RESEARCH ARTICLE

Association of Stroke Lesion Pattern and White Matter Hyperintensity Burden With Stroke Severity and Outcome

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Abstract

Background and Objectives

To examine whether high white matter hyperintensity (WMH) burden is associated with greater stroke severity and worse functional outcomes in lesion pattern–specific ways.

Methods

MR neuroimaging and NIH Stroke Scale data at index stroke and the modified Rankin Scale (mRS) score at 3–6 months after stroke were obtained from the MRI–Genetics Interface Exploration study of patients with acute ischemic stroke (AIS). Individual WMH volume was automatically derived from fluid-attenuated inversion recovery images. Stroke lesions were automatically segmented from diffusion-weighted imaging (DWI) images, parcellated into atlas-defined brain regions and further condensed to 10 lesion patterns via machine

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Glossary

AF = atrial fibrillation; **CAD** = coronary artery disease; **DM** = diabetes mellitus; **DWI** = diffusion-weighted imaging; **FLAIR** = fluid-attenuated inversion recovery; **HTN** = hypertension; **IPL** = inferior parietal lobule; **IQR** = interquartile range; **MCA** = middle cerebral artery; **MRI-GENIE** = MRI–Genetics Interface Exploration; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **WMH** = white matter hyperintensity.

learning–based dimensionality reduction. Stroke lesion effects on AIS severity and unfavorable outcomes (mRS score >2) were modeled within purpose-built Bayesian linear and logistic regression frameworks. Interaction effects between stroke lesions and a high vs low WMH burden were integrated via hierarchical model structures. Models were adjusted for age, age^2, sex, total DWI lesion and WMH volumes, and comorbidities. Data were split into derivation and validation cohorts.

Results

A total of 928 patients with AIS contributed to acute stroke severity analyses (age: 64.8 [14.5] years, 40% women) and 698 patients to long-term functional outcome analyses (age: 65.9 [14.7] years, 41% women). Stroke severity was mainly explained by lesions focused on bilateral subcortical and left hemispherically pronounced cortical regions across patients with both a high and low WMH burden. Lesions centered on left-hemispheric insular, opercular, and inferior frontal regions and lesions affecting right-hemispheric temporoparietal regions had more pronounced effects on stroke severity in case of high compared with low WMH burden. Unfavorable outcomes were predominantly explained by lesions in bilateral subcortical regions. In difference to the lesion location–specific WMH effects on stroke severity, higher WMH burden increased the odds of unfavorable outcomes independent of lesion location.

Discussion

Higher WMH burden may be associated with an increased stroke severity in case of stroke lesions involving left-hemispheric insular, opercular, and inferior frontal regions (potentially linked to language functions) and right-hemispheric temporoparietal regions (potentially linked to attention). Our findings suggest that patients with specific constellations of WMH burden and lesion locations may have greater benefits from acute recanalization treatments. Future clinical studies are warranted to systematically assess this assumption and guide more tailored treatment decisions.

A substantial fraction of adults experience a stroke in their lifetime.[1] Many patients with stroke have persistent sequelae, which often severely affect their daily lives.[2] An enhanced understanding of factors that are not yet consistently integrated in current stroke outcome prediction models[3] but potentially influence such sequelae after stroke could greatly improve clinical care.

Previous studies have demonstrated that individual outcomes after stroke are associated with prestroke brain health (or similarly brain frailty).[4,5] White matter hyperintensity (WMH) burden, a neuroradiologic marker of small vessel disease,[6,7] may serve as one relevant proxy of this preexisting brain health. WMH burden is well known to correlate with a multitude of cardiovascular risk factors, such as hypertension (HTN), diabetes mellitus (DM), atrial fibrillation (AF), and smoking in both healthy and stroke populations.[8-10]

A growing body of literature additionally points toward deleterious effects of WHM burden specifically on stroke outcomes. WMH burden and decreased white matter integrity negatively influence both early[11] and long-term neurologic outcomes.[12,13] Higher WMH burden is also linked to higher risks of recurrent stroke, poststroke dementia, and all-cause mortality after stroke.[14] The effects of WMH burden are particularly well studied in case of language impairments after stroke: several studies have uncovered significant associations between WMH burden and (chronic) aphasia severity[15-17] as well as WMH burden and the efficacy of language treatment in chronic aphasia.[18]

The aim of the current study was to assess whether WMH burden increases the vulnerability to all strokes or only to those strokes affecting specific brain locations. Given the intricate links between WMH burden and language impairments apparent in previous stroke studies, we hypothesized to find that WMH burden would especially interact with lesions involving putative language areas. Hence, we expected stroke symptoms to be more severe and functional outcomes to be less favorable in situations of high WMH burden and left-hemispheric lesions in middle cerebral artery (MCA) territory.

The promise of our work is to enhance our neuroscientific understanding of how WMH burden is linked to acute and chronic stroke outcomes, as measured on the NIH Stroke Scale (NIHSS) and modified Rankin Scale (mRS). These insights could then be leveraged for the conceptualization of new clinical studies that tested the benefit of more aggressive acute treatment and rehabilitative efforts in case of a high WMH burden and certain lesion locations.

Methods

Stroke Patient Population

The present study capitalizes on data of 3,301 patients with AIS assembled within the framework of the international, multisite MRI–Genetics Interface Exploration (MRI-GENIE) study,[19] which, in turn, build on the infrastructure of the Stroke Genetics Network.[20] MRI-GENIE's main aim was the genetic analysis of acute and chronic cerebrovascular neuroimaging phenotypes as extractable from clinical-grade MRIs of patients with AIS. The study furthermore put a prime on the availability of Causative Classification of Stroke information (c.f., eMethods, links.lww.com/WNL/C189). We here considered all those MRI-GENIE patients with AIS with available high-quality diffusion-weighted imaging (DWI)-derived lesion segmentations,[21] fluid-attenuated inversion recovery (FLAIR)-derived WMH burden,[22] NIHSS-defined stroke severity, and/or mRS data (n = 1,107 patients in total). We performed complete case analyses and thus excluded patients if information on sociodemographic/clinical characteristics was missing (age, sex, and comorbidities; c.f., eMethods for a sample size calculation).

Standard Protocol Approvals, Registrations, and Patient Consents

Patients gave written informed consent in accordance with the Declaration of Helsinki. The study protocol was approved by Massachusetts General Hospital's Institutional Review Board (Protocol #: 2001P001186 and 2003P000836).

