Original Contribution

Stroke Location Is an Independent Predictor of Cognitive Outcome

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Background and Purpose—On top of functional outcome, accurate prediction of cognitive outcome for stroke patients is an unmet need with major implications for clinical management. We investigated whether stroke location may contribute independent prognostic value to multifactorial predictive models of functional and cognitive outcomes.

Methods—Four hundred twenty-eight consecutive patients with ischemic stroke were prospectively assessed with magnetic resonance imaging at 24 to 72 hours and at 3 months for functional outcome using the modified Rankin Scale and cognitive outcome using the Montreal Cognitive Assessment (MoCA). Statistical maps of functional and cognitive eloquent regions were derived from the first 215 patients (development sample) using voxel-based lesion-symptom mapping. We used multivariate logistic regression models to study the influence of stroke location (number of eloquent voxels from voxel-based lesion-symptom mapping maps), age, initial National Institutes of Health Stroke Scale and stroke volume on modified Rankin Scale and MoCA. The second part of our cohort was used as an independent replication sample.

Results—In univariate analyses, stroke location, age, initial National Institutes of Health Stroke Scale, and stroke volume were all predictive of poor modified Rankin Scale and MoCA. In multivariable analyses, stroke location remained the strongest independent predictor of MoCA and significantly improved the prediction compared with using only age, initial National Institutes of Health Stroke Scale, and stroke volume (area under the curve increased from 0.697–0.771; difference=0.073; 95% confidence interval, 0.008–0.155). In contrast, stroke location did not persist as independent predictor of modified Rankin Scale that was mainly driven by initial National Institutes of Health Stroke Scale (area under the curve going from 0.840 to 0.835). Similar results were obtained in the replication sample.

Conclusions—Stroke location is an independent predictor of cognitive outcome (MoCA) at 3 months post stroke. (***Stroke*. 2016;47:00-00. DOI: 10.1161/STROKEAHA.115.011242.**)

Key Words: area under curve ■ cognition ■ prognosis ■ stroke ■ stroke location ■ stroke volume

Stroke is a leading cause of chronic morbidity because of functional impairment (mostly motor) and cognitive dysfunction.[1] Improving the prediction of functional and cognitive outcomes after an ischemic stroke is highly desirable because it can help to rapidly inform patients and their relatives and optimize patient care and management, particularly with respect to discharge planning and home adjustments.[2,3] In clinical research, predictive models can further be used to identify homogenous patient populations and improve the statistical power of trials.[3,4] Although functional outcome can be moderately predicted at baseline, accurate prediction of cognitive outcome remains more elusive.

For functional outcome, several clinical- and imaging-based predictive models have identified age, initial stroke severity, and stroke volume as important predictors.[5–7] Taken together, age and initial severity assessed by the National Institutes of Health Stroke Scale (NIHSS) correctly classify about 70% of the patients with respect to functional recovery.[5] These predictors seem to be less predictive of cognitive dysfunction. Age is an accepted predictor of cognitive outcome[8] but might be confounded by higher likelihood of prestroke cognitive dysfunction in older patients. NIHSS includes assessment of orientation, language, and inattention[9] but not that of other cognitive domains, such as memory, learning, or

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visuospatial functions. This probably explains why the initial NIHSS is modest,[10] if at all associated with higher risk of cognitive dysfunction after stroke.[11] Similarly, stroke volume is debated as predictor of cognitive outcome with some studies reporting volume as relevant[12] and others not.[13]

This indicates that additional factors influence outcome, especially for cognitive dysfunction. Stroke location is a promising candidate metric for predictive modeling because specific areas have been associated not only with functional recovery[14,15] but also with specific cognitive deficits, such as aphasia[12,16,17] and neglect.[18] We might even hypothesize an association between specific locations and more global cognitive dysfunction through disconnection of distant regions affecting network functioning. To address this issue, the eloquent regions should be ideally identified on a voxel-wise basis using a voxel-based lesion-symptom mapping (VLSM) technique[16] rather than using predefined, rough, substructures.[11,19] Furthermore, the clinical (age and initial NIHSS) and volumetric information should be combined with stroke location to provide an accurate multimodal model instead of considering location alone.[14–18] Ultimately, a prognostic model has to be validated on a replicating population with the purpose of its application at the individual scale in personalized medicine.

