white matter ultrastructural damage, not disability

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ABSTRACT

Objective: To determine whether cerebral small-vessel disease (SVD) is a specific risk factor for depression, whether any association is mediated via white matter damage, and to study the role of depressive symptoms and disability on quality of life (QoL) in this patient group.

Methods: Using path analyses in cross-sectional data, we modeled the relationships among depression, disability, and QoL in patients with SVD presenting with radiologically confirmed lacunar stroke (n = 100), and replicated results in a second SVD cohort (n = 100). We then compared the same model in a non-SVD stroke cohort (n = 50) and healthy older adults (n = 203). In a further study, to determine the role of white matter damage in mediating the association with depression, a subgroup of patients with SVD (n = 101) underwent diffusion tensor imaging (DTI).

Results: Reduced QoL was associated with depression in patients with SVD, but this association was not mediated by disability or cognition; very similar results were found in the replication SVD cohort. In contrast, the non-SVD stroke group and the healthy older adult group showed a direct relationship between disability and depression. The DTI study showed that fractional anisotropy, a marker of white matter damage, was related to depressive symptoms in patients with SVD.

Conclusion: These results suggest that in stroke patients without SVD, disability is an important causal factor for depression, whereas in SVD stroke, other factors specific to this stroke subtype have a causal role. White matter damage detected on DTI is one factor that mediates the association between SVD and depression. *Neurology*® 2014;83:1417–1423

GLOSSARY

ADL = Activities of Daily Living; **BMET** = Brief Memory and Executive Test; **CI** = confidence interval; **DTI** = diffusion tensor imaging; **EPI** = echo planar image; **FA** = fractional anisotropy; **GDS** = Geriatric Depression Scale; **IADL** = Instrumental Activities of Daily Living; **mRS** = modified Rankin Scale; **QoL** = quality of life; **SCANS** = St George's Cognition and Neuroimaging in Stroke; **SSQoL** = Stroke-Specific Quality of Life Scale; **SVD** = small-vessel disease.

Cerebral small-vessel disease (SVD) results from damage to small perforating end arteries supplying white matter and subcortical gray matter, and is characterized by lacunar infarcts and leukoaraiosis. Common features include lacunar stroke, cognitive impairment, and reduced quality of life (QoL).[1,2] More recently, depression[3] has been associated with SVD, and can occur before the onset of other symptoms.[4]

It has been hypothesized that SVD may predispose individuals to depression by disruption of cortical-subcortical circuits underlying mood.[5] White matter lesions are more common in late-onset depression compared with nondepressed controls,[6–8] and lacunar infarcts and leukoaraiosis are risk factors for chronic poststroke depression.[9–11] However, not all studies confirm these associations[12–15]; one possible reason is that other variables, such as physical disability and cognitive impairment, may mediate the relationship between stroke and depression.[16]

Depression is common after all subtypes of stroke, and relates to the degree of disability.[17] If SVD has a specific causal role in depression via disruption of cortical-subcortical circuits, one would predict an association between depression and SVD stroke that persists after controlling

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for the degree of physical disability. However, in non-SVD stroke, depression would be related to the degree of physical disability with the association attenuated after controlling for disability. To address this question, we first compared structural equation models of depression in SVD and non-SVD stroke samples. Next, we used diffusion tensor imaging (DTI) to investigate the hypothesis that the SVD-depression association is mediated by white matter damage.

METHODS **Study design.** Cross-sectional observational investigation of structural equation models in SVD, non-SVD stroke, and healthy control groups.

SVD population. SVD was defined as a clinical lacunar stroke syndrome[18] with radiologic (MRI) confirmation of an anatomically corresponding lacunar infarct seen on diffusion-weighted imaging for acute MRI, or for nonacute MRI (>2 weeks poststroke) by a hypodense region on T1 or fluid-attenuated inversion recovery sequences consistent with lacunar infarction of <1.5 cm diameter. Exclusion criteria included inability or unwillingness to consent, and evidence of any stroke mechanism other than SVD: any cortical infarction, subcortical infarcts >1.5 cm in diameter, cardioembolic source, and extracranial or intracranial large-artery stenosis (>50%). For all patients with SVD, assessments were performed >3 months poststroke to reduce acute effects of ischemia on cognitive and other measures. Two SVD cohorts (discovery and replication) were recruited. Both had identical inclusion and exclusion criteria. Thirty percent of all patients with SVD met the Geriatric Depression Scale (GDS) criteria for depression.[19] Sample size for the discovery cohort was chosen to provide a sample comparable to that used in a previous report on depression in SVD.[3]

Discovery cohort. One hundred patients (60 male; mean [SD] age 71.1 [8.5] years) were recruited from specialized stroke services in 3 district hospitals in South London, UK, between March 2007 and September 2009. These formed part of the early recruitment to the St George's Cognition and Neuroimaging in Stroke (SCANS[20]) Study and the Brief Memory and Executive Test (BMET[21]) Study.