Clinical and Neuroimaging Data

Sociodemographic and clinical data included information on age, sex, HTN, coronary artery disease (CAD), DM, AF, history of smoking, and prior stroke. Outcomes of interest were the acute NIHSS-based stroke severity, measured at index stroke, that is, during the acute hospital stay (0–42, 0: no measured deficits, 42: maximum stroke severity), and the long-term mRS score obtained between day 60 and day 190 poststroke, binarized to favorable (0–2) vs unfavorable (3–6) outcome.[23]

Neuroimaging Data, Preprocessing, and Low-Dimensional Lesion Embedding

Axial T2-FLAIR and DWIs were acquired between 2003 and 2011, with most scans being obtained within 48 hours of hospital admission (median: 2 days, interquartile range 1–4 days, 61% in the first 2 days, 91% in the first week). Given the multisite character of MRI-GENIE and neuroimaging acquisition in routine clinical practice, imaging parameters differed slightly between centers as outlined in detail in our eMethods (links.lww.com/WNL/C189). WMH lesion volume was derived from FLAIR images by a previously developed, fully automated deep learning-based segmentation pipeline.[22] In brief, the segmentation pipeline featured total brain extraction and intensity normalization as preprocessing steps. WMH lesions were then automatically segmented using concatenated convolutional neural networks, which were specifically designed for WMH lesions. Scans and segmentations were carefully quality controlled via automatic and manual routines.[22] Similarly, we automatically obtained DWI-based stroke lesion segmentations via an ensemble of 3-dimensional convolutional neural networks.[21] DWIs and DWI lesions were subsequently nonlinearly normalized to MNI reference space and comprehensively quality controlled by 2 experienced raters (A.K.B. and M.B.). Successively, the number of lesioned voxels within atlas-defined regions, that is, 94 cortical, 15 subcortical regions,[24] and 20 white matter tracts,[25] was computed. To further reduce the high dimensionality of the brain region and white matter tract space, we used nonnegative matrix factorization to obtain 10 unique spatial lesion patterns. The number of 10-lesion patterns was chosen in line with our previous work[26-29] and represents a trade-off between retaining as much lesion information as possible, while substantially reducing the lesion dimensionality. Importantly, such a drastic dimensionality reduction, from ~7 million voxels to 10 lesion patterns, was necessary to render our Bayesian hierarchical analyses feasible. We ensured a good lesion representation in principle by correlating original and inverse-transformed lesion load information. However, some information on the supplying artery territory was lost when computing regional lesion loads, given that our atlas-defined regions could combine tissue from various blood supply territories. For example, lesioned voxels in the thalamus could originate from occlusions of the anterior, middle, or posterior cerebral artery. When now considering the total lesion load, that is, the number of lesioned voxels per region, there was no possibility of inferring the exact vascular territory.

Identifying WMH-Dependent Brain Substrates of Acute Stroke Severity

The derived 10 lesion patterns represented the input of main interest to our Bayesian hierarchical regression framework.[30,31] We aimed to infer the interaction effects of high and low WMH burden and lesion patterns in explaining stroke severity and functional outcomes. We, therefore, estimated relevances of lesion patterns separately for patients with high vs low WMH burden within our hierarchical model framework (c.f., model specifications in eMethods, links.lww.com/WNL/C189). We designated groups of patients as high and low WMH burden based on the median WMH burden after adjustment for patient age (resulting breakpoint: −5.3, c.f., Table for the median of WMH burden in high and low burden groups). To test the generalizability of our findings, we furthermore split the entire cohort into a multicenter derivation cohort and a single-center (Massachusetts General Hospital)[32] validation cohort. Any of the regression analyses described in the following were thus performed separately in both cohorts for derivation and validation, respectively. We decided on this derivation/validation splitting procedure, instead of bootstrapping or similar internal validation techniques, in view of the high computational burden of our Bayesian models.

Next, we first aimed to explain the acute NIHSS-based stroke severity via hierarchical linear regression. Second, we explained unfavorable outcomes (mRS score >2) via hierarchical logistic regression. Consequently, we fitted regression

Table Clinical Characteristics: Derivation Cohort (Acute Stroke Severity)

	All participants (n = 664)	Low WMH burden (n = 332)	High WMH burden (n = 332)	Statistical comparison of patients with low and high WMH burden (FDR corrected for multiple comparisons) *p* value
Age, y, mean (SD)	64.8 (14.5)	63.6 (13.2)	66.0 (15.7)	0.08
Sex (female), %	40.0	41.0	39.2	0.88
NIHSS, median (IQR)	4 (5)	4 (5)	4 (5)	0.50
Normalized DWI-derived stroke lesion volume, mL, median (IQR)	3.1 (16.9)	4.8 (25.6)	2.3 (12.1)	0.08
Vascular lesion side, %				
Left	43.8	43.1	44.6	0.90
Right	40.7	40.4	41.0	0.94
Both	7.5	8.1	6.9	0.88
WMH lesion volume, mL, median (IQR)	5.77 (13.3)	2.47 (3.03)	15.35 (17.78)	<0.001[a]
Cardiovascular risk factors, %				
Hypertension	64.8	58.1	71.4	0.002[a]
Diabetes mellitus type 2	22.3	16.6	28.0	0.06
Atrial fibrillation	18.2	18.7	17.8	0.84
Coronary artery disease	17.9	16.0	19.9	0.39
Smoking	55.7	52.7	58.7	0.22
Prior stroke	6.8	3.6	9.9	0.005[a]
TOAST classification, %				
Cardioembolic	23.3	23.8	22.9	0.90
Large artery sclerosis	16.4	19.3	13.6	0.12
Small vessel occlusion	14.9	19.3	18.4	0.06
Stroke of undetermined etiology	28.6	27.1	30.1	0.64
Stroke of other determined etiology	3.9	5.7	2.1	0.08

Abbreviations: DWI = diffusion-weighted imaging; FDR = false discovery rate; IQR = interquartile range; NIHSS = NIH Stroke Scale; TOAST = Trial of ORG 10172 in Acute Stroke Treatment; WMH = white matter hyperintensity.
We here present mean (SD) values, unless otherwise noted. We compared the groups of patients with low and high WMH burden via 2-sample *t* tests or a 2-sided Fisher exact test as appropriate.
[a] Significant differences after family-wise error correction for multiple comparisons.

models of stroke severity and unfavorable outcomes both in the derivation and subsequently in the validation cohort. When modeling both of these outcomes, we accounted for several further covariates in addition to the lesion patterns: (mean-centered) age, age^2, sex, smoking, HTN, DM type 2, AF, CAD, and prior stroke as well as the log-transformed, overall stroke lesion volume, and WMH lesion volume. All of these variables were determined a priori based on their conceivable associations with stroke severity and functional outcomes, as well as in line with our previous work.[26-28] We included both age and age^2 to carefully adjust for age-specific effects: by including both values, we could correct for not only linear effects (via the variable age) but also nonlinear U-shaped age effects (via age^2). Hypothetically, the variable age can capture linear effects of age on the outcome (e.g., the older a patient, the higher the stroke severity), whereas age^2 can depict nonlinear U-shaped age effects (e.g., the outcome is affected similarly in both younger and older patients but not middle-aged patients). Importantly, we also included the continuous WMH lesion volume to test for main effects of WMH burden in addition to interaction effects with stroke lesion patterns.

In accordance with the recommendations in Gellman and Hill (Chapter 3, p. 45–47),[30] we tested the independence of errors assumption of the Bayesian linear regression model and

hence ensured the absence of any systematic violations of this assumption. We evaluated model performance via the coefficient of determination R-squared score (stroke severity model and linear regression) or the area under the curve (functional outcomes and logistic regression). We investigated differences in lesion pattern effects in patients with high and low WMH burden by comparing their posterior distributions (c.f., WMH burden–specific lesion pattern effects in eMethods, links.lww.com/WNL/C189). To decrease the likelihood of any biasing effects due to varying parcel-wise lesion volumes or frequencies of how often a parcel was affected by a lesion, we tested for differences between the groups of high and low WMH burden via independent 2-sample t tests or 2-sided Fisher exact tests (level of significance: $p < 0.05$, Bonferroni corrected for multiple comparisons). We performed 2 ancillary sensitivity analyses. First, we repeated the described analysis workflow after assigning a low and high WMH burden status based on the median value of the raw WMH lesion volume, without initially regressing out an individual's age. Second, we reran Bayesian regression analyses in the validation cohort after excluding all patients with a clinical diagnosis of prior stroke.

