Cerebral White Matter Lesions and Lacunar Infarcts Contribute to the Presence of Mild Parkinsonian Signs

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Background and Purpose—Mild parkinsonian signs (MPS) are common in elderly people and may be an early stage of parkinson(ism). They might be related to cerebral small-vessel disease, although this association remains incompletely understood. To identify subjects at early stages of the disease, we investigated whether the presence of MPS was dependent on the severity and location of small-vessel disease, including white matter lesions and lacunar infarcts.

Methods—Four hundred thirty individuals, with small-vessel disease, aged between 50 and 85 years, without dementia or parkinsonism, were included in this analysis and underwent MRI scanning. The number and location of lacunar infarcts were rated. White matter lesion volume was assessed by manual segmentation with automated delineating of different regions. Presence of MPS was based on the motor section of the Unified Parkinson’s Disease Rating Scale. Associations were determined using logistic regression analysis adjusted for age, sex, and total brain volume.

Results—Severe white matter lesions and the presence of lacunar infarcts were independently associated with the presence of MPS (OR, 2.6; 95% CI, 1.3–4.9 and OR, 1.8; 95% CI, 1.0–3.0). Frontal and parietal white matter lesions and, to a lesser extent, lacunar infarcts in the thalamus were associated with a higher risk of MPS. The presence of lacunar infarcts was independently related to the bradykininesia category of parkinsonian signs.

Conclusions—This study shows that severe small-vessel disease, especially at certain locations, is associated with MPS signs in older adults. Our findings suggest that small-vessel disease interrupts basal ganglia-thalamocortical circuits involving both the frontal and parietal lobes and hence may result in MPS.

Key Words: lacunar infarcts ■ MRI ■ parkinsonian signs ■ white matter disease

Individuals with small-vessel disease (SVD), including white matter lesions (WMLs) and lacunar infarcts, may not only exhibit cognitive impairment, but also motor disturbances, including mild parkinsonian signs (MPS) such as bradykininesia, rigidity, tremor, and gait/balance disturbances. They are common in older adults with a prevalence of 20% to 30% and are associated with increased morbidity and mortality. Because isolated MPS usually progress, they could be considered a prodromal stage of more full-blown parkinsonism.

In contrast to the well-studied associations between vascular risk factors and lesions and (mild) cognitive impairment, less attention has been paid to motor perfor-
Methods

Study Population
This study is embedded in the Radboud University Nijmegen Diffusion tensor and MRI Cohort (RUN DMC) study, a prospectively conducted cohort study that investigates risk factors and clinical consequences of brain changes as assessed by MRI among older adults with cerebral SVD. The primary outcome of the longitudinal part of the RUN DMC study is the development of dementia or Parkinsonism.15 Recruitment methods and other details of the RUN DMC design are described elsewhere.15 In short, in 2006, 503 consecutive individuals with SVD, referred to the Department of Neurology between October 2002 and November 2006, were selected for participation. The reasons for referral in this group included those corresponding to symptoms of SVD, for example, transient ischemic attack/minor stroke, and cognitive and motor complaints. As suggested for clinical studies, patients were primarily selected on brain imaging features, because clinical symptoms of SVD are more heterogeneous and typically mild at the onset of cerebral SVD.16 Therefore, inclusion criteria were (1) age between 50 and 85 years; and (2) WMHs and/or lacunar infarcts/s on neuroimaging. Subsequently, acute (transient ischemic attack or lacunar syndrome) or subacute (cognitive, motor or depressive) symptoms of SVD were assessed by standardized structured assessments. These 503 individuals had symptoms of transient ischemic attack or lacunar syndrome (n=219), cognitive disturbances (n=245), motor disturbances (n=97), depressive symptoms (n=100), or a combination thereof. A motor disturbance was defined as a reported history of one or more fall(s) during the past year or a self-reported slowing of gait.