Consequently, we investigated whether stroke location could provide significant added value, when combined with established clinical and imaging variables, toward predicting functional impairment and global cognitive disability. To do so, we prospectively included patients that were imaged with structural magnetic resonance imaging (MRI) within 24 to 72 hours of a stroke and assessed for functional and cognitive outcomes 3 months later. A first part of the population was used as a development sample to map the eloquent regions with VLSM and to build multivariate prediction models with or without inclusion of stroke location. The second part of the population was used as an independent replication sample to confirm the prior findings.

Material and Methods

Patients

We prospectively recruited 428 consecutive patients presenting a suspected supratentorial ischemic stroke from June 2012 to February 2015. The study was approved by the local research ethics committee and all patients, or their relatives, gave written informed consent before inclusion.

Primary inclusion criteria were men and women, older than 18 years old, with a clinical diagnosis of minor-to-severe supratentorial cerebral infarct (NIHSS between 1 and 25) between 24 and 72 hours after the onset. Exclusion criteria were history of symptomatic cerebral infarct with functional deficit (prestroke modified Rankin Scale [mRS] score ≥1), infratentorial stroke, history of severe cognitive impairment (dementia), or psychiatric troubles matching to axis 1 of the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria except for major depression, coma, pregnant or breast-feeding women, and contraindications to MRI.

Clinical Assessment

At baseline, the NIHSS was recorded between 24 and 72 hours after stroke onset, at the time of the MRI scan. Prestroke cognitive state was estimated by IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly) which was completed by the patient's relative at the time of admission. At 3-month follow-up, all patients underwent a standardized battery of clinical testing including, among others, the mRS to assess functional deficits and the Montreal Cognitive Assessment (MoCA) to assess cognitive deficits. We chose the mRS as a measure of global disability because it is the most widely used end point in clinical trials[20] and the MoCA[21] as it is recommended by National Institute of Neurological Disorders (NINDS) and Stroke-Canadian Stroke Network to screen vascular cognitive impairment. It can rapidly evaluate global cognitive dysfunctions by testing the following cognitive domains in a 30-point test: short-term memory, visuospatial abilities, executive functions, attention, language, and orientation in time and space.

MRI Protocol

MRI examinations were performed on a 3-T Discovery MR750w scanner (GE Medical Systems, Milwaukee, WI) between 24 and 72 hours (mean delay, 57 hours and 6 minutes±17 hours and 36 minutes). Within a complete 45-minute protocol, we used diffusion-weighted images and 3-dimensional (3D) T1-weighted images for the purpose of this study. The diffusion-weighted image sequence parameters were: 38 slices; repetition time, 9000 ms; echo time set to minimum; slice thickness, 4 mm; gap, 0.5 mm; matrix, 128×128; and field of view, 24 cm×24 cm; and b values, 0 and 1000 s/mm^2. The 3D T1-weighed sequence was a 3D inversion recovery-prepared fast spoiled gradient-echo with the following parameters: 196 sagittal slices; repetition time, 8.60 ms; echo time, 3.27 ms; inversion time, 450 ms; flip angle, 12°; slice thickness, 1 mm; matrix, 256×256; and field of view, 24 cm×24 cm.

Data Analysis

The 289 patients with complete data set were divided into 2 samples (Figure 1): (1) a development sample, constituted by the first 215 consecutive patients to map the eloquent regions and to develop the models of prediction for both, functional and cognitive, outcomes with the strongest accuracy and (2) a replication sample, constituted by the last 74 consecutive patients to assess the predictive performances in independent patients.

Lesion Segmentation

Stroke lesions were segmented on diffusion-weighted images using a semiautomatic tool available in 3D Slicer (http://www.slicer.org) blinded from clinical information. Diffusion-weighted images and lesion masks were coregistered to the native 3D T1 images, and both were registered to the standard MNI152 space atlas with the SPM8 software package (Statistical Parametric Mapping, Wellcome Trust Center for Neuroimaging, London, United Kingdom).

Development Sample: Maps of Eloquent Regions and Prediction Models

Building the Maps of Eloquent Regions. We used the VLSM method implemented in the nonparametric mapping toolbox included in the MRIcron software package (MRIcron, Verion 6.6.2013).[22] This method establishes a relationship between the presence or lack of a lesion and a behavioral score on a voxel-by-voxel basis.[16] For each voxel, a Brunner–Munzel rank order test was performed to determine whether the behavioral score is significantly different between the lesioned and nonlesioned group. We built maps of functional and cognitive eloquent regions using, respectively, mRS and MoCA measured at 3 months as behavioral scores. A subanalysis was conducted on a short MoCA (sMOCA) in which the items naming and language have been removed. The resulting Z score maps were controlled for multiple comparisons using the false discovery rate correction to ensure a false-positive rate of $P<0.05$. The eloquent regions were identified using the Automated Anatomic Labeling,[23] Brodmann, and JHU-WhiteMatter-labels-1mm atlases available in the MRIcron software package.