Replication cohort. One hundred patients (71 male; mean [SD] age 65.1 [9.9] years) were recruited from specialized stroke services across the United Kingdom as part of 2 ongoing studies determining cognitive impairment in SVD (SCANS[20] and BMET multicenter extension). For both studies, recruitment was from acute stroke units and outpatient minor stroke/TIA services between September 2009 and November 2013.

Non-SVD ischemic stroke population. Fifty patients with nonlacunar ischemic stroke (28 male; mean [SD] age 63.5 [11.6] years), matched for disability level with the SVD cohorts, were recruited from stroke clinics at St George's Hospital, London, between November 2010 and February 2013. Inclusion criteria were any cortical infarction (with or without associated subcortical infarction), or nonlacunar subcortical infarction >2 cm in maximum diameter. Exclusion criteria included Fazekas leukoaraiosis grade >1 on MRI.[22] All cases were reviewed by a single consultant neurologist and classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) stroke classification[23]: large-artery = 14%; cardioembolic = 26%; other = 6%; and unknown = 54%. Review of MRIs showed that 35 (70%) had cortical infarction, and 15 (30%) had nonlacunar subcortical infarction. No patients were

tested during the acute stroke phase; 43 (86%) were tested at least 3 months poststroke, and all were tested at least 6 weeks poststroke. Twenty percent of the non-SVD stroke patients met the GDS criteria for depression.[19]

Healthy control population. A control group (85 male; mean [SD] age 67.1 [9.4] years), consisting of 203 healthy individuals without previous stroke or other major neurologic disorder, was recruited by random sampling of family doctor practices in South London between January 2012 and January 2013. All patients in the United Kingdom are registered with a family doctor and therefore this is representative of the community population. Eleven percent of the control population met the GDS criteria for depression.

DTI SVD subgroup. A subset of patients with SVD (n = 101), 66 from the discovery cohort and 35 from the replication cohort, all from the SCANS Study,[20] underwent DTI in addition to conventional MRI, as well as an extensive cognitive and functional disability assessment.

Demographics of the patient and control groups are shown in table 1.

Study protocol approvals, registrations, and patient consents. All research was conducted as a part of studies approved by a UK NHS ethics committee. Full written consent was obtained from all participants.

Behavioral measures. All patient and control groups were assessed using the same scales as follows. Depression was assessed using the 30-item GDS.[19] This includes items with yes/no responses: for example, "Do you feel that your life is empty?" and "Are you in good spirits most of the time?" Data on depressive symptoms were collected on a continuous scale of 0 to 30 rather than a binary scale of depressed vs not depressed, so as to retain maximum variance in the data.

QoL was assessed using the Stroke-Specific Quality of Life Scale (SSQoL[24]). This scale was developed for use in stroke trials with established internal reliability and sensitivity to change. For the purpose of this study, the scale items were presented in the present tense to reflect current experiences (e.g., "I often have to stop and rest during the day"). Total QoL score was based on 11 of the 12 subscales (without the mood subscale to avoid overlap with the depression scale). Scores were calculated pro-rata to account for intermittent missing responses.

Disability was measured using the modified Rankin Scale (mRS[25]), a 7-point rating scale developed specifically to measure disability during stroke, and the Barthel Activities of Daily Living (ADL[26]) Scale, which covers levels of basic physical function and independent living. For the subgroup of patients with SVD in study 2, two additional aspects of behavior were assessed (n = 101; see table 1): higher-order living skills, measured using the Instrumental Activities of Daily Living (IADL) Scale (see reference 27), which focuses on abilities such as managing finances or using public transportation; and global cognition, which was tested using a broad cognitive assessment undertaken by a neuropsychologist at the same time as measuring other indices of function, producing an overall index of performance across all tasks, as summarized in table e-1 on the *Neurology*® Web site at Neurology.org.

