

Physical Performance in Memory Clinic Patients: The Potential Role of the White Matter Network

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BACKGROUND/OBJECTIVES: Memory clinic patients commonly also have declined physical performance. This may be attributable to white matter injury, due to vascular damage or neurodegeneration. Quantifying white matter injury is made possible by new magnetic resonance imaging (MRI) techniques, including diffusion-weighted imaging (DWI) of network connectivity. We investigated whether physical performance in memory clinic patients is related to white matter network connectivity.

DESIGN: Observational cross-sectional study.

SETTING: Memory clinic.

PARTICIPANTS: Patients referred to a memory clinic with vascular brain injury on MRI (n = 90; average age = 72 years; 60% male; 34% with diagnosis Alzheimer disease).

MEASUREMENTS: We reconstructed structural brain networks from DWI with fiber tractography and used graph theory to calculate global efficiency, fractional anisotropy (FA), and mean diffusivity (MD) of the white matter, and nodal strength (mean FA or MD of all white matter tracts connected to a node). Assessment of physical performance included gait speed, chair stand time, and Short Physical Performance Battery (SPPB) score.

RESULTS: Lower global efficiency, lower FA, and higher MD correlated with poorer gait speed, SPPB scores, and chair stand times (R range = 0.23-0.42). Global efficiency and FA explained 5% to 16% of the variance in gait speed, chair stand times, and SPPB scores, independent of age and sex. Moreover, global efficiency and FA explained an additional

4% to 5% of variance on top of lacunar infarcts and white matter hyperintensities. Regional analyses showed that, in particular, the connectivity strength of prefrontal, occipital, striatal, and thalamic nodes correlated with gait speed.

CONCLUSION: Poorer physical performance is related to disrupted white matter network connectivity in memory clinic patients with vascular brain injury. The associations of these network abnormalities are partially independent of visible vascular injury. *J Am Geriatr Soc* 67:1880-1887, 2019.

Key words: brain connectivity; cognitive impairment; diffusion-weighted imaging; gait

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Loss of function in memory clinic patients not only includes cognitive impairment, but often also a decline in physical performance, such as gait impairment.^{1,2} Declining physical performance is in itself associated with disability and predicts falls, frailty, and mortality.^{3,4}

Underlying mechanisms of declining physical performance are particularly complex and multifactorial in older people, and they include musculoskeletal, pharmacological, or neurological causes. Cerebral causes of declining physical performance in memory clinic patients include vascular brain damage and Alzheimer disease (AD), which result in gray, but also white, matter injury.^{1,5-7} The white matter injury is only partly visible on magnetic resonance imaging (MRI), particularly as markers of small-vessel disease (SVD).⁸ Yet, the so-called normal-appearing white matter (NAWM) can also be disrupted, as shown by diffusion-weighted imaging (DWI) studies.⁹

More recently, DWI techniques have been combined with graph theory to explore large-scale network models of the white matter.¹⁰ These models enable quantification of the efficiency with which the brain integrates information between multiple, remote, and interconnected regions, by

considering both the integrity and the spatial organization of the network. Network measures can, independently of visible injury, explain function loss, like cognitive impairment in SVD^{11,12} and early AD.^{13,14}

Like higher-order cognitive functions, physical performance depends on a network of multiple brain regions.^{15,16} However, the extent to which disrupted network connectivity relates to declined physical performance is unclear. DWI studies have related physical performance to the integrity of the white matter,^{17,18} but they have rarely considered network measures.

This study investigated whether global and regional measures of white matter network connectivity relate to physical performance in memory clinic patients with vascular brain injury.

METHODS

Participants

Patients were recruited from memory clinics of the University Medical Center Utrecht. Patients were eligible if they had undergone a standardized workup, including clinical history, an MRI with a sufficient DWI sequence, neuropsychological assessment, and physical performance assessment.