Because we wanted to study the association between SVD and parkinsonian signs in the earliest symptomatic manifestation of parkinsonism (ie, MPS), we excluded patients with (1) parkinsonism17,18; and (2) dementia.19 Other exclusion criteria were: (3) intracranial hemorrhage; (4) life expectancy of <6 months; (5) intracranial space-occupying lesion; (6) (psychiatric) disease interfering with cognitive testing or follow-up; (7) recent or current use of acetylcholine-esterase inhibitors, neuroleptic agents, L-dopa or dopa-antagonists; (8) non-SVD-related WMHs (eg, multiple sclerosis, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL], and Fabry disease); (9) prominent visual or hearing impairment; (10) language barrier; and (11) MRI contraindications or claustrophobia. Additional exclusion criteria for this study were: (12) conditions not related to SVD that affected assessment of MPS with the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRSm).20 (eg, joint fusion, amputation, severe arthritis, psychogenic gait disturbance; n=16); and (13) territorial infarcts, because they were considered potential confounders (n=56). Tissue segmentation was not possible in one scan, yielding a final sample size of 430 for this study. All participants signed an informed consent form. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.

MRI Scanning and Processing
All MRI scans of all subjects were acquired on a single 1.5-T scanner (Siemens, Erlangen, Germany). The protocol included a 3-dimensional T1 magnetization-prepared rapid gradient-echo sequence (repetition time/echo time/inversion time 842/2200 ms; voxel size 1.0×1.2×5.0 mm plus an interslice gap of 1.0 mm).

All imaging analyses were performed by raters blinded to clinical information (including UPDRS scores). White matter signal hyperintensities on fluid-attenuated inversion recovery scans, which were not, or only faintly, hypointense on T1-weighted images, were considered WMHs, except for gliosis surrounding infarcts. WMHs were manually segmented on the fluid-attenuated inversion recovery images by 2 trained raters. Each of them rated 60% of all the scans. The interrater variability for total WMH volume, in a random sample of 10%, was good (intraclass correlation coefficient 0.99). In addition, we computed WMH volume of predefined volumes of interest taken from an inversely normalized (parameters taken from the T1 normalization) Talairach-based atlas23 (WFU Pickatlas, Version 2.3), including the frontal, parietal, occipital, temporal lobe, and sublobar (basal ganglia, thalamus, internal, and external capsule, insula) and limbic area (cingulate gyrus), brain stem, and cerebellum.

Lacunar infarcts were rated and defined as areas with a diameter >2 mm and ≤15 mm with low signal intensity on T1 and fluid-attenuated inversion recovery, ruling out enlarged perivascular spaces and infratentorial pseudolacunae.24 Intra- and interrater reliability for the number of lacunar infarcts in a random sample of 10% yielded a weighted k of 0.80 and 0.88.

Automated segmentation on the T1 images was conducted using Statistical Parametric Mapping (SPM5; www.fil.ion.ucl.ac.uk/spm/) to obtain grey and white matter and cerebrospinal fluid probability maps.23 These were binarized by applying a 0.5 threshold and summed to total volumes. Total brain volume was then calculated as the sum of total gray and white matter volumes.