Extraction of Location-Based Variables. The objective was to use the VLSM maps, which showed the eloquent areas in terms of mRS

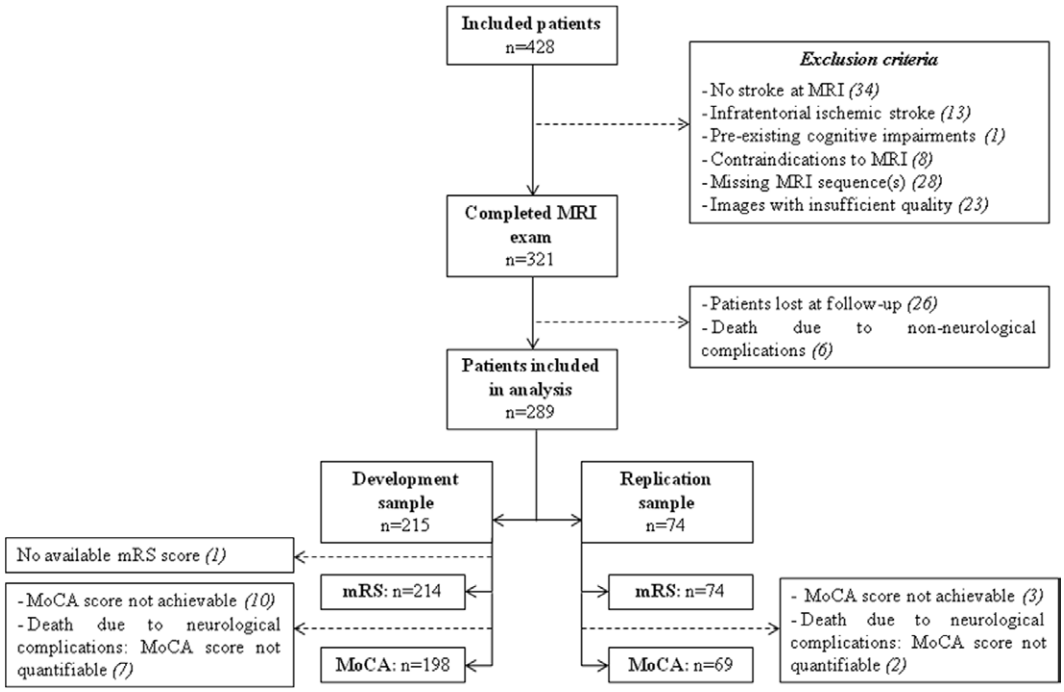

Figure 1. Flow diagram of the study population. MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; and mRS, modified Rankin Scale.

and MoCA scores, to predict, respectively, the functional and cognitive outcomes at 3 months for a new stroke patient. For that purpose, we overlapped the patient's lesion binary mask on each VLSM map. Then, we extracted all significant *Z* scores (corresponding to eloquent voxels that survived a 5% false discovery rate cutoff threshold) contained in the lesion, using a home-made program developed in Matlab (Mathworks Natick, Massachusetts). Finally, using the R software package (Version 3.0.1), we calculated the number of eloquent voxels. This quantitative variable contains the information of location and will be referred to as stroke location in the following sections.

Development of Prediction Models. The dependent variables to predict were the dichotomized mRS or the dichotomized MoCA scores. A cutoff mRS value ≤1[24] was used to discriminate good functional outcome. A favorable cognitive outcome was defined as a MoCA score >25.[25] By analogy, favorable cognitive outcome on the sMoCA was defined as sMoCA >20. Comparisons used parametric Student *t* tests or Mann–Whitney statistics when appropriate. We implemented a logistic regression to build prediction models using the Logistic procedure of the SAS software (v9.3, SAS Institute, Cary). The first model (referred as model 1) included the following usual variables: baseline NIHSS, age, and the infarct volume. A second model (referred as model 2) included all the previous parameters plus stroke location to test its independent added value. Shapes of the association were analyzed using fractional polynomials.[26] We assessed the overall discrimination of model 1 and model 2 for mRS and MoCA by calculating the area under the receiver operating characteristics curve (AUC) and its 2-sided 95% confidence interval (CI).