For this study, we included patients with vascular brain injury on MRI, defined as: (a) moderate to severe white matter hyperintensities (WMHs) (Fazekas score of 2 or higher); (b) Fazekas score of 1 and 2 or more vascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity, currently smoking, or history of vascular events other than stroke); (c) one or more lacunar infarcts; (d) one or more nonlacunar infarcts; (e) one or more cerebral microbleeds; or (f) one or more intracerebral hemorrhages.¹⁹ Patients with a Clinical Dementia Rating of 2 or higher were excluded. Patients were also excluded if they had nonvascular and nonneurodegenerative etiologies that

caused their physical or cognitive impairment, if they had neurodegenerative or other neurologic diseases that primarily cause motor symptoms, or if they had severe musculoskeletal conditions or orthopedic interventions affecting walking ability. Finally, patients were excluded if the network reconstructions failed (Figure 1).

Clinical diagnoses were determined by a memory clinic physician, a neuropsychologist, and a nurse at a multidisciplinary meeting, according to established diagnostic criteria.^{20,21}

The study was approved by the local medical ethics committee of the University Medical Center Utrecht (Utrecht, The Netherlands). All patients provided written informed consent prior to undergoing research-related procedures.

The raters of physical performance were blinded for MRI ratings and vice versa. MRI raters of visible vascular damage were blinded to the network data, and vice versa. Hence, the combined data of physical, vascular, and network variables were only available for the current authors, after the database was closed.

Study Sample Characteristics

We gathered information about age, sex, medical history, vascular risk factors,¹⁹ diagnosis, clinical dementia rating, and global cognitive functioning, according to the Mini-Mental State Examination. Any minor musculoskeletal conditions or orthopedic interventions that can affect physical performance (eg, total hip or knee replacement, osteoarthritis, and gout) were identified on the basis of medical history and physical examination.

MRI Protocol

MRI data were acquired on a Philips 3.0-T scanner with a standardized protocol that consisted of a three-dimensional T1-weighted sequence (192 slices; voxel size = 1.00 × 1.00 × 1.00 mm); a T2*-weighted scan (48 continuous slices;

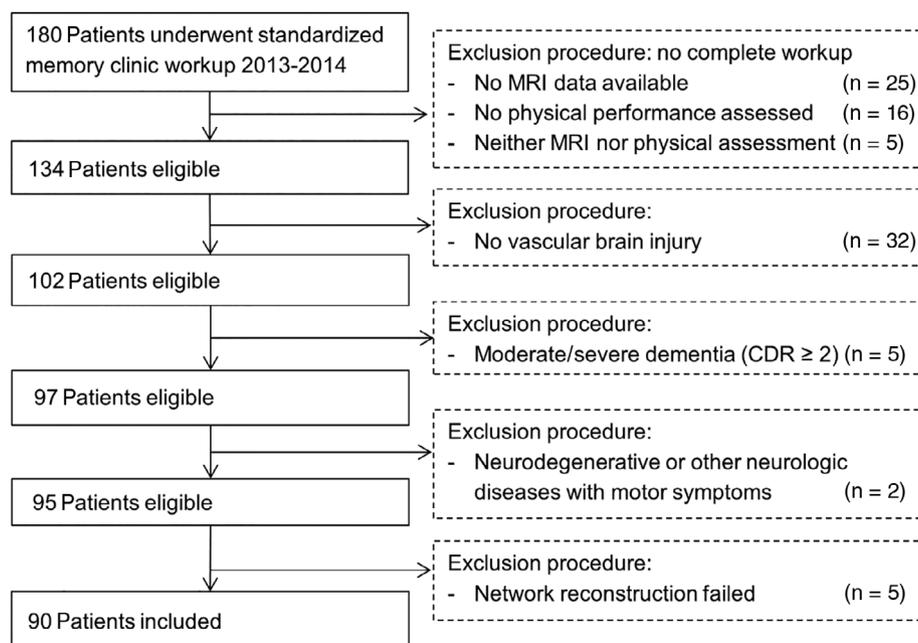


Figure 1. Flowchart of the inclusion of patients. CDR indicates Clinical Dementia Rating; MRI, magnetic resonance imaging.

reconstructed voxel size = $0.99 \times 0.99 \times 3.00$ mm); a fluid-attenuated inversion recovery scan (48 continuous slices; reconstructed voxel size = $0.96 \times 0.95 \times 3$ mm); and a DWI scan (48 slices; voxel size = $1.72 \times 1.72 \times 2.50$ mm; repetition time/echo time = 6600/73 milliseconds; 45 gradient directions with a b value of 1200 s/mm^2 and one $b = 0 \text{ s/mm}^2$ image).