Diffusion tensor imaging. DTI data were acquired on a 1.5T General Electric Signa HDxt MRI system (General Electric, Milwaukee, WI) as previously reported.[20] Axial single-shot spin echo planar images (EPIs) (echo time = 93.4 milliseconds; repetition time = 15,600 milliseconds) were acquired to give isotropic voxels and whole brain coverage (2.5 mm³; field of view = 240 × 240 mm²; acquisition matrix = 96 × 96). After 4 acquisitions without

Table 1 Patient demographics and results from the different assessments

	SVD discovery	SVD replication	Non-SVD stroke	Healthy controls	SVD-DTI subgroup
No.	100	100	50	203	101
Age, y, mean (SD); range	71.1 (8.5); 46–89	65.1 (9.9); 44–88	63.5 (11.6); 39–86	67.1 (9.4); 42–84	70.1 (9.5); 46–88
Sex, male, n (%)	60 (60)	71 (71)	28 (56)	85 (42)	70 (69)
Time since last stroke, y, mean (SD)	3.7 (5.6)	1.5 (3.0)	0.5 (0.9)	—	2.7 (5.5)
Stroke subtype, n (%)					
Large-artery	0 (0)	0 (0)	7 (14)	—	0 (0)
Cardioembolic	0 (0)	0 (0)	13 (26)		0 (0)
Small-vessel	100 (100)	100 (100)	0 (0)		100 (100)
Other	0 (0)	0 (0)	3 (6)		0 (0)
Indeterminate	0 (0)	0 (0)	27 (54)		0 (0)
Stroke location, n (%)					
Cortical	0 (0)	0 (0)	35 (70)	—	0 (0)
Subcortical	100 (100)	100 (100)	15 (30)		100 (100)
Leukoaraiosis grade, n (%)					
0	6 (6)	32 (32)	—	—	3 (3)
1	19 (19)	13 (13)			13 (13)
2	45 (45)	21 (21)			46 (45)
3	30 (30)	34 (34)			39 (39)
Disability mRS, mean (SD)	1.2 (1.3)	1.0 (1.0)	1.29 (1.0)	0.60 (0.8)	1.1 (1.0)
Hypertensive treatment, n (%)	87 (87)	80 (80)	34 (71)	63 (31)	89 (88)
Treated hypercholesterolemia, n (%)	88 (88)	81 (81)	43 (88)	57 (28)	91 (90)
Diabetes mellitus, n (%)	23 (23)	39 (39)	14 (28)	18 (9)	37 (37)
Smoking, n (%)					
Never	41 (41)	43 (43)	25 (50)	122 (60)	45 (45)
Ex	39 (39)	39 (39)	19 (38)	60 (30)	37 (37)
Current	20 (20)	18 (18)	6 (12)	20 (10)	18 (18)
Treated depression, current, n (%)	4 (4)	7 (7)	1 (2)	11 (5)	7 (7)
30-Item GDS, mean (SD)	8.2 (6.5)	7.9 (6.8)	5.5 (5.7)	4.3 (4.9)	8.9 (6.6)
SSQoL minus the mood subscale, mean (SD)	191.6 (34.4)	181.1 (30.3)	184.5 (28.8)	200.3 (18.4)	190.5 (31.1)

Abbreviations: DTI = diffusion tensor imaging; GDS = Geriatric Depression Scale; mRS = modified Rankin Scale; SSQoL = Stroke-Specific Quality of Life Scale; SVD = small-vessel disease.

diffusion weighting (b = 0 s·mm^{-2}), diffusion-sensitized images were acquired with gradients applied (b = 1,000 s·mm^{-2}) in 25 noncollinear directions. This was repeated to acquire a further 4 b = 0 s·mm^{-2} images and the negative of the 25 directions. The 8 b = 0 s·mm^{-2} images were coregistered and averaged to give a T2-weighted EPI, which was used to realign diffusion images and remove eddy-current distortions using the FSL Linear Image Registration Tool (FLIRT, FMRI Software Library, FSL version 4.1; FMRIB Analysis Group, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl).[28] The geometric average of the positive and negative acquisitions was taken to eliminate gradient cross-terms.[29]

FSL's TBSS software[30] was used to analyze diffusion data. EPIs were brain-extracted using BET (Brain Extraction Tool) and fractional anisotropy (FA) images created by fitting a tensor model using FDT. All subjects' FA data were then nonlinearly aligned into a common space and then projected to a mean FA skeleton. Median FA was calculated as the 50th percentile of nonzero voxels from each subject's TBSS skeleton. We used median FA as an index of white matter structural integrity throughout the whole brain.