Internal Validation. Internal validation used the 10-fold cross-validation procedure to correct the AUC of both models for optimism and estimate added value of model 2 versus model 1 for predicting functional and cognitive outcomes. Bootstrap technique with 1000 replications was performed to estimate 2-sided 95% confidence intervals of each AUC and the added value.[27]

Replication Sample

The 74 last consecutive patients, who were used neither to map the eloquent regions nor to build the prediction models, were considered as an independent population for validation. The prognostic models determined from the previous steps were applied to this sample to calculate the probability for these new patients to have a good functional outcome (mRS ≤1) and a good cognitive outcome (MoCA>25 or sMoCA>20). The AUC and its 2-sided 95% confidence interval were calculated to quantify the added value of model 2 versus model 1 for predicting functional and cognitive outcomes. Comparison of AUC between both models used the DeLong test for correlated data.[28]

Results

Patient Characteristics

Among the 215 patients of the development sample, there were 138 men (64.2%) and 77 women (35.8%), 119 patients (55.3%) with a stroke involving the left hemisphere, 118 (55.1%) with a good functional outcome (mRS score ≤1), and 77 (38.9%) with a good cognitive outcome (MoCA>25). None of the patients had prestroke cognitive impairment (mean IQCODE score, 3±0.3).

Among the 74 patients in the replication sample, there were 50 men (67.6%) and 24 women (32.4%), 40 patients (54.1%) with a stroke involving the left hemisphere, 32 (43.2%) with a good functional outcome (mRS score ≤1), and 32 (46.4%) with a good cognitive outcome (MoCA>25). No patients had prestroke cognitive impairment (mean IQCODE score, 2.9±0.5). Other baseline characteristics are shown in Tables 1 and 2.

Voxel-Based Lesion-Symptom Mapping Analysis

The VLSM maps associating tissue damage to mRS (Figure 2A and 2B) and MoCA (Figure 2C and 2D) at 3 months post stroke are shown in Figure 2. After false discovery rate correction ($P<0.05$) to correct for multiple comparisons, a maximum *Z* score value was set to −3.79 for VLSM analysis on

mRS (Figure 2B), and a minimum *Z* score value was set to 1.73 for VLSM analysis on the MoCA (Figure 2D).

VLSM analysis on mRS highlighted a lateralization with more regions associated with a worse functional outcome on the left hemisphere. Most of these regions are part of the motor pathway. VLSM analysis on MoCA highlighted an even stronger left lateralization with a predominance of not only the prefrontal, cingulate, peri-insular, middle, and superior temporal cortex but also amygdala, hippocampus, and deep nuclei, including the thalamus. Details of the main eloquent functional regions are found in the Table I in the online-only Data Supplement.

Development Sample

Development of Prediction Models

The prediction models were as follows:

$$\text{mRS}=\frac{e^{\text{Intercept}+\beta_1\times(\text{NIHSS})+\beta_2\times(\text{Age})+\beta_3\times(\text{Age}^2)+\beta_4\times(\text{Volume})}}{1+e^{\text{Intercept}+\beta_1\times(\text{NIHSS})+\beta_2\times(\text{Age})+\beta_3\times(\text{Age}^2)+\beta_4\times(\text{Volume})}}$$

for model 1 and

$$\text{mRS}=\frac{e^{\text{Intercept}+\beta_1\times(\text{NIHSS})+\beta_2\times(\text{Age})+\beta_3\times(\text{Age}^2)+\beta_4\times(\text{Volume})+\beta_5\times(\log\text{ stroke location})}}{1+e^{\text{Intercept}+\beta_1\times(\text{NIHSS})+\beta_2\times(\text{Age})+\beta_3\times(\text{Age}^2)+\beta_4\times(\text{Volume})+\beta_5\times(\log\text{ stroke location})}}$$

for model 2.

The formulas did not include the age-squared as variable for the MoCA.

Functional Outcome

Stroke location was significantly different between the groups with good (mRS score ≤1) and poor (mRS score >1) outcomes, with a median of only 3 eloquent voxels for patients with mRS score ≤1 versus 128 eloquent voxels for patients with mRS score >1 ($P\leq0.001$). Baseline NIHSS, age, and stroke volume also significantly discriminated both groups ($P\leq0.001$; Table 1).

In multivariate analysis, the association between stroke location and mRS did not persist, baseline NIHSS (β=–0.320; 95% CI, –0.443 to –0.196) being the only independent predictor of functional outcome (Table 3). This was illustrated by the absence of a relevant difference between the AUC of the 2 models after the internal validation step (Table 4; difference=–0.005; 95% CI, –0.021 to 0.014; Figure 3A).