Diffusion Tensor Imaging

Y.R. processed the diffusion-weighted scans in ExploreDTI (<http://www.exploredti.com>) in accordance with previous studies.^{22,23} In brief, the scans were corrected for subject motion and eddy current induced geometric distortions before the calculation of the diffusion tensors.²⁴ Whole-brain white matter tractography was performed using constrained spherical deconvolution, which allows for the reconstruction of fibers that go through crossing fiber regions.^{25,26}

Seed samples were uniformly distributed throughout the white matter at 2-mm isotropic resolution. Fiber tracts were terminated when they deflected in an angle of 45° or greater or when they entered a voxel with a fiber orientation distribution threshold of 0.1 or less. The whole-brain fiber tract reconstructions were parcellated into 90 gray matter regions or “nodes” (45 for each hemisphere, excluding the cerebellum) using the automated anatomical labeling atlas.²⁷ To avoid partial volume effects of gray matter tissue and cerebral spinal fluid, the fractional anisotropy (FA) of the white matter connections was thresholded at 0.2. Two brain nodes were considered to be connected if a tract was present with two end points located in these nodes. Each connection was multiplied by the mean FA of that connection, yielding a 90×90 weighted connectivity matrix that was used to calculate the measures of network connectivity.

White Matter Network Measures

We used the brain connectivity toolbox (<https://sites.google.com/site/bctnet>)²⁸ to calculate characteristics of the white matter network. Measures of global connectivity included *global network efficiency* and the *mean FA* and *mean diffusivity (MD)* of the supratentorial white matter. Global efficiency was selected as a measure of global information processing (ie, the ability to efficiently integrate information between each pair of brain regions). It is calculated by averaging the inverse of the minimum number of FA-weighted connections between each pair of brain regions. Global efficiency has shown robust relationships with cognition.^{11,12,14} FA and MD of the supratentorial white matter were obtained using the International Consortium of Brain Mapping-Diffusion Tensor Imaging-81 (DTI) template.²⁹ We used the *nodal strength* as a measure of regional connectivity, which is calculated as the mean FA or MD of all connections to a node.

Ratings of Vascular Brain Injury

Lacunar infarcts, cerebral microbleeds, nonlacunar (sub)cortical infarcts, and intracerebral hemorrhages were rated according to established criteria.²⁴ WMHs were rated according to the Fazekas scale. The ratings were performed under supervision of a neuroradiologist (who was in training).

Physical Performance Assessment

General physical performance was measured with the Short Physical Performance Battery (SPPB).³ This sum scale consists of three individual measurements of gait, chair stand, and balance. The scoring rules were the same as previously described.³⁰ The scale ranges from 0 to 12 points, with a higher score indicating a better performance.

Mean gait speed (m/s) at a usual pace and from a standing start was measured using the 4-m walk test.

The ability to rise from a chair was measured using the chair stand test. The time needed for five stands was used.

Statistical Analyses

The association between measures of global network connectivity (global efficiency, FA, and MD) and physical performance (gait speed, chair stand time, and SPBB scores) was first analyzed with partial correlations adjusted for age and sex. Then, to investigate the extent to which the measures of global network connectivity explain physical performance, independently of age, sex, WMHs, and lacunar infarcts, we performed hierarchical linear regression analyses. In the first model, age and sex were entered as covariates. In the second model, measures of global network connectivity were separately added to the first model. In the third model, WMHs and lacunar infarcts were added to the first model. In the fourth model, measures of global network connectivity were separately added to the third model. We calculated the explained variance R^2 for each model and the P value of the change in explained variance. A P value of .05 was used to test for statistical significance.

The association between measures of regional network connectivity (FA- and MD-weighted nodal strength) and physical performance was analyzed with partial correlations, adjusted for age and sex. To account for multiple testing, we applied the false discovery rate (FDR) correction. We excluded the SPPB score from the regional analyses, because this is a composite score based on different physical functions and involves multiple underlying networks.