<table>
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<tr>
<th>Table 1. Characteristics of the Study Population</th>
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<tr>
<td>Characteristics</td>
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<tr>
<td>Demographic and clinical characteristics</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Female, no.</td>
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<tr>
<td>Mini-Mental State Examination</td>
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<td>Barthel Index</td>
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<td>Depressive symptoms, no.</td>
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<td>Mild parkinsonian signs, no.</td>
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<td>Bradykinesia, no.</td>
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<td>Rigidity, no.</td>
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<td>Tremor, no.</td>
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<td>Gait-balance, no.</td>
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<td>Neuroimaging characteristics</td>
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<tr>
<td>Total brain volume, mL</td>
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<td>White matter volume, mL</td>
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<td>White matter lesion volume, mL²</td>
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<td>Frontal</td>
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<td>Occipital</td>
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<td>Infratentorial</td>
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<tr>
<td>Lacunar infarcts, no.</td>
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<td>Frontal</td>
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<td>Parietal</td>
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Data represent no. of subjects (%), mean (SD), or median (interquartile range).
of 0.90. MPS were defined, in accordance with that used in other large scale studies investigating MPS, as present when the participant had either: (1) ≥2 items with a score of 1; or (2) one item with a score of ≥2. Subsequently, we divided the UPDRSm into 4 categories: bradykinesia (based on 9 items), tremor (based on 7 items), rigidity (based on 5 items), and gait/balance/axial function (based on 6 items). A category was considered present when the participant had in that category either: (1) ≥2 items with a score of 1; or (2) one item with a score of ≥2. Parkinsonism was considered present when the following condition was met: ≥2 items with a score of ≥2 in at least 2 different categories. These patients were excluded from this part of the study.

Other Measurements
We considered age, sex, and depressive symptoms (score ≥16 on the Center of Epidemiological Studies on Depression Scale and/or the present use of antidepressive medication) as possible confounders. Because SVD is correlated with the total brain volume and cerebral atrophy is a predictor of MPS, total brain volume could also be considered a potential confounder. We used the Mini-Mental State Examination score (range, 0–30) to assess global cognitive status. Functional independence was assessed using the Barthel Index (range, 0–20).

Statistical Analysis
Baseline characteristics are summarized as mean with SD, median with interquartile range, or absolute numbers with percentages.

First, the proportion of MPS (dependent variable) was analyzed by quintiles of the WML distribution (independent variable) by analysis of covariance with adjustment for age, sex, presence of depressive symptoms, total brain volume, and the number of lacunar infarcts. In another model, the same was done with lacunar infarcts divided into 5 groups (0, 1, 2, 3, or ≥3 lacunar infarcts) with adjustment for age, sex, depressive symptoms, total brain volume, and WML volume.

Second, the risk of the presence of MPS (dependent variable) in subjects with severe WMLs (upper quintile, >20.6 mL WMLs; independent variable) was assessed with logistic regression analysis with the other 4 quintiles as reference, adjusting for age, sex, depressive symptoms, and total brain volume (Model 1). This was based on our previous study, in which we found that subjects with a WML volume in the upper quintile had a worse gait performance than subjects in the other quintiles. Subsequently, we additionally adjusted for the total number of lacunar infarcts (Model 2). Next, we analyzed the risk of the presence of MPS (dependent variable) in subjects with or without lacunar infarct(s). In the first model we adjusted for age, sex, depressive symptoms, and total brain volume and in the second model additionally for the total WML volume (in milliliters). All these analyses were repeated for the 4 categories of parkinsonian signs. Data are presented as ORs with 95% CIs. Finally, the association between the location of severe WMLs or presence of lacunar infarct(s) on MPS was assessed by means of logistic regression analysis adjusted for the former mentioned variables (Model 1). In each region, WML volume in the upper quintile was considered as severe. The subsequent model was additionally adjusted for the presence of severe WMLs and lacunar infarcts in the other regions than the one under study (Model 2).

Table 2. Association Between Cerebral Small-Vessel Disease and Risk of (Mild) Parkinsonian Signs