Data and Code Availability

The authors agree to make the data available to any researcher for the express purposes of reproducing the here presented results and with the explicit permission for data sharing by Massachusetts General Hospital's and individual sites' institutional review boards. The Harvard-Oxford and JHU DTI-based white matter atlases are accessible online (fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). Bayesian analyses were implemented in Python 3.7.

Results

Stroke Patient Population

A total of 1,107 patients were included in this complete case analysis study. The lesion data of all these 1,107 patients contributed to the derivation of the low-dimensional stroke representation. NIHSS and/or mRS scores were available for 931 of these 1,107 patients and hence contributed to respective regression analyses. More precisely, we considered 928 patients in our stroke severity analyses (split into n = 664 derivation and n = 264 validation, overall mean age: 65.0 (14.5) years, sex: 40% women) and 698 patients in our functional outcome analyses (split into n = 542 derivation and n = 156 validation, overall mean age: 65.9 (14.7) years, sex: 41% women). The median NIHSS-based stroke severity at index stroke was 4 (interquartile range [IQR] 1–7) in the derivation and 3 (IQR 0–6) in the validation cohort. With respect to long-term outcomes, 27.9% in the derivation and 26.9% in the validation cohort experienced an unfavorable outcome (mRS score >2). The WMH lesion volume was on average 5.77 mL (median, IQR 13.3 mL) in the stroke severity derivation and 6.2 mL (IQR 13.5 mL) in the stroke severity validation cohort. Further patients' characteristics for the stroke severity derivation cohort are summarized in the Table; an overlay of stroke lesions is presented in Figure 1.

Anatomy of the Extracted Lesion Patterns in Patients With Stroke

We derived a low-dimensional stroke lesion representation via first computing lesion volumes per brain region and subsequent machine learning–based unsupervised dimensionality reduction. A high correlation between the original and reconstructed lesions indicated that important lesion information was retained despite dimensionality reduction ($r = 0.83$, $p < 0.001$). The resulting 10 lesion patterns comprised unique combinations of lesioned brain regions. Centers of these lesion patterns varied from anterior to posterior and from subcortical to cortical regions. They were largely symmetrical for left- and right-sided lesions (Figure 2).

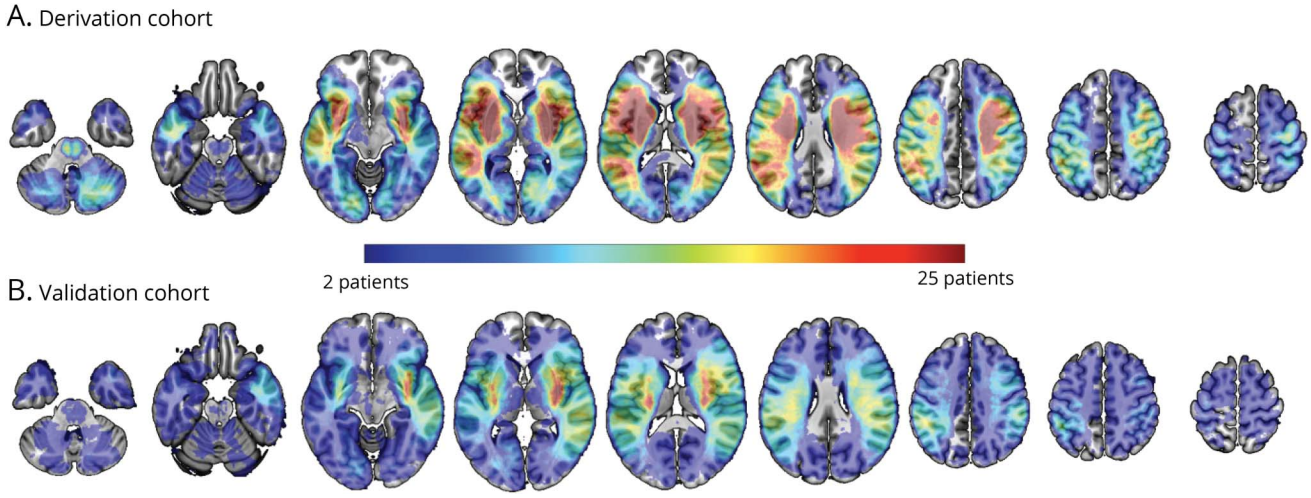
Each patient's individual lesion was represented by a combination of these 10 lesion patterns and was thus not assigned to exclusively 1 pattern. For example, a patient with a lesion in left precentral and postcentral brain regions would be characterized by high values for lesion patterns 6 and 8, but very low values for all other patterns. Because both lesion pattern 6 and lesion pattern 8 overlapped in precentral and postcentral regions, these regions would receive the highest weights.

Explaining Acute Stroke Severity

Successively, we aimed to explain acute stroke severity within the framework of our Bayesian hierarchical model, taking the 10 lesion patterns as main inputs. Importantly, we modeled lesion pattern effects separately for patients with high and low WMH burden. WMH burden groups did not differ significantly with respect to the integrated covariates age, sex, stroke severity, stroke lesion volume, and most comorbidities, except for HTN and prior stroke (HTN: $p = 0.002$, prior stroke: $p = 0.005$, other covariates: $p > 0.05$, false discovery rate corrected for multiple comparisons, Table). Six lesion patterns (i.e., lesion patterns 1, 2, 3, 6, 7, and 8, c.f., Figures 2 and 3) substantially explained stroke severity across both high and low WMH burden groups. Lesion patterns comprising the brainstem and bilateral subcortical regions had the highest mean posterior weights and were thus the most relevant in explaining stroke severity (lesion patterns 2, 3, and 7, Figure 3). With respect to individual brain regions, the highest weights were assigned to bihemispherical subcortical nuclei and white matter tracts, such as the anterior thalamic radiation, the corticospinal tract, and the inferior fronto-occipital and superior longitudinal fasciculus (Figure 4A). Cortical contributions were highest for the insula and opercular cortex and left hemispherically pronounced precentral and postcentral cortex, inferior frontal, superior, and middle temporal and supramarginal, as well as angular gyrus.