Statistical analysis. Variables were corrected such that higher values equated to higher levels of depressive symptoms, disability, functional disability, and cognitive deficit, and lower levels of QoL and white matter integrity. Missing data were examined and found to be few and sporadic (SSQoL = 0.4%; 30-item GDS = 2.4%; mRS = 0.4%; ADL = 0.6%; IADL = 1%; median FA = 0%; global cognition = 0%). Therefore, these data were imputed using an expectation maximization algorithm, as part of SPSS's Missing Value Analysis Tool, for each variable and group separately.

Study 1. To investigate simultaneously the relationships among disability, depression, and QoL for each study population, analyses were performed using AMOS 5.0 SEM (structural equation modeling) software. Disability was defined as a latent variable with loadings from 2 disability measures, ADL and mRS.

Depression and QoL were defined as observed variables with total scores taken from the 30-item GDS and SSQoL, respectively. The variance in the endogenous variables accounted for by age and sex was controlled for in the models. Each model had 21 sample moments and 15 parameters to be estimated = 6 degrees of freedom. For robustness and to account for any nonnormality in the data, bootstrap analyses (using nonparametric resampling, 2,000 repetitions) were conducted for direct and indirect effects in the model.

Study 2. An extended model using the DTI data was created to determine the role of loss of white matter integrity on depression and disability, as well as the role of IADL and global cognition. For this analysis, a subgroup of patients with SVD taken from the discovery and replication cohorts were included (n = 101, age 70.1 [9.5] years, sex 70 male; see table 1). The extended model had 28 sample moments and 22 parameters to be estimated = 6 degrees of freedom. For robustness and to account for any nonnormality in the data, bootstrap analyses (using nonparametric resampling, 2,000 repetitions) were conducted for direct and indirect effects in the model.

RESULTS Study 1: Depression, disability, and QoL. We hypothesized in our initial theoretical model that in SVD, both depression and disability would directly affect QoL, and that disability would affect depression leading to an indirect effect on QoL. We also included age and sex in the model to account for group differences.

SVD discovery cohort. Path analyses indicated that the direct path from depression to QoL was highly significant (β = 0.53, *p* < 0.001; 95% confidence interval [CI] = 0.41, 0.64) as was the direct path from disability to QoL (β = 0.53, *p* < 0.001; 95% CI = 0.41, 0.66). However, the direct path between disability and depression was not significant (β = 0.19, *p* = 0.08; 95% CI = −0.02, 0.41). The indirect path from disability to QoL via depression was not significant (β = 0.10, *p* = 0.06; 95% CI = −0.01, 5.8).

SVD replication cohort. The initial model was applied to the replication SVD cohort. Path analyses revealed a very similar pattern of results to that seen in the discovery cohort. The direct paths from depression to QoL (β = 0.51, *p* < 0.001; 95% CI = 0.36, 0.67) and disability to QoL (β = 0.58, *p* < 0.001; 95% CI = 0.37, 0.78) were highly significant with similar β values to the discovery group. The direct path between disability and depression was not significant (β = 0.21, *p* = 0.15; 95% CI = −0.07, 0.49) and the indirect path from disability to QoL via depression was also not significant (β = 0.11, *p* = 0.13; 95% CI = −0.03, 0.13). See figure 1.

Non-SVD ischemic stroke. When the same model was applied to the non-SVD stroke group, there was a different pattern of results to that seen in SVD. The direct path from depression to QoL was highly significant (β = 0.67, *p* < 0.001; 95% CI = 0.22, 0.88) and the direct path from disability to QoL was significant (β = 0.25, *p* < 0.05; 95% CI = 0.01, 0.57). In addition, the non-SVD group showed a highly significant path from disability to depression (β = 0.47, *p* < 0.05; 95% CI = 0.07, 0.74) and a significant indirect path from disability to QoL via depression (β = 0.31, *p* = 0.01; 95% CI = 0.13, 0.55). See figure 2.