Cognitive Outcome

Stroke location was significantly different between the groups with good (MoCA >25) and poor (MoCA ≤25) outcomes, with a median of only 2 eloquent voxels for patients with MoCA >25 versus 224 eloquent voxels for patients with MoCA ≤25 ($P\leq0.001$). Baseline NIHSS, age, and stroke volume also significantly discriminated both groups ($P\leq0.05$; Table 2).

In multivariate analysis, the association between stroke location and MoCA persisted (β=–0.293; 95% CI, –0.421 to –0.165) and was the variable with the highest significance followed by baseline NIHSS (β=–0.158; 95% CI, –0.264 to –0.051) and age (β=–0.048; 95% CI, –0.074 to –0.021; Table 3). This was illustrated by the significantly higher AUC of model 2 (AUC=0.771) compared with that of model 1 (AUC=0.697) after the internal validation step (Table 4; difference=0.073; 95% CI, 0.008–0.155; Figure 3B).

We conducted a subanalysis on the prediction of a sMoCA score without the items naming and language to further test that our results reflect the prediction of global cognitive impairment and were not driven by aphasia only. This subset analysis produced similar results, stroke location still significantly improving the accuracy of the logistic regression model (Model 1: AUC=0.701; Model 2: AUC=0.762; difference=0.062; 95% CI, 0.001–0.147).

Replication Sample

We used the 74 finally included patients of the study as a replication sample and confirmed our main findings despite the lower statistical power of this smaller sample. Stroke location did not provide any additional predictive value compared with the other predictors when included together in the logistic regression model of functional outcome (Table 4; difference=–0.004; 95% CI, –0.032 to 0.023; *P*=0.75; Figure 3C). In contrast, stroke location was significantly different between patients with good and poor cognitive outcomes (median of 25 eloquent voxels for MoCA >25 versus 138 eloquent voxels for MoCA ≤25; *P*=0.001; Table 2) and significantly improved the logistic regression model of cognitive outcome (Table 4; difference=0.119; 95% CI, 0.035–0.203; *P*=0.005; Figure 3D). Analyzing the sMoCA, stroke location still improved the accuracy of the logistic regression model (Model 1:

Table 1. Characteristics of Patients According to Their Functional Outcome

	Development Sample			Replication Sample		
	All	Poor Outcome mRS Score >1 (n=96)	Good Outcome mRS Score ≤1 (n=118)	All	Poor Outcome mRS Score >1 (n=42)	Good Outcome mRS Score ≤1 (n=32)
mRS						
Baseline NIHSS	4 (1–25)	8 (1–25)	2 (1–21)*	3 (1–25)	4 (1–25)	2 (1–6)†
Age, y	68 (29–95)	74 (29–95)	65 (30–88)*	69 (27–90)	74 (27–90)	62 (39–87)†
Volume, cm^3	16 (0–351)	33 (0–351)	10 (0–139)*	9 (0–293)	17 (1–293)	3 (0–100)†
Stroke location	14 (0–2690)	128 (0–2690)	3 (0–1880)*	14 (0–2527)	14 (0–2527)	14 (0–821)

Values are median (range). mRS indicates modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.
*Significant at the 0.001 level (Mann–Whitney *U* statistics).
†Significant at the 0.05 level.

Table 2. Characteristics of Patients According to Their Cognitive Outcome

	Poor Outcome MoCA ≤25 (n=121)	Good Outcome MoCA >25 (n=77)	Poor Outcome MoCA ≤25 (n=37)	Good Outcome MoCA >25 (n=32)
MoCA				
Baseline NIHSS	4 (1–25)	3 (1–10)*	3 (1–24)	3 (1–13)
Age, y	69 (34–95)	60 (29–84)*	74 (27–89)	62 (39–87)†
Volume, cm^3	17 (0–211)	6 (0–196)†	12 (1–293)	3 (0–245)
Stroke location	224 (0–29875)	2 (0–11823)*	138 (0–13359)	25 (0–4063)†

Values are median (range). MoCA indicates Montreal Cognitive Assessment; and NIHSS, National Institutes of Health Stroke Scale.

*Significant at the 0.001 level (Mann–Whitney *U* statistics).

†Significant at the 0.05 level.

AUC=0.632; Model 2: AUC=0.763; difference=0.132; 95% CI, 0.047–0.216; *P*=0.0022).