We ascertained substantial differences between WMH groups in 2 lesion patterns. A lesion pattern in the left hemisphere,

Figure 1 Lesions Overlap of All Patients in the Stroke Severity Derivation Cohort (A, n = 664) and Validation Cohort (B, n = 264)



In both the derivation and the validation cohort, the stroke lesion burden was evenly distributed between the left and right hemisphere with the maximal lesion overlap located bilaterally in subcortical brain regions. When comparing groups of patients with high and low WMH burden, there were no widespread systematic differences in the frequencies of how often each cortical and subcortical gray matter region or white matter tract was affected or in the numbers of lesioned voxels within each region of interest. In case of the NIHSS derivation cohort, patients with low WMH burden had a significantly higher frequency for how often the left insular cortex was affected (Fisher exact test: $p = 0.002$, Bonferroni corrected for multiple comparisons, all further parcels: $p > 0.05$). In addition, patients in this low WMH burden group had a higher lesion load in the left putamen (2-sided t test $p = 0.01$, Bonferroni corrected for multiple comparisons, all further parcels: $p > 0.05$). We do not expect these subtle differences to have a substantial effect on our results, especially as they were not observable in our validation cohort. While beyond the scope of this current study, this less frequent affection of left-hemispheric MCA-territory tissue in patients with high WMH burden may be worth further investigation. In fact, our findings of more severe strokes in case of a high WMH burden and left-hemispheric strokes near the insular cortex prompt the hypothesis that exactly those patients (high WMH burden and left MCA stroke) may be underrecruited in clinical studies in view of their proportionally even higher stroke severity and probable language impairments. MCA = middle cerebral artery; NIHSS = NIH Stroke Scale; WMH = white matter hyperintensity.

combining insular and opercular as well as inferior frontal brain regions, and a second right-hemispheric lesion pattern focused on temporoparietal brain regions were substantially more relevant in patients with a high WMH burden than with low burden (Figure 5, B and C). In contrast, the overall, continuous WMH burden did not possess any additional substantial explanatory relevance (Figure 5A).

Similar results emerged when repeating the regression analysis of stroke severity in our validation cohort. In particular, the same 2 lesion patterns relating to left insular, opercular, and inferior frontal and right temporoparietal brain regions were more relevant in patients with a high WMH burden (c.f., eResults and eFigure 1A, links.lww.com/WNL/C189).

Explaining Unfavorable Functional Outcomes

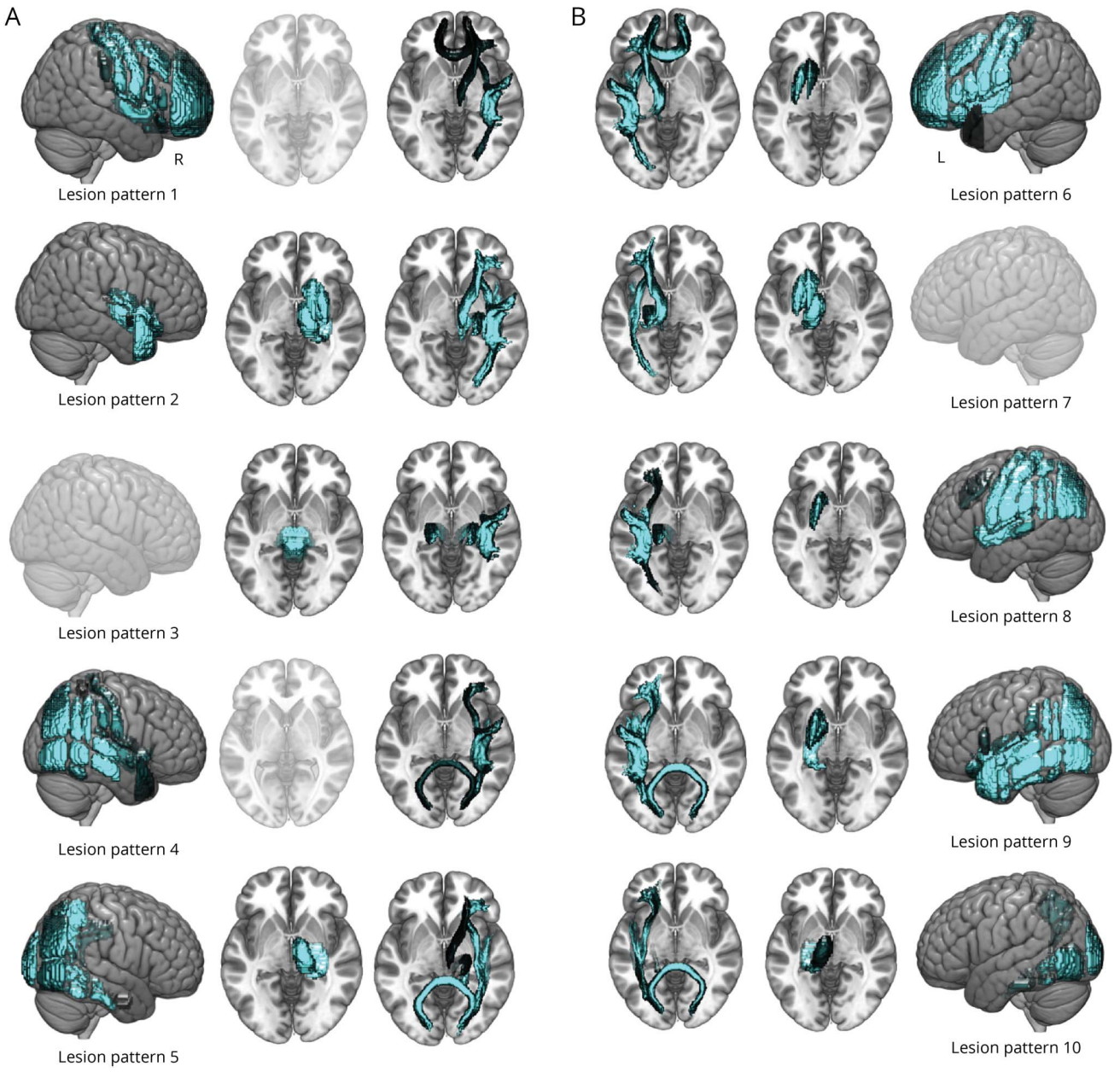
Our second aim was to investigate the effect of WMH burden on functional outcomes on average 3 months after stroke. We thus modeled favorable vs unfavorable functional outcome (cutoff: mRS score >2) via Bayesian logistic regression, again disentangling effects for groups of high and low WMH burden by separately estimating their lesion pattern effects. None of the 10 lesion patterns substantially explained unfavorable outcomes individually, as their posterior distributions rarely substantially deviated from zero (exception: lesion pattern 4 for the high WMH group). Yet, when interpreting individual brain region effects, bilateral subcortical gray matter regions and white matter tracts were the most relevant. Cortical regions were overall not as strongly implicated as in stroke severity, yet showed a left-hemispheric predominance, especially in the higher WMH burden group (Figure 4B). There were no substantial differences in lesion pattern effects between the high and low WMH burden groups. However, the total continuous amount of total WMH burden was associated with higher odds of unfavorable outcomes. More intuitively, our findings implied that patients with a higher WMH burden had higher odds of unfavorable outcomes, independent of the location of the actual stroke lesion.

Results in our validation cohort were broadly similar: subcortical regions in both hemispheres and cortical regions in the left hemisphere were the most relevant ones. Nonetheless, the overall effect of total WMH burden could not be replicated (c.f., eResults and eFigure 1B, links.lww.com/WNL/C189).

