The Real Estate Factor
Quantifying the Impact of Infarct Location on Stroke Severity

Nina M. Menezes, PhD; Hakan Ay, MD; Ming Wang Zhu, MD; Chloe J. Lopez, MA; Aneesh B. Singhal, MD; Jari O. Karonen, MD, PhD; Hannu J. Aronen, MD, PhD; Yawu Liu, MD, PhD; Juho Nuutinen, MD; Walter J. Koroshetz, MD; A. Gregory Sorensen, MD

Background and Purpose—The severity of the neurological deficit after ischemic stroke is moderately correlated with infarct volume. In the current study, we sought to quantify the impact of location on neurological deficit severity and to delineate this impact from that of volume.

Methods—We developed atlases consisting of location-weighted values indicating the relative importance in terms of neurological deficit severity for every voxel of the brain. These atlases were applied to 80 first-ever ischemic stroke patients to produce estimates of clinical deficit severity. Each patient had an MRI and National Institutes of Health Stroke Scale (NIHSS) examination just before or soon after hospital discharge. The correlation between the location-based deficit predictions and measured neurological deficit (NIHSS) scores were compared with the correlation obtained using volume alone to predict the neurological deficit.

Results—Volume-based estimates of neurological deficit severity were only moderately correlated with measured NIHSS scores ($r=0.62$). The combination of volume and location resulted in a significantly better correlation with clinical deficit severity ($r=0.79$, $P=0.032$).

Conclusions—The atlas methodology is a feasible way of integrating infarct size and location to predict stroke severity. It can estimate stroke severity better than volume alone. (Stroke. 2007;38:194-197.)

Key Words: infarcts • magnetic resonance imaging • models • outcome • statistical • stroke

Linking the anatomical characteristics of brain injury to cognitive and behavioral deficits is a key issue in vascular neurology. Stroke can affect any part of the brain and often includes multiple functional areas, making it particularly challenging to predict neurological status based on lesion characteristics. Final infarct volume correlates to a limited extent with brain function ($r=0.3$ to 0.6$^2$). In addition to volume, infarct location is fundamentally linked to neurological deficits. There is currently no methodology to systematically quantify the effect of the complex spatial pattern of injury on the severity of neurological function/dysfunction. In the current study, we sought to quantify the impact of location on neurological deficit severity and to delineate this impact from that of volume. To do so, we constructed brain atlases composed of location-weighted values indicating the relative importance in terms of neurological deficit severity for each voxel of the brain. We tested these atlases in patients with ischemic stroke to generate estimates of neurological deficit severity and compared the results to estimates based on infarct volume alone.

Methods

Patients
This study was conducted in 2 academic centers in the US and Finland and included patients with first-ever clinical ischemic stroke who had T2-weighted MR images and a National Institutes of Health Stroke Scale score (NIHSS) recorded just before hospital discharge or during the first outpatient visit. Patients in the US Center were retrospectively identified from a stroke database that listed all admissions. Patients in the Finland Center were identified from the cohort of a prospective study of the natural history of stroke. Patients who had brain surgery, hemorrhage causing anatomical distortion, motion artifacts, and mass effect attributable to brain edema were excluded, as were those who had been enrolled in clinical drug trials. The study was approved by the Institutional Review Boards of both institutions.

Imaging
T2-weighted MR images were obtained at 1.5T using a fast spin echo sequence with 25 axial slices, repetition time=4000 to 6300 ms, echo
time = 100 to 110 ms, in-plane resolution = 0.9 to 1.0 mm, and section thickness = 5 mm. A neuroradiologist manually outlined each infarct to create a binary mask (1 = lesion, 0 = no lesion) using Alice (Hayden Imaging Processing Solutions). Datasets were coregistered using FLIRT (FMRIB). The resulting binarized lesion datasets had a resolution of 2 mm.3