Control group. The results for the control group showed significant paths from depression to QoL (β = 0.45, *p* = 0.003; 95% CI = 0.26, 0.60), disability to QoL (β = 0.43, *p* = 0.002; 95% CI = 0.23, 0.63), and from disability to depression (β = 0.32, *p* = 0.007; 95% CI = 0.10, 0.59). There was also a significant indirect effect of disability on QoL via depression (β = 0.14, *p* = 0.004; 95% CI = 0.05, 0.26). See figure 3.

Time from stroke analysis. Because time from last stroke was not matched between groups, a regression analysis was performed in SPSS version 19 (IBM Corp., Armonk, NY) to determine whether time from stroke had an effect on depression. The results

Figure 1   SVD models

A. SVD exploratory model

B. SVD replication model
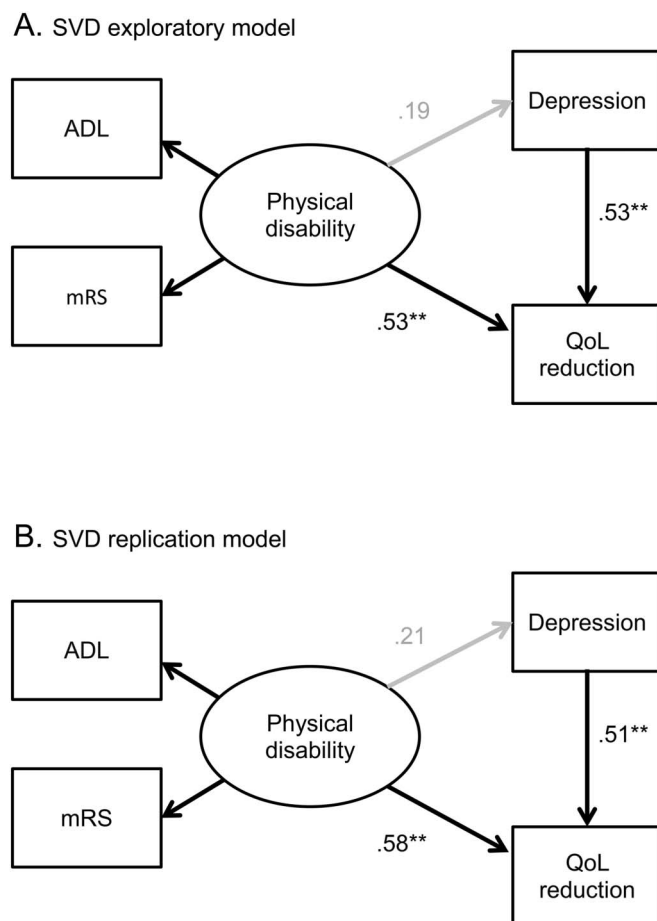
(A) SVD exploratory model of the relationships among physical disability, depression, and reduction in QoL, in SVD. (B) SVD replication analysis of model 1 in a second independent SVD patient group. Standardized β weights are shown for each path. **Significant at the 0.001 level. For depression, higher = worse depression; QoL reduction, higher = poorer QoL; disability, higher = worse disability. ADL = Activities of Daily Living; mRS = modified Rankin Scale; QoL = quality of life; SVD = small-vessel disease.
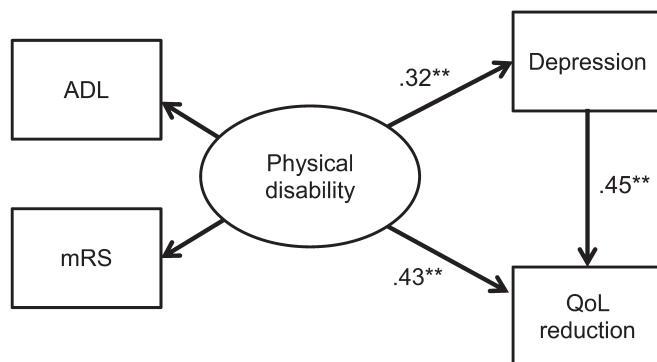
Figure 2   Non-SVD stroke model
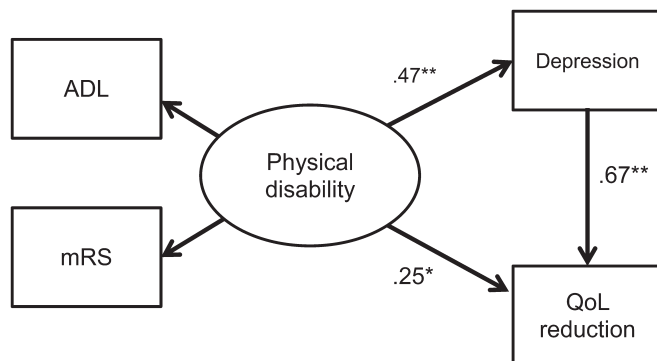
Replication analysis in a non-SVD stroke patient group. Standardized β weights are shown for each path. *Significant at the 0.05 level; **significant at the 0.001 level. ADL = Activities of Daily Living; mRS = modified Rankin Scale; QoL = quality of life; SVD = small-vessel disease.