<table>
<thead>
<tr>
<th>Severe Cerebral Small-Vessel Disease*</th>
<th>Presence of Mild Parkinsonian Signs OR (95% CI)</th>
<th>Presence of Bradykinesia OR (95% CI)</th>
<th>Presence of Rigidity OR (95% CI)</th>
<th>Presence of Tremor OR (95% CI)</th>
<th>Presence of Gait/Balance Disturbances OR (95% CI)</th>
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<tr>
<td>Upper quintile of WML volume</td>
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<tr>
<td>Model 1</td>
<td>3.4 (1.9–6.1)†</td>
<td>2.8 (1.3–5.9)‡</td>
<td>2.2 (1.0–4.7)‡</td>
<td>2.1 (0.8–5.8)</td>
<td>3.1 (1.0–9.1)‡</td>
</tr>
<tr>
<td>Model 2</td>
<td>2.6 (1.3–4.9)‡</td>
<td>1.7 (0.7–4.1)</td>
<td>2.0 (0.8–4.6)</td>
<td>2.0 (0.7–5.9)</td>
<td>1.7 (0.5–5.9)‡</td>
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<tr>
<td>Presence of lacunar infarct(s)</td>
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<td></td>
<td></td>
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<tr>
<td>Model 1</td>
<td>2.1 (1.3–3.6)‡</td>
<td>3.1 (1.6–6.5)‡</td>
<td>1.7 (0.8–3.4)</td>
<td>1.0 (0.4–2.6)</td>
<td>2.3 (0.8–6.5)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.8 (1.0–3.0)‡</td>
<td>2.7 (1.3–5.6)‡</td>
<td>1.4 (0.7–3.0)</td>
<td>0.8 (0.3–2.3)</td>
<td>1.9 (0.6–5.6)</td>
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</table>

Model 1: adjustment for age, sex, depressive symptoms, and total brain volume. Model 2: additional adjustment for no. of lacunar infarcts or white matter lesion (WML) volume.

†Upper quintile of the WML volume distribution or presence of lacunar infarcts.
‡Motor section of the Unified Parkinson’s Disease Rating Scale ≥2.
§P<0.05.
¶P<0.001.
Small-Vessel Disease and Presence of Mild Parkinsonian Signs

<table>
<thead>
<tr>
<th>Severe Cerebral Small-Vessel Disease*</th>
<th>Presence of Mild Parkinsonian Signs†</th>
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<tr>
<td></td>
<td>Model 1 OR (95% CI)</td>
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<tr>
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<tr>
<td>Frontal</td>
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<tr>
<td>WML volume</td>
<td>3.2 (1.8–5.9)§</td>
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<tr>
<td>Lacunar infarcts</td>
<td>1.6 (0.8–3.4)</td>
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<td>Parietal</td>
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<tr>
<td>WML volume</td>
<td>3.1 (1.7–5.6)§</td>
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<tr>
<td>Lacunar infarcts</td>
<td>1.2 (0.4–3.2)</td>
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<tr>
<td>Occipital</td>
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<tr>
<td>WML volume</td>
<td>1.8 (1.0–3.2)‡</td>
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<td>Lacunar infarcts</td>
<td>1.6 (0.5–5.8)</td>
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<td>Temporal</td>
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<tr>
<td>WML volume</td>
<td>2.5 (1.4–4.8)‡</td>
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<td>1.0 (0.2–5.1)</td>
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<td>Sublobar</td>
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<tr>
<td>WML volume</td>
<td>1.9 (1.0–3.5)‡</td>
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<td>Lacunar infarcts</td>
<td>2.0 (1.1–3.7)‡</td>
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<td>Limbic</td>
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<tr>
<td>WML volume</td>
<td>2.3 (1.3–4.1)‡</td>
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<td>Lacunar infarcts</td>
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<td>Infratentorial</td>
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<tr>
<td>WML volume</td>
<td>2.7 (1.6–4.7)§</td>
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<tr>
<td>Lacunar infarcts</td>
<td>1.1 (0.4–3.0)</td>
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Table 3. Association Between Location of Cerebral Small-Vessel Disease and Presence of Mild Parkinsonian Signs

Legend:
- §P<0.05
- ‡P<0.001
- †Motor section of the Unified Parkinson’s Disease Rating Scale ≥2

Discussion

We found that severe WMLs, especially in the frontal and parietal lobe, were associated with an increased risk of MPS. Lacunar infarcts, particularly in the thalamus, were also independently associated with an increased risk of MPS, mainly due to the presence of bradykinesia.