Ancillary Analyses

In our main analyses, we accounted for the effect of aging on the WMH burden when defining the low and high WMH burden groups. In ancillary analyses, we defined low and high WMH groups based on the median of the raw WMH burden (breakpoint: 5.77 mL). This breakpoint resulted in pronounced and significant age differences between the WMH burden groups (stroke severity: low WMH burden group:

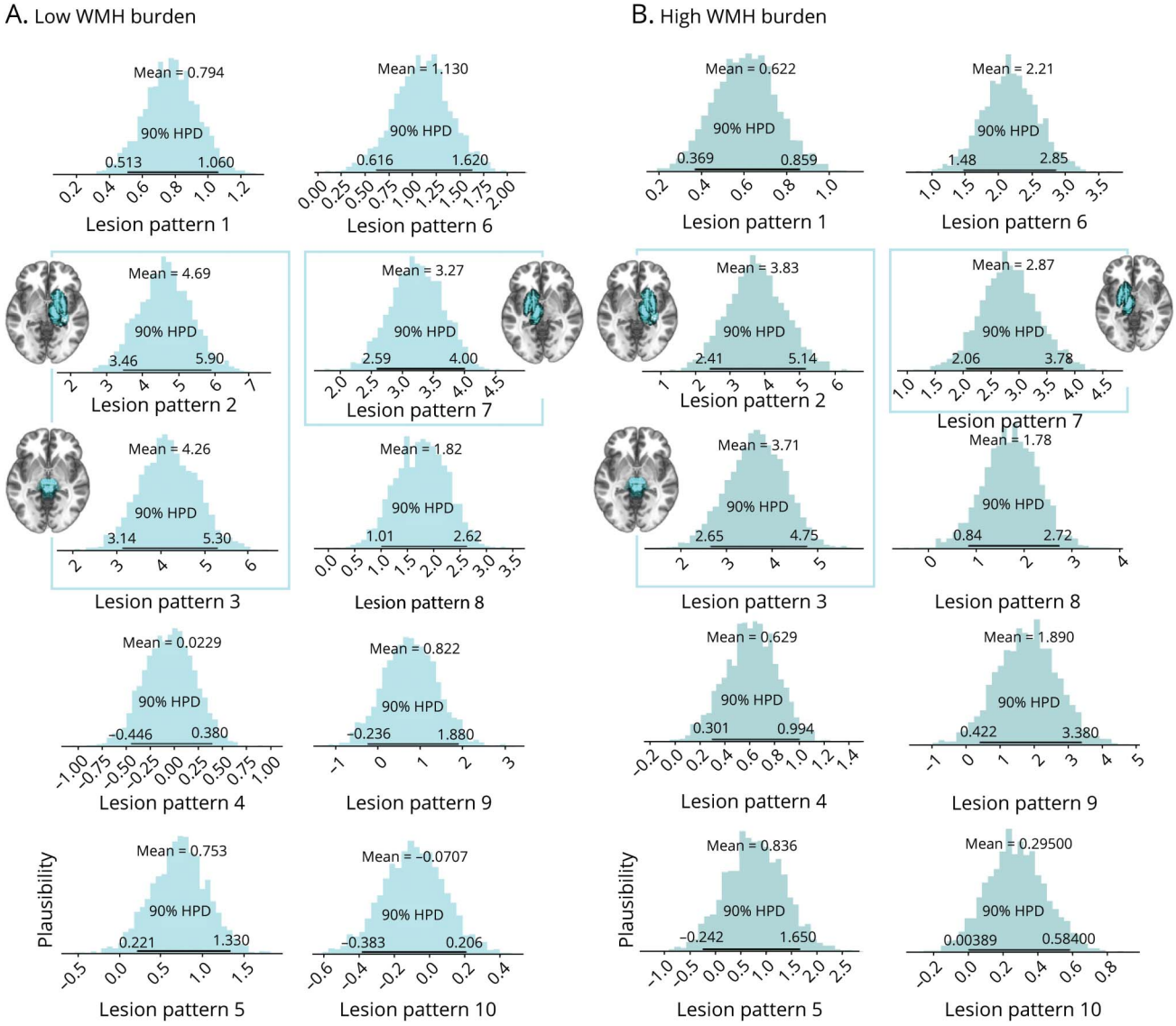
Figure 2 Individual Stroke Lesions Captured in Low Dimensions via Unsupervised Machine Learning Techniques



Our automatically derived 10 unique lesion patterns represented mainly right- (A) and left-hemispheric (B) strokes. The patterns featured anatomically plausible collections of brain regions with varying emphases ranging from cortical-subcortical and anterior-medial-posterior regions. Of note, there were 5 clearly left-hemispheric lesion patterns and 4 right-hemispheric ones. Lesion pattern 3 primarily comprised the brainstem, yet was nonetheless assigned to right-hemispheric strokes because of right hemispherically more pronounced white matter tract contributions. Disregarding minor cortical and subcortical contributions, most right-hemispheric lesion patterns had a left-hemispheric pendant (i.e., lesion patterns 1 and 6, lesion patterns 2 and 6, lesion patterns 4 and 9, and lesion patterns 5 and 10). More specifically, lesion pattern 1 on the right and lesion pattern 6 on the left reflected infarcts involving mainly cortical territory, extending from the frontal pole to precentral and postcentral gyrus, including the insular and opercular cortex. The left-sided version of this pattern furthermore comprised subcortical nuclei, that is, the dorsal striatum. Lesion patterns 2 and 7 were mostly focused on subcortical nuclei, that is, thalamus and the basal ganglia as well the thalamic radiation and longitudinal and fronto-occipital WM tracts. Although the right-hemispheric pattern additionally gave weight to insular and opercular regions, there was no cortical contribution to the left-hemispheric one. Lesion pattern 3 was unique in predominantly representing the brainstem and predominantly right-hemispheric white matter tracts, with an emphasis on the corticospinal tract. Lesion pattern 8, on the other hand, featured left-hemispheric lesions in precentral and postcentral regions, insular, opercular, and parietal regions and did not have a direct analog among the right-hemispheric lesion patterns. In contrast, lesion patterns 4 and 9 reflected similarly configurated temporoparietal lesions in the right and left hemisphere, respectively. Their main difference related to the inclusion of subcortical nuclei in case of the left-hemispheric version. Finally, lesion patterns 5 and 10 depicted lesions with a focus on posterior circulation strokes, for example, including the visual cortex and fusiform gyrus. Individual patients' lesions were recreated by the weighted combination of lesion pattern. For example, a patient with a lesion in left subcortical brain regions would be characterized by high values for lesion pattern 7 but very low values for all other patterns. Renderings are shown in transparent in case of missing contributions from respective (sub)cortical regions.

mean age: 58.2 [15.1] years, high WMH burden group: mean age: 71.3 [10.4] years, $p < 0.001$; functional outcomes: low WMH burden group: mean age: 58.8 [15.3] years, high WMH burden group: mean age: 71.6 [9.8] years, $p < 0.001$). Bayesian hierarchical model results, however, remained broadly similar. When modeling stroke severity, lesion pattern

Figure 3 Bayesian Posterior Distributions Indicating Lesion Pattern Relevances in Explaining Stroke Severity in Patients With a Low (A) and High (B) Prestroke WMH Burden