Discussion

To the best of our knowledge, we designed the first predictive models of functional and cognitive outcomes, including a location voxel-based variable, for example, the number of outcome-specific eloquent voxels, which were tested and confirmed on an independent replication sample. We identified stroke location as an independent predictor of cognitive outcome as measured by MoCA at 3 months. Actually, adding this variable in a model including the usual clinical and imaging parameters known as independent predictors of stroke outcome, for example, baseline NIHSS,[5,6] age,[5,6] and lesion size,[7] improved significantly the accuracy of the prediction. By contrast, most of the prediction of the functional outcome is driven by the initial NIHSS and including the eloquent regions associated with poor functional recovery was insufficient to further improve the prediction.

Our main result about the significant impact of location on the prognosis of cognitive function is in line with previous studies, which showed that anterior infarct or cortical locations were associated with cognitive scores.[11,29] At that time, location was nevertheless only roughly defined as regional or territorial. Whether the relevant predictor was stroke volume or actual location remained consequently elusive as the 2 variables were strongly confounded within such analyses.[11,29] In contrast, a method, such as VLSM, can highlight eloquent voxels of a specific cognitive domain, such as spatial neglect and[18] speech production,[16,17] and has become more widely used over recent years. Our VLSM map of MoCA highlights eloquent areas in left inferior frontal gyrus and left superior temporal gyrus, which are well known for speech production and speech comprehension similarly to Phan et al.[30] Furthermore, additional eloquent areas are highlighted in the hippocampus, parahippocampal gyrus, and the left middle temporal gyrus, which are known to be involved in poststroke memory dysfunction.[31] Executive functions are associated not only with prefrontal cortex but also with cingulate cortex, basal ganglia, and thalamus[29]; all of them appear as eloquent in our MoCA-related VLSM map. A large extent of the left thalamus is associated with a worse MoCA score in our map, which is in agreement with previous studies[32,33] that have highlighted the role of relay of the thalamus in several cognitive domains (attention, working memory, visuospatial abilities, orientation, long-term memory, and executive functions). All cognitive functions are further associated with a widely distributed network and so cognitive dysfunction may also be due to deafferentation through white matter fiber damages.[34] Our VLSM map of MoCA also shows that presenting cognitive impairment at 3 months post stroke is mainly associated with lesions in the left hemisphere. This is consistent with previous

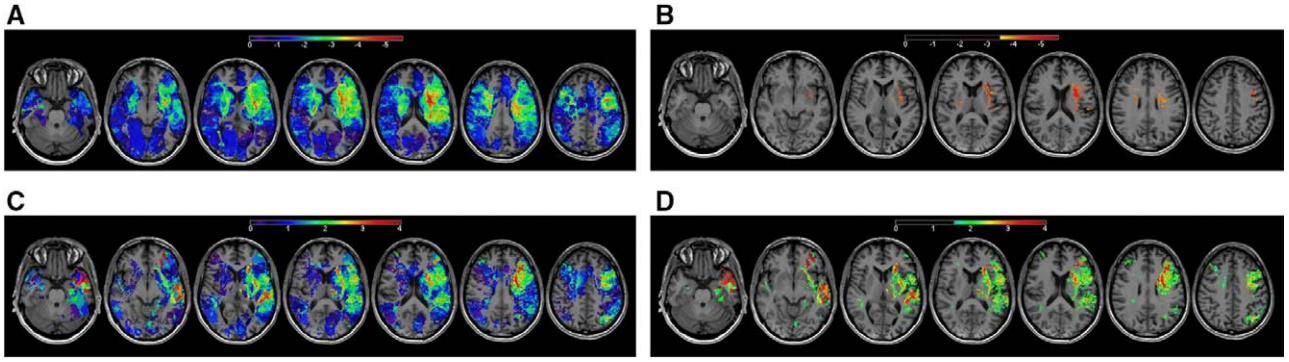

Figure 2. Voxel-based lesion-symptom mapping (VLSM) of the impact on modified Rankin Scale (mRS; **A** and **B**) and Montreal Cognitive Assessment (MoCA; **C** and **D**) at 3 months post stroke overlaid on a 3-dimensional T1-weighted image registered to the standard MNI152 space atlas. The color range indicates *Z* scores resulting from Brunner–Menzel testing. **A**, VLSM map for mRS not corrected for multiple comparisons and (**B**) after false discovery rate at *P*=0.05 resulting in a threshold for *Z* score of –3.79. **A** and **B**, Lower *Z* scores (red) indicate brain regions associated with worse functional outcome (mRS). **C**, VLSM map for MoCA not corrected for multiple comparisons and (**D**) after false discovery rate at *P*=0.05 resulting in a threshold for *Z* score of 1.73. **C** and **D**, Higher *Z* scores (red) indicate brain regions associated with worse cognitive outcome (MoCA).