Additionally, we constructed a “gait subnetwork” based on the results of the regional analyses. We selected the regions that were significantly related to gait speed in the regional analyses (Figure 2A,B). These regions were used as input for a new connectivity matrix to calculate the FA-weighted efficiency of this subnetwork. This efficiency was then related, via partial correlation analyses, to the global efficiency of the whole-brain network and the physical performance measure on which the network was based. To calculate the explained variance in physical performance by subnetwork efficiency, we also added this measure to models 2 and 4.

We performed three sensitivity analyses on the partial correlation analyses between global network measures and physical performance only, including: (1) patients without musculoskeletal conditions; or (2) patients without a clinical diagnosis of probable or possible AD; or (3) patients without nonlacunar infarcts or intracerebral hemorrhages. All statistical analyses were performed with IBM SPSS, version 24.

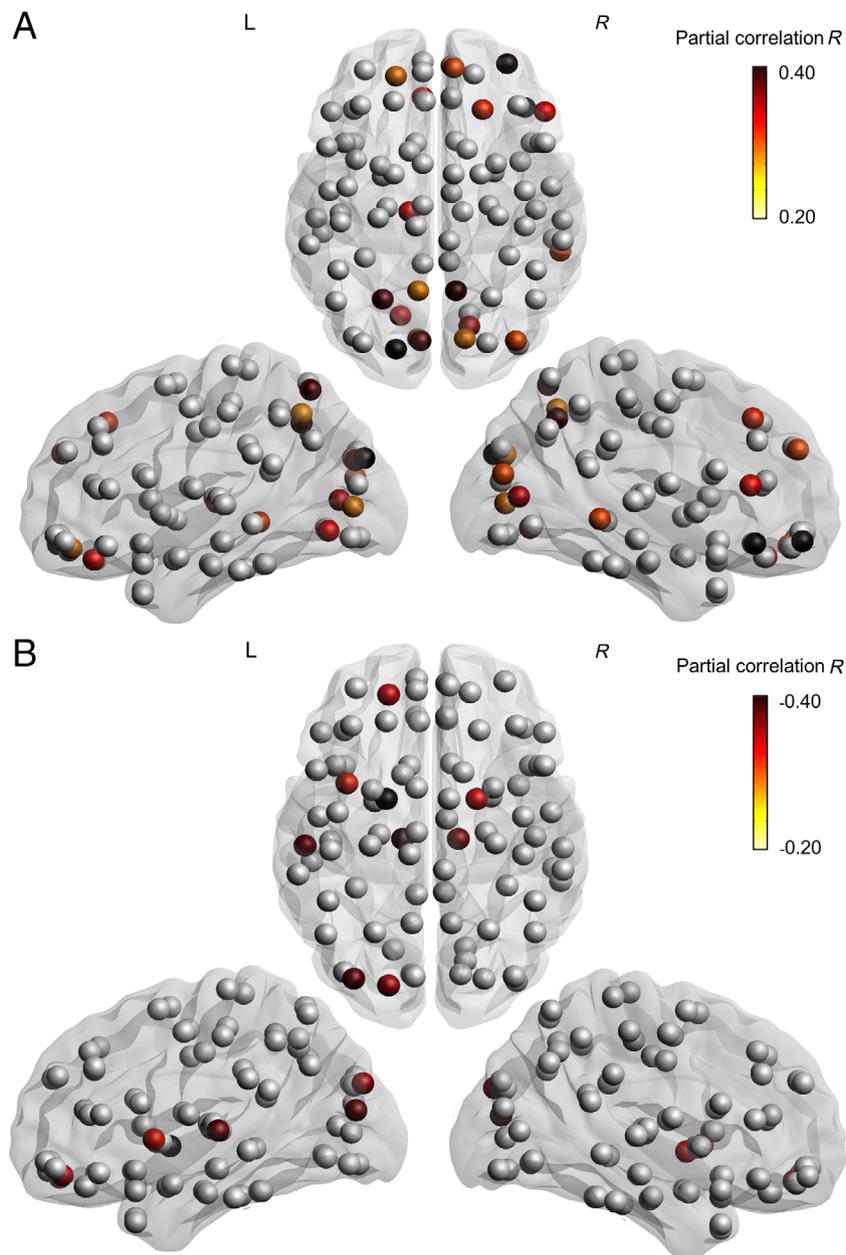


Figure 2. Association between regional network strength and gait speed. (A) Fractional anisotropy (FA). (B) Mean diffusivity (MD). Axial and lateral sagittal projections of the nodes of which the FA- and MD-weighted strength correlated with gait speed, adjusted for age and sex. Nodes are colored if they have correlations of 0.20 or greater for FA and -0.20 or less for MD. L indicates left; R, right.