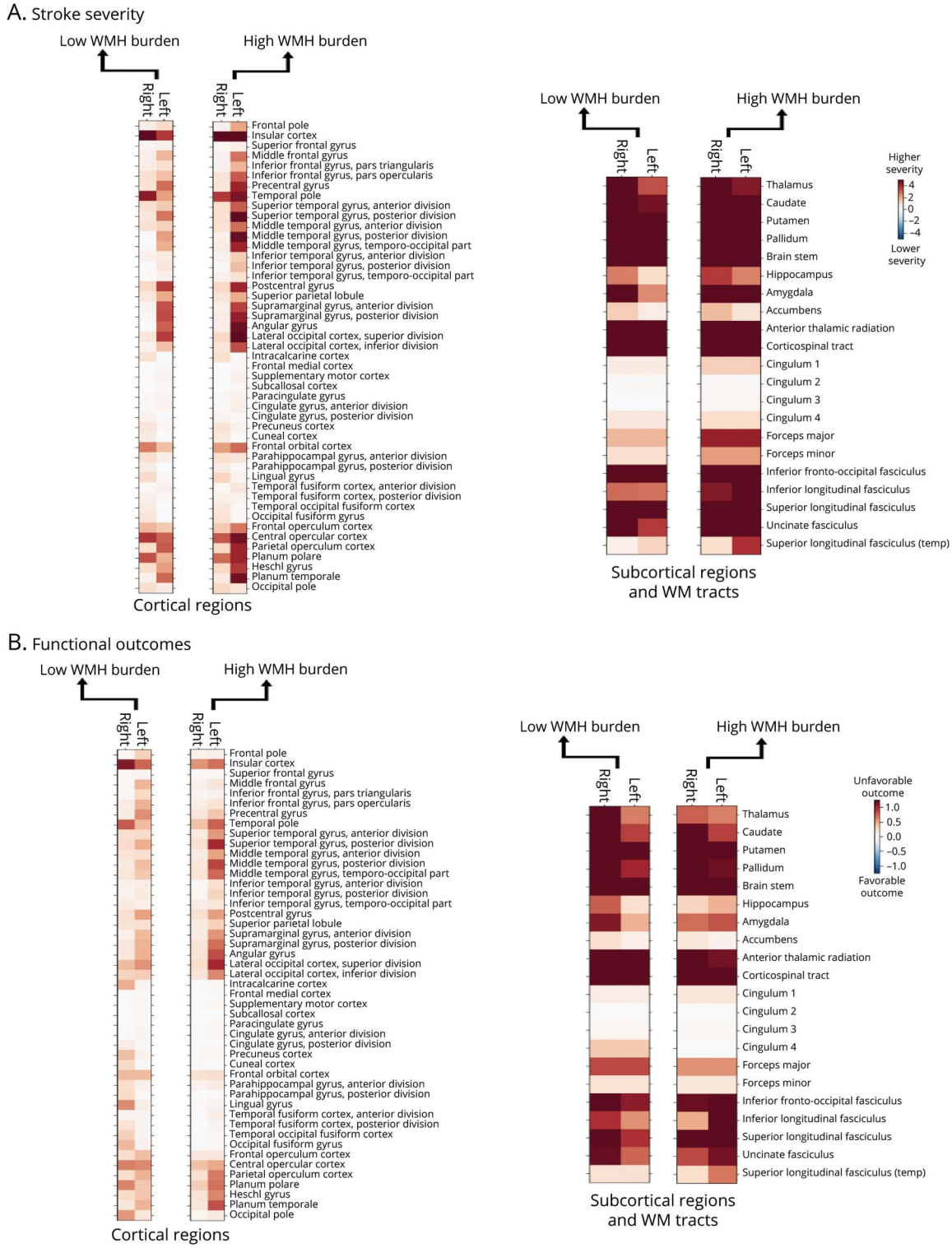
Six lesion patterns, lesion patterns 1, 2, 3, 6, 7, and 8, substantially explained stroke severity in both the low and the high WMH burden group, as indicated by the Bayesian posteriors distributions not substantially overlapping with zero (lower bound of the HPDI of the posterior distribution covering 90% certainty >0). The 3 lesion patterns with the highest overall weights, lesion patterns 2, 3 of the right hemisphere and lesion pattern 7 of the left hemisphere, are specifically accentuated, that is, framed and accompanied by brain renderings of the respective lesion pattern (low WMH burden: lesion pattern 2: mean of the posterior distribution = 4.7, 90% HPDI = 3.5 to 5.9; lesion pattern 3: mean = 4.3, 90% HPDI = 3.1–5.3; lesion pattern 7: mean = 3.3, 90% HPDI = 2.6 to 4.0; high WMH burden: lesion pattern 2: mean = 3.8, 90% HPDI = 2.4 to 5.1; lesion pattern 3: mean = 3.7, 90% HPDI = 2.7 to 4.8; lesion pattern 7: mean = 2.9, 90% HPDI = 2.1 to 3.8). Together, these 3 patterns predominantly featured the brainstem and bilateral subcortical gray matter regions (c.f., Figure 4A). HPDI = highest probability density interval; WMH = white matter hyperintensity.

6 was the most reliably emerging one: patients with a high WMH burden were characterized by a substantially higher relevance of lesion pattern 6 than those with a low WMH burden. In contrast, the substantial difference in lesion pattern 4 was not ascertainable anymore. In case of functional outcomes, the relevance of the overall continuous raw WMH burden remained apparent in the derivation cohort and was not present in the validation cohort, alike in the main derivation analyses. Similarly, all reported main results, as reported for the validation cohort, remained essentially unaltered after exclusion of patients with prior stroke.