Table 3. Logistic Regression Analysis: Predictors of Good Functional and Cognitive Outcomes in the Development Sample (Model 2: n=214 for mRS and n=198 for MOCA)

	mRS		MoCA	
	β	95% CI	β	95% CI
Intercept	−1.222	7.864 to 5.420	4.262	2.356 to 6.167
Baseline NIHSS	−0.320	−0.443 to −0.196*	−0.158	−0.264 to −0.051*
Age	0.156	−0.058 to 0.369	−0.048	−0.074 to −0.021*
Age-squared	−0.002	−0.003 to 0.000	…	…
Volume, cm^3	−0.000	−0.012 to 0.011	0.009	−0.004 to 0.022
Log stroke location	−0.094	−0.260 to 0.071	−0.293	−0.421 to 0.165*

β indicates regression coefficient; CI, confidence interval; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Statistically independent predictors of functional or cognitive outcomes.

studies that have shown that left hemispheric stroke was an independent predictor of cognitive outcome at 3 months post stroke.[1,29,31,35] The left-sided predominance is not only driven by language deficit but may also be explained by the close relation between language and complex cognitive functions.[29,36] This is supported by our analysis on a subscore in which the most language-dependent items have been removed and which confirmed the improvement of the prediction after adding stroke location as variable.

About functional outcome, stroke location was not an independent predictor of mRS at 3 months when considering the other predictors. This result is in agreement with the recent data from Wu et al,[37] who showed using VLSM maps on mRS that several locations highlighted as eloquent are no longer significant after accounting for age and stroke volume. This suggests that the impact of stroke location is decreased if other established predictors are considered. Furthermore, Wu et al[37] did not include initial NIHSS as a covariate. Nevertheless, NIHSS has clearly emerged as an independent predictor and is usually recommended in core outcome predictive model.[5,7] NIHSS is further easier to collect than imaging metrics, especially location-based, and it dominates the prediction of the functional outcome. In our study, the NIHSS was assessed between 24 and 72 hours, when the deficit was established, reinforcing the correlation with functional outcome. The interest of stroke location assessed by VLSM[15] or other methods, such as simple topology, from Alberta Stroke Program Early CT (ASPECT) score[19] might thus be dampened if initial NIHSS is considered while location is still strongly relevant for cognition that is more difficult to predict only using clinical variables.

Our study is not without limitation. Our cohort contained mild ischemic stroke patients. This might be because of the fact that severe stroke patients are less tolerant of the MRI procedure and more prone to motion artifacts. But otherwise, no selection was done, and all patients who were suspected of stroke were included; agitated patients being secondarily excluded if images were not assessable. Furthermore, although the replication sample was of moderate size, it provided an important confirmation step. Especially, both development and replication samples were different in terms of outcome, with more patients having a poor functional outcome (mRS score >1) and more patients having a good cognitive outcome (MoCA >25) in the replication sample, which further supports the possible generalization of our results and the capability of stroke location to discriminate patients with or without cognitive impairment at 3 months post stroke whatever the characteristics of the population. Regarding our VLSM maps, only few voxels remained eloquent after false discovery rate correction, especially for mRS, even if the highlighted regions are in agreement with recent studies.[15,37] This may be explained by the choice of the clinical scale, which is an ordinal scale of only 7 grades. In the future, using a continuous motor scale, such as the Fugl-Meyer, could better highlight regions associated with motor performance and in turn could be more adequate to detect an increased number of eloquent voxels. Finally, other potential predictors, such as the type and duration of rehabilitation, were not taken into account and should be considered in future predictive models.