showed that there was no relationship for the SVD discovery cohort (β = 0.01, p = 0.947), the SVD replication cohort (β = 0.06, p = 0.580), or the non-SVD cohort (β = −0.1, p = 0.456).

Study 2: Extended model incorporating DTI data. In the subgroup of participants with SVD who underwent DTI MRI, we added median FA (a measure of global white matter damage), global cognitive deficit, and functional disability to the model. The analysis revealed significant paths from median FA to depression (β = 0.25, p = 0.03; 95% CI = 0.03, 0.47), disability (β = 0.40, p = 0.001; 95% CI = 0.22, 0.56), and global cognition (β = 0.36, p = 0.004; 95% CI = 0.13, 0.54). There was no significant direct path from FA to QoL (β = 0.05, p = 0.48; 95% CI = −0.10, 0.21); however, there was a significant indirect effect of FA on QoL via other functional variables (β = 0.36, p = 0.001; 95% CI = −0.03, 0.19). There was also a significant indirect path to functional disability via global cognition

Figure 3   Control model

Replication analysis in a healthy older adult group. Standardized β weights are shown for each path. **Significant at the 0.001 level. ADL = Activities of Daily Living; mRS = modified Rankin Scale; QoL = quality of life.

(β = 0.09, p = 0.005; 95% CI = 0.02, 0.19). See figure 4.

DISCUSSION The results of study 1 demonstrated that, in SVD, depression had a major effect on QoL, as did physical disability. However, the magnitude of the depressive symptoms was not significantly related to the degree of disability in this population. This was confirmed in a replication analysis of an independent sample, with strikingly similar results. By contrast, the same analysis in a stroke population in whom stroke was due to causes other than SVD and in whom radiologic evidence of SVD was excluded on MRI, found a significant relationship between depressive symptoms and degree of physical disability, in addition to the relationship between depression and QoL and disability and QoL. Taken together, these findings suggest that in stroke patients without SVD, disability is an important causal factor in depression, while in SVD stroke, other factors specific to this stroke subtype have a causal role.

The results of study 2, which included DTI to measure white matter ultrastructural damage, support the hypothesis that one factor that explains the specific association of SVD with depression is white matter damage. When median FA, an index of global white matter integrity, was added to the model along with global cognition and functional disability, the results showed that loss of white matter integrity was associated with depressive symptoms. In addition, FA had a significant direct effect on physical disability and global cognition, a significant indirect effect on QoL via physical disability and depression, and a significant indirect effect on functional disability via global cognition. These findings highlight the major impact of white matter damage on function, and are consistent with white matter tract disruption having a direct role in depression in patients with SVD.

Previous studies have reported that white matter hyperintensities are associated with late-onset depression[31] and have shown that radiologic evidence of SVD is associated with depression in stroke populations.[10,11] These results have been used to suggest that white matter ischemia and subsequent white matter tract damage produces disruption of cortical-subcortical connections underlying complex networks involved in mood regulation.[32,33] Understanding the interrelationships of other factors such as physical disability on SVD and depression is complex, and studies have shown mixed results.[3,16] In this report, we identified differential models of depression, disability, and QoL in stroke populations with and without SVD, and demonstrated the direct role of white matter damage on depression in an SVD population. These findings suggest that SVD may have a direct role in driving depression. Further studies focused on specific regions are required to better