Discussion

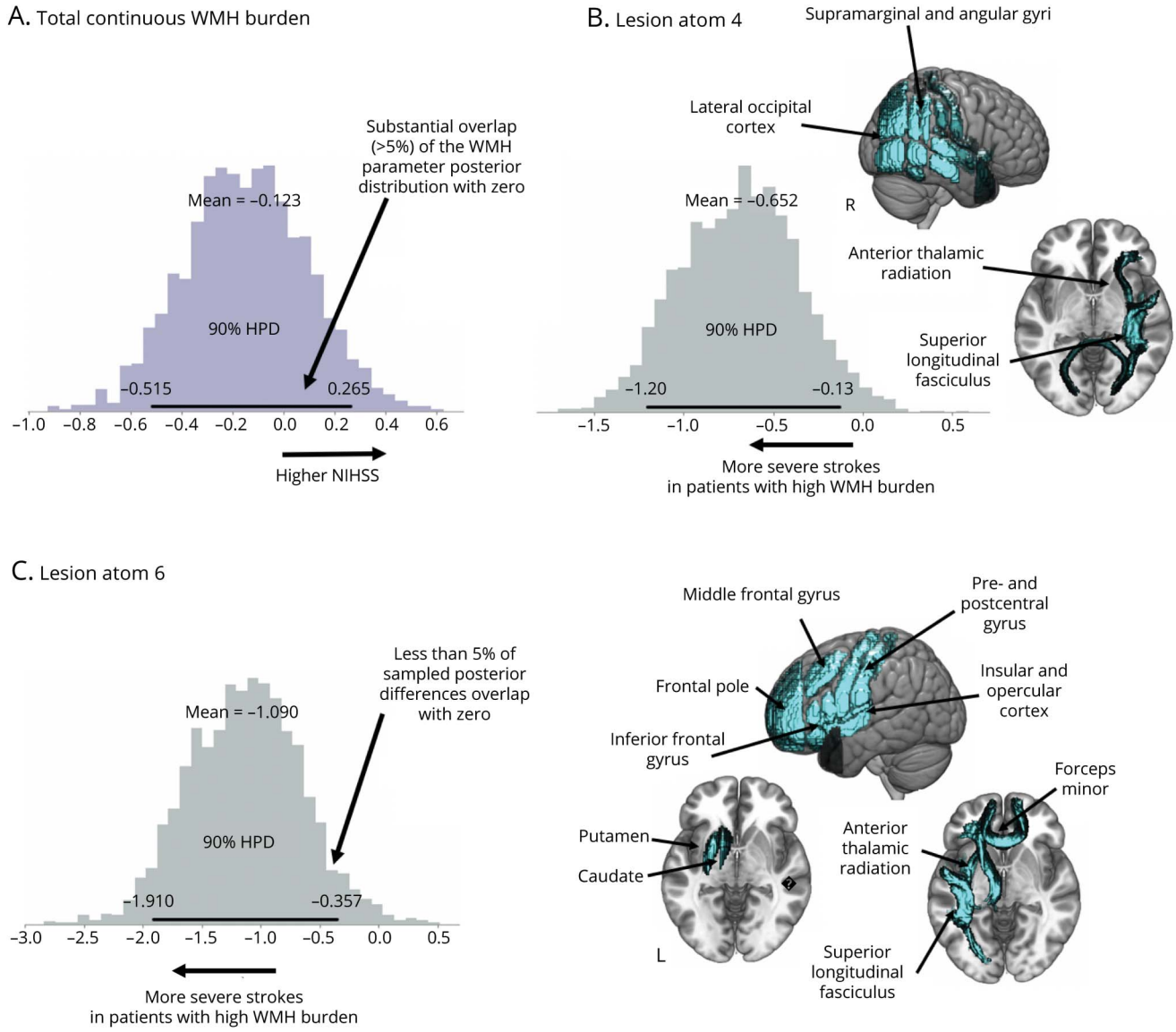
Facilitated by our generative hierarchical modeling framework, we here investigated whether a preexisting WMH burden is associated with stroke severity and functional outcomes depending on the location of stroke lesions. We present evidence that, indeed, a higher level of prestroke WMH burden is linked to an aggravation of acute stroke severity only in case of specific lesion locations. That is, WMH burden was not linked to higher acute stroke severity in general. Instead, we observed that lesions relating to left-hemispheric insular

Figure 4 Relevance of Each Cortical and Subcortical Brain Region and White Matter Tract in Explaining NIHSS-Based Stroke Severity (A) and mRS-Defined Functional Outcomes (B) in the Derivation Cohort



Darker red color translates to a more pronounced effect of a specific region, indicating a higher stroke severity or odds of unfavorable outcome, when lesioned. Results are grouped separately for cortical regions and subcortical regions/white matter tracts. For an eased comparison of results for patients with varying WMH burdens, results for patients with a lower WMH burden are illustrated on the left-hand side in direct proximity to results for patients, with a higher WMH burden on the right-hand side. Altogether, bilateral strokes affecting subcortical gray matter brain regions and white matter tracts explained higher stroke severity and higher odds of unfavorable outcomes in case of patients with both low and high WMH burden. In the case of stroke severity, left-lateralized cortical lesions had additionally relevant contributions that were more pronounced for patients with a high WMH burden (c.f., Figure 5). The effect of cortical lesions was altogether weaker in the case of functional outcomes. mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; WMH = white matter hyperintensity.

Figure 5 Substantial Differences in Lesion Pattern Effects for Patients With Low and High WMH Burden



(A) Bayesian posterior distribution of total WMH burden effect. There was a substantial overlap (>5%) with zero for the Bayesian posterior distribution of the total WMH burden. Therefore, there was no evidence of an overarching total WMH burden effect on stroke severity. (B) Substantially enhanced lesion pattern 4 effect in patients with a high WMH burden. We evaluated how much the Bayesian posterior distributions of coefficients for patients with a high and low WMH burden differed from one another by subtracting one posterior distribution from the other one, which resulted in difference distributions. In case of lesion pattern 4, a right-hemispheric lesion pattern, prominently featuring temporoparietal brain regions, a higher stroke severity was specifically linked to those patients with a high WMH burden. This circumstance was inferable from the nonsubstantial overlap of the difference Bayesian posterior distribution with zero (lesion pattern 4 [low − high WMH burden difference distribution]: mean = −0.7, 90% HPDI = −1.2 to −0.1). (C) Substantially enhanced lesion pattern 6 effect in patients with a high WMH burden. In addition, lesions of left-hemispheric brain regions, among others featuring the insular and opercular cortex as well as inferior and middle frontal gyrus and precentral and postcentral gyrus, were associated with a higher stroke severity in patients with a high WMH burden (lesion pattern 6 [low − high WMH burden difference distribution]: mean = −1.1, 90% HPDI = −1.9 to −0.4). HPDI = highest probability density interval; WMH = white matter hyperintensity.

and inferior frontal brain regions as well as lesions affecting right-hemispheric temporoparietal brain regions were associated with a higher stroke severity explicitly in those patients with a high WMH burden compared with those with a low WMH burden. Illustrative examples are as follows: a patient with a lesion affecting right temporoparietal brain regions would be predicted to have a substantially higher stroke severity if they had higher prestroke WMH burden even if all other characteristics such as age, sex, stroke lesion volume, and comorbidities were kept unchanged. The same could be said about a patient featuring lesions to left insular and opercular as well as inferior frontal brain regions. Predicted stroke severity would be substantially higher in case of high WMH burden, even if nothing else about lesion or clinical characteristics was changed. However, in case of stroke lesions primarily affecting brain regions other than the just named ones, the predicted stroke severity score would be the same independent of the WMH burden. This lesion location–

specific effect did not hold for long-term functional stroke outcomes: rather, the overall WMH burden was associated with higher odds of unfavorable outcomes across all strokes.

All in all, our findings have both neuroscientific and clinical implications. Neuroscientifically, our findings elicit the hypothesis that the combination of a high WMH burden and certain stroke lesion locations may entail an exacerbated disruption of cerebral network integrity. This disproportional deterioration could then explain the higher stroke severity. This hypothesis could be tested in future functional imaging studies that simultaneously considered information on stroke and WMH lesions. Clinically, our findings have the potential to become particularly relevant. For example, our findings suggest that patients with a high WMH burden may benefit from a more aggressive acute treatment and intense rehabilitation in case they experience left-hemispheric lesions near the insula or right-hemispheric temporoparietal regions. Especially if confirmed in future prospective studies, these finding could prompt a WMH burden–tailored clinical management of AIS.

The involvement of the left inferior frontal gyrus suggests a potentially detrimental effect of global WMH burden on language function. This assumption of language-specific WMH effects is further supported by a wealth of stroke studies reporting associations of WMH with worse language outcomes,[15,16] declines in language performance,[17] and worse language recovery after stroke.[18] Previous studies have shown that WMH predominantly impairs long-range fiber function.[15,33] Such a restriction of long-range fiber function, in turn, appears to mediate negative WMH effects on language outcomes.[15] Furthermore, intact language function is thought to depend on the integrity of both local, task-specific, as well as distributed domain-general networks.[34,35] Hence, language function after focal lesions of language areas, such as Broca area, may be more excessively impaired in the case of concurrent diffuse prestroke brain pathology due to WMHs, which affect the integrity of spatially distributed brain networks.[36]

Overall, our findings motivate the more precise evaluation of WMH burden for patients presenting with left-hemispheric lesions in language areas. We here assessed only rather coarse-grained behavioral scores. As a first step, future studies could therefore specify the effect of WMH and stroke lesion interaction effects on individual NIHSS items or more detailed language outcomes.[37] In addition to corroborating the here reported detrimental effects of WMH burden and stroke lesion interactions, these studies could also estimate their clinical relevance further. Moreover, a more consistent consideration of the WMH burden in models of language-related outcomes may substantially increase their prediction performance.