In conclusion, we have validated a new model, including stroke location as voxel-based variable, which significantly improved the accuracy of the prediction of cognitive outcome as measured by MoCA at 3 months. We think our results will be helpful to rapidly identify patients at risk of cognitive impairment, which might preclude them from returning

Table 4. Logistic Regression Analysis: AUCs

	Development Sample		Internal Validation		Replication Sample	
mRS	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
AUC (95% CI)	0.870 (0.822–0.919)	0.871 (0.823–0.919)	0.840 (0.773–0.899)	0.835 (0.764–0.896)	0.734 (0.621–0.848)	0.730 (0.616–0.844)
MoCA						
AUC (95% CI)	0.740 (0.673–0.808)	0.811 (0.751–0.870)	0.697 (0.607–0.781)	0.771* (0.686–0.841)	0.660 (0.529–0.791)	0.779* (0.667–0.891)

Model 1 included baseline NIHSS, age, and stroke volume. Model 2 included baseline NIHSS, age, stroke volume, and stroke location. AUC indicates area under the curve; CI, confidence interval; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Significant difference between the AUC of the 2 models (see text for difference and its CI).

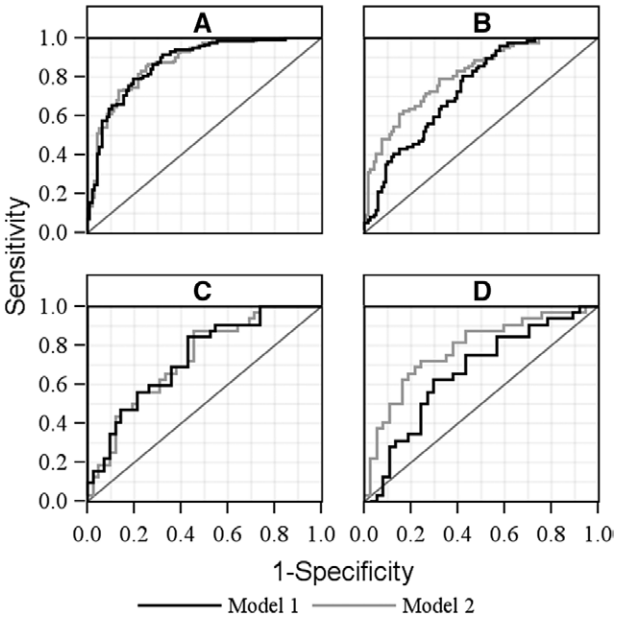

Figure 3. Receiver operating characteristic curves of the prediction models of modified Rankin Scale, for the development sample (**A**) and the replication sample (**C**), and Montreal Cognitive Assessment, for the development sample (**B**) and the replication sample (**D**).

to their previous occupations despite mild–minor functional disability. We expect this to be helpful in stratifying rehabilitation strategies in clinical routine and to power trials using cognitive performance as an end point in the future.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Supplemental Table I. Main eloquent functional and cognitive regions

Outcome	Main eloquent regions	Range of Z-scores
Functional outcome (mRS)	Left anterior corona radiata	[-6.68; -3.89]
	Left superior corona radiata	[-6.17; -3.89]
	Left external capsule	[-5.88; -3.82]
	Left putamen	[-5.22; -3.85]
	Left posterior limb of internal capsule	[-5.22; -3.84]
	Left retrolenticular part of internal capsule	[-4.54; -3.89]
	Left insula	[-4.51; -3.82]
	Left rolandic operculum	[-4.23; -3.82]
	Right posterior limb of internal capsule	[-5.81; -3.89]
	Right superior corona radiata	[-4.71; -3.79]
Cognitive outcome (MoCA)	Left external capsule	[1.89; 4.40]
	Left posterior cingulate gyrus	[3.04; 3.89]
	Left middle frontal gyrus, orbital part	[2.12; 3.89]
	Left inferior frontal gyrus, orbital part	[1.90; 3.89]
	Left putamen	[1.83; 3.89]
	Left inferior frontal gyrus, triangular part	[1.93; 3.72]
	Left hippocampus	[1.81; 3.72]
	Left middle temporal gyrus	[1.82; 3.62]
	Left superior temporal gyrus	[1.73; 3.54]
	Left middle frontal gyrus	[1.80; 3.39]
	Left amydala	[1.83; 3.35]
	Left thalamus	[1.77; 3.35]
	Left anterior corona radiata	[1.74; 3.32]
	Left pallidum	[1.75; 3.29]
	Left temporal pole: middle temporal gyrus	[2.27; 3.26]
	Left parahippocampal gyrus	[1.76; 3.11]
	Left anterior cingulate gyrus	[2.29; 3.09]
	Left caudate	[1.76; 2.96]
	Left rolandic operculum	[1.81; 2.90]
	Left inferior frontal gyrus, opercular part	[2.10; 2.89]
	Left posterior limb of internal capsule	[1.74; 2.32]

Stroke Location Is an Independent Predictor of Cognitive Outcome

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