RESULTS

A flowchart of the patient enrollment is presented in Figure 1. The patients were, on average, 72 years old and 60% of them were male (Table 1). Of all the patients, 79% had cognitive impairment, of whom 52% had dementia. Among those with dementia, 84% had a clinical diagnosis of probable or possible AD. MRI-visible vascular brain injury largely consisted of markers of SVD: 53% of the patients had moderate-to-severe WMHs, 44% had one or more lacunar infarcts, and 42% had one or more microbleeds. In addition, 18% had a non-lacunar infarct and 9% had an intracerebral hemorrhage.

The mean global efficiency of the white matter network was 0.190 (SD = 0.016), the mean FA was 0.419 (SD = 0.024),

and the mean MD was 0.88×10^{-3} mm²/s (SD = 0.06×10^{-3} mm²/s). Patients had a mean gait speed of 1.09 m/s (SD = 0.27 m/s), stood up from a chair five times in a mean time of 14.7 seconds (SD = 5.0 seconds), and had a mean score on the SPPB of 9.4 points (SD = 2.4 points).

Lower global efficiency, lower FA, and higher MD correlated with poorer gait speed, chair stand times, and SPPB scores (Table 2). Patients with minor musculoskeletal conditions ($n = 36$; 40%) had no differences in physical performance or white matter network connectivity compared to patients without these conditions. The sensitivity analyses in selected patient samples showed that the correlations were essentially similar to those in the complete sample (Supplementary Tables S1-S3).

Table 1. Sample Characteristics (n = 90)

Characteristics	Value
Age, mean \pm SD, y	71.5 \pm 9.2
Sex, male, No. (%)	54 (60)
Diagnosis, No. (%) of total	
No objectified cognitive impairment	19 (21)
Mild cognitive impairment	34 (38)
Dementia	37 (41)
Alzheimer disease, No. (%) of dementia	31 (84)
Vascular dementia, No. (%) of dementia	6 (16)
Clinical Dementia Rating, median (IQR)	0.5 (0.5)
Mini-Mental State Examination, mean \pm SD	25.8 \pm 3.6
Minor musculoskeletal conditions, No. (%)	36 (40)
Hypertension, No. (%)	82 (91)
Hypercholesterolemia, No. (%)	59 (66)
Diabetes mellitus, No. (%)	27 (30)
Obesity, No. (%)	14 (16)
Current smoker, No. (%)	14 (16)
History of vascular events other than stroke, No. (%)	23 (26)

Abbreviation: IQR, interquartile range.

Global efficiency and FA explained 9% to 16% of the variance in gait speed on top of age and sex (Table 3). The association between these network measures and gait speed was also independent of WMHs and lacunar infarcts, with an added explained variance of 4% to 5% over the model including only these vascular lesions and age and sex. We found similar results for the association between global efficiency and FA and the SPPB score: the explained variance on top of age and sex was 13% to 16%. In the model that also included WMHs and lacunar infarcts, the added explained variance by global efficiency and FA was 4% to 5%. Global efficiency and FA also explained variance in chair stand time on top of age and sex (added explained variance = 5%-10%), but these associations lost significance after additionally adjusting for WMHs and lacunar infarcts. Finally, MD explained 10% to 13% of the variance in gait speed, chair stand time, and SPPB scores on top of age and sex. These associations lost significance after additionally adjusting for WMHs and lacunar infarcts.