Some limitations of this study need to be considered. MPS were assessed by clinical examination by means of the UPDRS5m score, which has a subjective nature. It is sometimes difficult to distinguish among rigidity, spasticity, or paratonia and between bradykinesia and pyramidal or non-neurological slowing, especially in subjects with minimal impairment. We tried to overcome this problem by rating all subjects by 2 experienced residents in neurology with a high interrater agreement. Second, we here report on cross-sectional data, which prevents us from making causal inferences. The RUN DMC study has a longitudinal design and follow-up is already planned to evaluate the effect of progression of SVD on (changes in) MPS. Strengths of this study are the large sample size, the high response rate, and the recruitment of subjects in a single research center. Moreover, we were able to study the importance of the location as well as overall severity of SVD in relation to the presence of MPS. However, there are some statistical difficulties. The correlation between the presence of lacunar infarcts and severe WMLs may have led to an underestimation of the independent effect of each of them on the presence of MPS (global as well as local). Therefore, we present both the adjusted and unadjusted estimates. Moreover, due to some colinearity between SVD at any one location and SVD globally and due to the smaller number of lesions in each region, the statistical power to detect regional associations is also reduced. This probably explains the fact that despite independent associations between lacunar infarcts and MPS, there were no independent associations between lacunar infarcts in any specific region and MPS. Another issue is that of potential confounding by depressive symptoms and total brain volume. Both can be considered to be a real confounder in the relation between SVD and MPS. However, they could also act as an intermediate in this relation (and thereby not fulfill qualifications of a true confounder). We therefore present here the associations independent of depressive symptoms and total

SVD and MPS

The proportion of subjects with MPS was only significantly higher in those with severe WMLs (>20.6 mL; 37.7% MPS) compared with all other quintiles (eg, to mild WMLs [<2.8 mL] 18.3%; P=0.005). A possible threshold effect was also found with regard to the number of lacunar infarcts: the proportion MPS in the group patients with >3 lacunar infarcts was higher (44.7%) than that, for example, in the group with an infarct (18.3%; P=0.004; Figure).

When expressed as ORs, subjects with severe WMLs were almost 3 times more likely to have MPS than the reference group (OR, 2.6; 95% CI, 1.3–4.9) independent of the number of lacunar infarcts. They had an increased risk of bradykinesia (OR, 2.8; 95% CI, 1.3–5.9), rigidity (OR, 2.2; 95% CI, 1.0–4.7), and gait/balance disturbances (OR, 3.1; 95% CI, 1.0–9.1). These associations disappeared after additional adjustment for the number of lacunar infarcts. The presence of lacunar infarcts was independently associated with an increased risk of MPS (OR, 1.8; 95% CI, 1.0–3.0) due to a higher risk of bradykinesia (OR, 2.7; 95% CI, 1.3–5.6; Table 2).

When analyzing according to lesion location, severe WMLs in the frontal (OR, 2.8; 95% CI, 1.2–6.2) and parietal (OR, 2.3; 95% CI, 1.0–5.1) lobe appeared most strongly related to MPS, even after additional adjustment for WMLs and lacunar infarcts in the other parts of the brain (Table 3).

Subjects with lacunar infarcts in the sublobar area (basal ganglia, thalamus, internal and external capsule) had a higher risk of MPS (OR, 2.0; 95% CI, 1.1–3.7), which was mainly driven by infarcts in the thalamus (OR: 3.5; 95% CI, 1.4–8.9). This risk disappeared after adjusting for WMLs and lacunar infarcts in the other regions.
brain volume. We realize that this may have led to an underestimation of the real effect of the lesions on MPS. Longitudinal studies such as our follow-up study may unravel this issue. We intentionally did not correct for vascular risk factors such as hypertension or diabetes, because they were considered part of the causal chain between SVD and MPS. Although all subjects were seen at a university hospital, most of them were seen as a first opinion. We therefore feel that our results may be generalized to other subjects with SVD referred to a general Department of Neurology. We even think that our study may be generalized to independently living community-dwelling people with SVD because in the general population, a minimal degree of WMLs is found in >80% of individuals >50 years of age.11 Moreover, because we excluded patients with parkinsonism or dementia, our cohort is relatively healthy and independently functioning. In addition, the prevalence of MPS (21.4%) is very similar to those of population-based cohorts of older adults (15.7%–21.9%).1,5

