vibration thresholds in our patients (Table 1), and that very poor vibration thresholds associated with worse balance. These findings are consistent with a previous study which reported ankle vibration thresholds were often worse in older people with objectively impaired balance, unexplained dizziness and disequilibrium, when compared to age-matched controls (Fife and Baloh, 1993) – in the absence of overt peripheral neuropathy. The authors suggested impaired vibration sense contributes to disequilibrium and dizziness in some older people. Our results support their view. Why vibration thresholds are impaired in patients with idiopathic dizziness is not immediately clear. One possible explanation is the co-existence of subclinical neuropathy (Fife and Baloh, 1993). Another is the presence of more central deficits in sensory processing – given vibration thresholds assessed by tuning fork are also known to depend on central somatosensory function (Lin et al., 2005). Our findings of correlation between cerebral small vessel disease burden and ankle vibration thresholds, and of similarity between patients and controls in the difference between knee and ankle thresholds (linked to peripheral nerve function), suggest central factors

are important and that cerebral small vessel disease associates with vibration threshold deficits.

We propose the somatosensory and small vessel disease associations of idiopathic dizziness may be accounted for a common vascular risk environment – hypertension being, for example, associated with cerebral small vessel disease and subclinical peripheral neuropathy. Peripheral neuropathy occurs in animal models of hypertension (Nukada et al., 2016), and in humans, subclinical impairment of peripheral and central somatosensory function has been shown to associate with hypertension (Branch, 2011; Edwards et al., 2010). Though an explicit link between cerebral small vessel disease and peripheral neuropathy has not been defined, extra-cerebral microangiopathic associations of cerebral small vessel disease are recognised in other organ systems, for example in cardiac and renal vasculature (Berry Colin et al., 2019; Thompson and Hakim, 2009). In principle, microangiopathy due to hypertension and other vascular risk factors could explain the co-occurrence of somatosensory deficits and the observed small vessel disease associations of idiopathic dizziness.

This study has a number of limitations. First, we used automated white matter hyperintensity segmentation as a marker of SVD which offers a limited view of the pathologies seen in SVD compared to expert rating and quantification of neuroimaging markers such as microinfarcts, microbleeds, perivascular spaces and lacunar infarcts (Staals et al., 2015). Combined rater-derived measures including more SVD markers would be expected to increase sensitivity of analyses to SVD. Our inclusion of diffusion imaging which has been shown to be highly sensitive to white matter damage in SVD (Zeestraten et al., 2016) nonetheless supported the recovery of associations between idiopathic dizziness and SVD. Second, automated segmentation methods may be susceptible to biases associated with thresholding and local image acquisition parameters; our acquisition of all images on the same scanner reduces this risk. Third, to allow adequate clinical characterisation which limited previous work (Colledge et al., 2002; Lorbeer et al., 2017), we recruited patients from a specialist clinic which undoubtedly excluded alternative diagnoses. This selectivity however means our patient population may not be representative of older people with unexplained dizziness in the community. On the other hand, it is known that dizziness in the community frequently includes well defined and treatable conditions such as benign paroxysmal positional vertigo, vestibulopathy and orthostatic hypotension which if not excluded would have rendered our work futile. Fourth, the sample size - though similar to other neuroimaging studies applying these methods – is relatively small. Studies of larger populations will be needed to clarify potentially complex relationships between dizziness, psychological symptoms, balance and small vessel disease burden.

In summary, our results show dizziness co-associates with impaired balance in older people and microvascular injury to frontal white matter relevant to the control of balance in cerebral small vessel disease. Idiopathic dizziness may be a precursor to SVD-related cognitive decline and gait dysfunction.

CRediT authorship contribution statement

Richard T. Ibitoye: Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Patricia Castro:** Investigation, Writing – review & editing. **Josie Cooke:** Investigation, Writing – review & editing. **John Allum:** Methodology. **Qadeer Arshad:** Writing – review & editing. **Louisa Murdin:** Resources, Writing – review & editing. **Joanna Wardlaw:** Writing – review & editing. **Diego Kaski:** Conceptualization, Resources, Writing – review & editing, Supervision. **David J. Sharp:** Methodology, Resources, Supervision. **Adolfo M. Bronstein:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

J. Allum worked as a consultant for the company (Balance Int Innovations GmbH) producing the posturographic equipment used in this study. The remaining 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103098.

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