Figure 4 Extended SVD model including functional disability, global cognitive deficit, and white matter damage (taken as median FA with signs reversed)
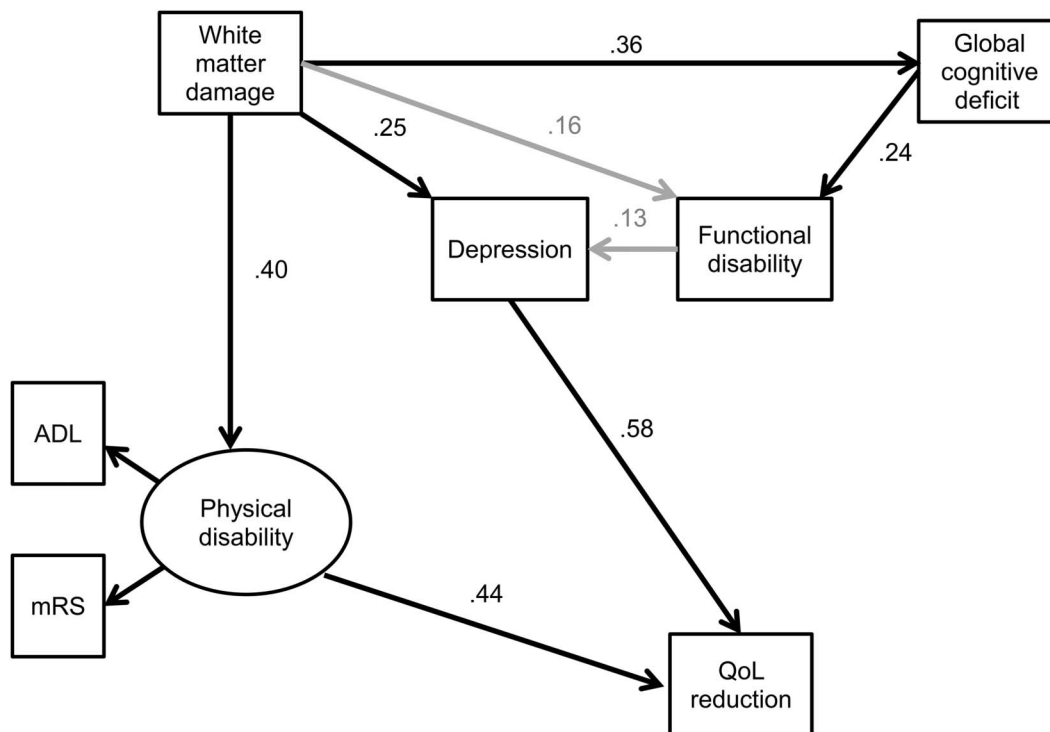
Standardized β weights are shown for each path. For clarity, only paths significant at the 0.05 level are presented in black, and paths approaching significance are presented in gray. ADL = Activities of Daily Living; FA = fractional anisotropy; mRS = modified Rankin Scale; QoL = quality of life; SVD = small-vessel disease.

understand the disruption of specific pathways and may provide further evidence for the vascular depression hypothesis.

Our results have some clinical implications. First, they highlight that both depression and disability lead to significant reductions in QoL across stroke subtypes. This is important given the high rates of patients meeting the clinical criteria for depression in our sample compared with the numbers receiving treatment. Second, they suggest that mood may be an important outcome of SVD.

The use of subjective measures, such as the GDS and the SSQoL, may produce a reporting bias related to the presence of anosognosia, or neglect associated with right hemisphere lesions. This is not an issue in the group of patients with SVD, who do not display these symptoms, but could influence results in the stroke group.

SVD appears to be a specific risk factor for depression, independent of disability levels, and this association is at least partially mediated by reduced white matter integrity. Furthermore, expectations that depression results from physical or cognitive disability may contribute to the underrecognition of depression in this patient group. Depression is an important consequence of SVD, and further studies to understand the mechanisms of depression in this population as

well as treatment trials may result in improved QoL in this patient group.

AUTHOR CONTRIBUTIONS

R.L.B. and H.S.M. contributed substantially to the design of the study. R.L.B., V.H., A.J.L., R.G.M., and H.S.M. contributed to the interpretation and preparation of the manuscript. Neuroimaging data were acquired and processed by A.J.L. Behavioral data for the SCANS cohort were acquired and interpreted by A.J.L. and R.G.M. Behavioral data for the BMET cohort were acquired and interpreted by R.L.B. and V.H. Data analysis was completed by R.L.B. The study was supervised by H.S.M. and R.G.M.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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