The association between severe WMLs and the presence of MPS, independent of lacunar infarcts, is consistent with that found in another large study,1 but our finding of an independent higher risk of MPS in subjects with lacunar infarct(s) is novel. Although data from previous smaller-sized studies reporting on the relation between lacunar infarcts and bradykinesia were conflicting,2,3 we found that the increased risk of MPS in subjects with lacunar infarct(s) was mainly due to a higher risk of bradykinesia. Moreover, we found that only those with several lacunar infarcts or severe WMLs had MPS more often. This suggests that a certain amount of damage to the structural integrity of the white matter is needed before disruption of white tracts and subsequently MPS occur. The increased risk of MPS in subjects with severe WMLs seemed to be explained by the presence of bradykinesia, rigidity, or gait/balance disturbances, although the significance disappeared after adjustment for lacunar infarcts. This may be due to a lack of power (Type II error) because the size of the groups with bradykinesia, rigidity, or gait/balance was small (17–40 subjects). In addition, the UPDRSIII is not the most sensitive way to investigate gait/balance because it only addresses some aspects in a semiquantitative way. Another point is that especially MPS in the legs (lower body parkinsonism) has traditionally been attributed to vascular factors and lesions. Unfortunately, due to small numbers of isolated MPS of the legs, we were not able to investigate this. However, we might be able to assess this in our follow-up study.

Another important factor leading to an increased risk of MPS in our study was the anatomic location of these WMLs and lacunar infarcts. Severe WMLs in the parietal and frontal lobe and to a lesser extent thalamic infarcts were associated with an increased risk of MPS. SVD in the latter 2 regions is suggested to interrupt the basal ganglia–thalamofrontal cortical circuits leading to a reduction in the thalamocortical drive and subsequently parkinsonism,26 but this concept is still somewhat controversial. Our findings provide additional evidence for this hypothesis, interestingly even at a preclinical level of parkinsonism. Other small-sized studies supporting this hypothesis are among subjects in the more severe part of the spectrum, that is, overt vascular parkinsonism.26–30 An intriguing finding in our study was the association between severe WMLs in the parietal lobe and MPS. This may suggest that altered somatosensory processing and sensorimotor integration contribute to the development of parkinsonian signs in patients with SVD. Our finding is indirectly supported by recent studies in patients with Parkinson disease. A diffusion tensor imaging study showed loss of integrity of the superior longitudinal fasciculus,31 connecting frontal with parietal areas and a resting-state functional MRI study showed decreased coupling between basal ganglia and the inferior parietal cortex in these patients.32

In conclusion, these findings support the hypothesis of a vascular contribution to MPS in older adults, especially in those with severe WMLs or several lacunar infarcts. This seems to be mainly due to damage to the basal ganglia–thalamocortical circuits of both the frontal and parietal lobe. Future studies are needed to investigate to what extent MPS are a marker of the subsequent development of parkinsonism and to provide more insight in causality of the found associations. If so, control of risk factors for SVD such as hypertension might halt progression of these lesions and hence prevent the development of (vascular) parkinsonism.

Sources of Funding
Dr de Leeuw received a personal fellowship of the Dutch Brain Foundation (H04-12) and a clinical fellowship of the Netherlands Organization for Scientific Research (project number 40-00703-97-07197). Prof Bloem was supported by a VIDI research grant of the Netherlands Organization for Scientific Research (project number 016-076-352). Dr van Dijk received a personal fellowship of the Dutch Brain Foundation.

Disclosures
None.

References
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Stroke. published online August 2, 2012;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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