Figure 2A,B show the network nodes for which reduced FA- or MD-weighted strength correlated with gait speed,

Table 2. Correlations Between Global Network Measures and Physical Performance (n = 78-90)

Measure	Gait speed, m/s	Chair stand time, s	SPPB score
Global efficiency	0.31 (.004)	-0.23 (.044)	0.36 (.001)
FA white matter	0.41 (<.001)	-0.33 (.003)	0.42 (<.001)
MD white matter	-0.37 (<.001)	0.32 (.003)	-0.38 (<.001)

Note: Data are presented as partial correlation coefficients (*P* value), adjusted for age and sex. High physical performance scores represent better performance, except for the chair stand time. FA and MD of the supratentorial white matter were obtained using the International Consortium of Brain Mapping-DTI-81 template.

Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; SPPB, Short Physical Performance Battery.

adjusted for age and sex. For the FA, 19 nodes showed a correlation with poorer gait speed (*P* lower than 0.05; FDR corrected), which were predominantly located in prefrontal and occipital regions. For the MD, nine nodes showed a correlation with poorer gait speed, including prefrontal and occipital regions, but also both the left and right thalamus and pallidum.

We then calculated the efficiency of the subnetwork composed of the 25 nodes that showed a correlation with gait speed in Figure 2A,B. The efficiency of this subnetwork was 0.214 (SD = 0.023), and it correlated strongly with whole-brain global efficiency (partial correlation $r = 0.80$; $P < .001$). Moreover, efficiency of the subnetwork showed a stronger correlation with gait speed (partial correlation $r = 0.38$; $P < .001$) than the whole-brain global efficiency did ($r = 0.31$; Table 2). Regarding explained variance, efficiency of the subnetwork explained 13% variance in gait speed on top of age and sex (corresponding with model 2; total R^2 of that model = 21%) and explained 8% variance on top of age, sex, WMHs, and lacunar infarcts (corresponding with model 4; total R^2 of that model = 27%).

DISCUSSION

Our results show that poorer physical performance (ie, gait speed, chair stand time, and SPPB score) is associated with global and regional measures of disrupted white matter network connectivity in memory clinic patients with vascular brain injury. The associations of these network abnormalities were also independent of visible vascular white matter injury.

Multiple factors can contribute to declining physical performance in memory clinic patients. With regard to white matter injury, most previous studies focused on visible markers of SVD. Particularly, severe WMHs are consistently related to declined physical performance,⁵ which corresponds to our results. More recently, DWI studies, applying global and regional DTI metrics, showed that physical performance decline also relates to subtle changes in the integrity of the NAWM, also in both healthy older people and patient populations other than memory clinic patients.^{1,2,9,17,18,31}

We are aware of only one previous study that used structural network measures to explore possible causes of physical performance decline. In line with our current observations, this study showed that global network efficiency was associated with gait speed in patients with severe cerebral amyloid angiopathy,³² a specific form of SVD.

With regard to the integrity of regional networks, disrupted connectivity of prefrontal, occipital, striatal, and thalamic nodes was associated with gait speed. Higher-order monitoring of motor programs in prefrontal regions,¹⁶ integration of vestibular, visual, and proprioceptive information in posterior regions,^{33,34} and regulation of automated movements and posture in the basal ganglia and thalamus¹⁵ are all essential for stable gait. Moreover, these regions are connected by tracts that run through periventricular or deep white matter regions that are vulnerable to SVD³⁵ and are associated with physical performance decline⁵ and falls³⁴ in memory clinic patients.

The efficiency of the gait subnetwork explained most of the variance in gait speed, on top of visible vascular injury.

Table 3. Explained Variance in Physical Performance by Measures of Network Connectivity (N = 82-90)

Model	Independent variables	Gait speed, m/s		Chair stand time, s		SPPB score	
		R^2	P for ΔR^2	R^2	P for ΔR^2	R^2	P for ΔR^2
1	Age + sex	0.08	.039	0.05	.159	0.10	.012
2a	Model 1 + global efficiency	0.17	.003	0.10	.039	0.23	.001
2b	Model 1 + FA white matter	0.24	<.001	0.15	.003	0.26	<.001
2c	Model 1 + MD white matter	0.20	<.001	0.15	.003	0.23	<.001
3	Model 1 + WMH + LI ^a	0.19	.005	0.15	.010	0.24	.002
4a	Model 3 + global efficiency	0.23	.039	0.17	.217	0.29	.018
4b	Model 3 + FA white matter	0.24	.017	0.17	.239	0.28	.028
4c	Model 3 + MD white matter	0.22	.076	0.17	.194	0.26	.105

Note: Data are presented as follows: the explained variance (R^2) is physical performance for each model, with the corresponding P value for the difference in explained variance (ΔR^2) between the model and the previous model. FA and MD of the supratentorial white matter were obtained using the International Consortium of Brain Mapping-DTI-81 template.