The WMH-modulated right-hemispheric lesion pattern detected in our analysis most prominently comprised inferior parietal lobule (IPL) brain regions, for example, supramarginal and angular gyrus. These brain regions are known to fulfill a rich variety of cognitive functions,[38-40] especially visuospatial attention.[41] Correspondingly, lesions of right IPL are frequently observed to lead to the clinical phenomenon of hemispatial neglect, that is, the inability to orient attention to the contralesional body side.[42] Intriguingly, previous work could demonstrate a link between neglect and increasing WMH burden.[43] As for language, spatial attention may heavily rely on the integrity of large-scale brain networks.[44] This dependence may underscore the importance of WM tracts connecting critical cortical brain regions. WMHs affecting these WM tracts may then compromise the integrity of these large-scale networks, which, in turn, may augment the detrimental effect of focal stroke lesions.

Given these findings, we hypothesize a greater benefit of acute recanalization treatments in patients with a high WMH burden and right temporoparietal lesion, which could be tested in future studies. In analogy to our considerations in the previous paragraph on language outcomes, we would expect an enhanced prediction performance of attention deficits once information on both WMH burden and stroke lesion location information was integrated in prediction models.

In our study, we did not observe any reliable lesion location–specific effect of WMH burden on mRS-defined functional outcomes. Instead, the total amount of WMH burden was associated with higher odds of unfavorable outcomes. This constellation of effects consequently stands in opposition to our findings for stroke severity. Although we uncovered lesion location–specific WMH burden effects on stroke severity, we did not find a significant association for the total amount of WMHs. Two considerations may contribute to the explanation of these diverging findings. First, the mRS is even more coarse grained than the NIHSS. Specific symptoms poststroke, such as aphasia and neglect, may thus not have been represented as well in the mRS as in the NIHSS to allow for the discovery of interaction effects with the WMH burden.[45] Second, the process of neurorecovery may precisely rely on the integrity of large-scale networks connected through WM tracts. Hence, a higher WMH burden might negatively affect the potential for neurorecovery independent of lesion location.

Several additional limitations should be considered. The exact time points of outcome score acquisition were rather variable. We here strove to maximize sample size and therefore accepted stroke severity scores that were obtained during the acute hospital stay and mRS scores recorded between 60 and 190 days after stroke. Moreover, neither the prestroke functional status nor the administration of acute stroke treatments such as thrombolysis or mechanical thrombectomy was systematically recorded in our cohort. Given that most of our data were obtained before 2011, expected numbers of treated patients are however low.[46] Our study cohort was slightly younger and more mildly affected than expected for an unselected stroke patient cohort.[46] This circumstance may be due to a more frequent failure to obtain informed consent from older and very severely affected patients. We expect that the inclusion of these older and more severely affected patients

would have enhanced, rather than decreased the here observed differences between patients with low and high WMH burden. We here focused on interpreting interaction effects of stroke lesion patterns and WMH burden. Although we corrected for important covariates, such as a patient's age, sex, and comorbidities, it was beyond the scope of this study to present an exhaustive evaluation of these factors' effects. Furthermore, we here relied on scans, as obtained in clinical routines in multiple countries and clinical sites. Hence, there are associated challenges arising through data heterogeneity. However, both the automatic stroke and WMH lesion segmentations comprised thorough quality control steps aiming to ensure a high quality of individual lesion segmentations.[21,22] In addition, our entire pipeline, especially the low-dimensional stroke lesion representation, could be easily transferred to completely new data. One limitation of our low-dimensional stroke lesion representation may be seen in the slight dilution of vascular territories. Nonetheless, this slight loss in lesion information may be an acceptable cost for rendering our Bayesian analyses possible. Importantly, we ensured a good lesion representation in principle by means of correlation analyses. In addition, the here extracted lesion locations as relevant for stroke severity and functional outcomes closely resemble those reported in other studies that relied on different lesion symptom mapping techniques[47,48] or used similar techniques but different stroke samples.[29] We did not account for the actual acute stroke lesion when computing the WMH burden. Of note, most patients in our study featured rather small lesions though, with a median size of 3.1 mL. Altogether, we thus do not estimate our results to be decidedly altered if stroke lesions were included in WMH estimation. Finally, although we did not find evidence that effects reported in this study were linked only to previous large vessel occlusions, it may be fruitful to incorporate precise information on WMH lesion locations or the categorization of WMH patterns into diffuse, strategic, or indicative of large vessel event in future studies. Conceivably, the disruption of specific, that is, strategic, WM tracts may entail disproportionally damaging effects on cortical function.

In this study, we investigated interaction effects of WMH burden and stroke lesion locations on stroke severity and functional outcomes. With respect to acute stroke severity, we observed that lesions of left-hemispheric insular and inferior frontal brain regions and right-hemispheric temporoparietal brain regions were associated with substantially higher scores in case of a high WMH burden. The spatial distribution of these lesion patterns implicates 2 of the most fundamental cognitive functions, language and spatial attention. On the other hand, functional outcomes ~3 months after stroke were influenced by the WMH burden in general, rather than in case of specific lesion locations. In their entirety, our findings suggest that patients with a high WMH burden and left-sided lesions near the insula or right-sided temporoparietal lesions could show greater improvements with more aggressive acute recanalization treatments. Once confirmed in further clinical studies, they may spur a lesion location– and WMH burden–specific management of acute ischemic stroke.

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Appendix *(continued)*

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Continued

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Ramin Zand, MD	Department of Neurology, Geisinger, Danville, PA	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Patrick McArdle, PhD	Division of Endocrinology, Diabetes and Nutrition, Department of Medicine, University of Maryland School of Medicine, Baltimore	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Bradford B. Worrall, MD, MSc	Departments of Neurology and Public Health Sciences, University of Virginia, Charlottesville	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Christina Jern, MD	Department of Laboratory Medicine, Institute of Biomedicine, the Sahlgrenska Academy, University of Gothenburg; Department of Clinical Genetics and Genomics, Sahlgrenska University Hospital, Gothenburg, Sweden	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Arne G. Lindgren, MD, PhD	Department of Neurology, Skåne University Hospital, Lund; Department of Clinical Sciences Lund, Neurology, Lund University, Sweden	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Jane Maguire, PhD	University of Technology Sydney, Australia	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data

Appendix (continued)

Name	Location	Contribution
Polina Golland, PhD	Computer Science and Artificial Intelligence Lab, Massachusetts Institute of Technology, Boston	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Danilo Bzdok, MD, PhD	Department of Biomedical Engineering, McConnell Brain Imaging Centre, Montreal Neurological Institute, Faculty of Medicine, School of Computer Science, McGill University; Mila–Quebec Artificial Intelligence Institute, Montreal, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Ona Wu, PhD	Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Natalia S. Rost, MD, MPH	J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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