Abbreviations: FA, fractional anisotropy; LI, lacunar infarct; MD, mean diffusivity; SPPB, Short Physical Performance Battery; WMH, white matter hyperintensity.

^aFazekas scores split into 2 to 3 vs 0 to 1.

Our results raise the possibility that gait impairments are primarily driven by disconnectivity between prefrontal, occipital, striatal, and thalamic brain regions. Since the gait network was reconstructed via a post hoc data-driven analysis, the exact composition of this network needs to be replicated by future studies.

This study has limitations. We extracted the gait sub-network based on univariate nodal analyses. However, other, multivariate statistical methods have been proposed that take into account the interdependency of nodes.³⁶ Future studies using these statistical methods should aim to reproduce our gait network. We included memory clinic patients using nonrestrictive criteria, which were not limited to certain diagnoses. Although all patients had MRI evidence of vascular brain injury, 34% of the patients had a clinical diagnosis of probable or possible AD; it should be acknowledged that this diagnosis was not supported by biomarker evidence. The cohort includes people with mixed diagnoses and mixed pathologies. However, this does reflect clinical practice as, in a memory clinic setting, vascular brain injury commonly co-occurs with other pathologies.⁷ The current findings are likely to be generalizable to other memory clinic patients. Data quantifying neurodegenerative atrophy were not available, preventing us from investigating the influence of AD-related pathology on physical performance. However, a sensitivity analysis, including only patients without a clinical diagnosis of probable or possible AD, showed largely similar results. Along the same lines, we did not limit our patient selection to specific subtypes of vascular injury. Sensitivity analyses excluding patients with large-vessel disease again showed largely similar results. Unfortunately, our study was underpowered to perform rigorous corrections for multiple hypothesis testing. However, the fact that we found moderate effect sizes that were consistent across outcome measures reduces the chance that our findings are due to a type I error. A significant strength of the study includes the use of high-quality multimodal MRI scans and the elaborate network analyses.

The implication of this study is that a decline in physical performance is partly attributable to disrupted white matter networks in memory clinic patients with vascular

brain injury. However, it is still questionable whether global network measures provide explanatory value beyond more common and easily measured DTI parameters. Particularly, white matter FA showed a similar association with physical performance in our multivariable model as global network efficiency. The following steps to further investigate underlying mechanisms include mediation analyses, addressing the progression of network changes over time, and localizing specific subnetworks related to physical performance. The necessity for a more in-depth investigation corresponds with the idea that higher-order cerebral functions depend on complex networks of remote, cooperating, and interconnected regions. The condition of the brain network is defined by the degree of (vascular) brain injury, but also by physiological factors like innate network structure, which can potentially determine capacity to compensate for brain injury.^{13,37} As such, network measures function as an integrated measure of disease burden and reserve capacity. A limitation is that they may have limited etiological specificity, although it may well be that different diseases have different network signatures. All in all, although investigating physical performance decline from a network perspective is still in an early stage, network analysis might provide insight into the structural basis of physical performance decline in the memory clinic setting and its associated adverse health outcomes.^{3,4}

In conclusion, poorer physical performance in memory clinic patients with vascular brain injury is related to disrupted white matter network connectivity. These findings suggest that physical performance relies on the efficient communication within the complex network of brain regions. The extent to which this network is disrupted is relevant for understanding gait problems and other declines in physical performance.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Correlations between global network measures and physical performance in patients without musculoskeletal conditions.

Supplementary Table S2. Correlations between global network measures and physical performance in patients without a clinical diagnosis of probable or possible AD.

Supplementary Table S3. Correlations between global network measures and physical performance in patients without large-vessel disease.