Atlases
Three types of brain atlases were constructed. First, experience-based knowledge about compartmentalization of brain function was incorporated by developing an “expert” atlas (EXPERT). This atlas consisted of the following anatomical regions that were manually outlined on MR images: prefrontal cortex, frontal eye field, Broca area, premotor, precentral and postcentral gyr, occipital lobe, dorsomedial parietal cortex, posterior parietal cortex, lateral temporal lobe, corona radiata and subcortical white matter, caudate nucleus, insula, lenticular nucleus, thalamus, external capsule, internal capsule (anterior and posterior limbs), hippocampus, mesencephalon, cerebellum, pons, and medulla. These regions were chosen because clinical syndromes associated with infarction of them are relatively well described. Two stroke neurologists (H.A., W.J.K.), blinded to the imaging data, independently assigned to each region the maximum NIHSSS thought to result from an infarction spanning that entire region. Where discrepant, the average score was chosen. Each voxel value in EXPERT was calculated by dividing the weight of the region it resided in by the number of voxels in that region:

\[
\text{EXPERT Voxel Value}_i = \frac{\text{EXPERT Region Weight}_i}{\text{EXPERT Region Volume}_i},
\]

where \(i\) refers to the \(i\)th voxel location. This atlas of voxel values was then multiplied (overlapped) by each patient’s binarized MRI (ie, outlined infarct on MRI) and the resulting voxel values summed to estimate the NIHSSS (Atlas Score) for each patient, \(j\):

\[
\text{Atlas Score}_j = \sum_{i=1}^{\text{# of voxels}} \text{Atlas Voxel Value}_i \cdot \text{MRI Voxel}_i,j
\]

A second, purely data-driven, atlas was also developed. In this model, each voxel in a given patient’s binarized MRI dataset was assigned a weight by multiplying by that patient’s corresponding NIHSSS and dividing by the lesion volume. The resulting datasets were averaged to produce an atlas in which each voxel value was determined by:

\[
\text{Data Driven Atlas Voxel Value}_i = \frac{1}{N_i} \sum_{j=1}^{\# of patients} \frac{\text{NIHSSS}_j}{\text{Infarct Volume}_j} \cdot \text{MRI voxel}_i,j
\]

where \(N_i\) is the number of infarcted voxels at the \(i\)th voxel location across the study population, and NIHSSS, and Infarct Volume, are the NIHSSS and the infarct volume for the \(j\)th patient. In order to eliminate bias, leave-one-out cross-validation (jacknifing) was used so that the data-driven atlas applied to a given patient was developed from the remaining patients.

Third, a hybrid atlas (HYBRID) was developed, in which patient data were used to modify the weights assigned to the regions designated in EXPERT using linear least squares regression (Matlab, Mathworks):

\[
\sum_{k=1}^{\# of regions} \rho_{jk} \cdot \text{HYBRID Region Weight}_k = \text{NIHSSS}_j,
\]

for \(j = 1\) to number of patients, where \(\rho_{jk}\) is the volume fraction of the \(k\)th region occupied by the \(j\)th infarct. Jacknifing was used such that the HYBRID atlas applied to a given patient was developed from the remaining patients.

Statistics
In order to gauge the impact of location, linear regression was used to develop estimates using lesion volume alone (VOLUME scores) such that, for each patient:

\[
\text{VOLUME Score}_j = \alpha_j + \beta_j \cdot \text{Infarct Volume}_j,
\]

where \(\alpha_j\) and \(\beta_j\) were determined by linearly regressing infarct volumes against NIHSSS of the remaining patients. Correlation analysis was performed for VOLUME scores versus NIHSSS and atlas scores (EXPERT, data-driven, HYBRID) versus NIHSSS by computing Pearson correlation coefficient and comparing the 2 correlation coefficients using Fisher r-to-Z transformation. \(P < 0.05\) was considered to be statistically significant.

Results
The study population included 80 patients with a mean age of 69 ± 13 years: 39 males and 41 females. Mean time to MRI was 8.1 ± 4.9 days (range = 3 to 31 days) and time to NIHSSS was 8.4 ± 5.1 days (range = 3 to 31 days). NIHSSS ranged from 0 to 24, and infarct volumes from 0.4 to 256 cm³. Infarcts were within the territory of the middle cerebral artery in 61, posterior cerebral artery in 8 (2 with brain stem involvement), anterior cerebral artery in 3, brain stem and cerebellum in 4, anterior choroidal artery in 2, and multiple territories in 2 patients. Excluding patients with bitemporal infarcts, 42 patients had right- and 30 had left-hemisphere infarcts. There was no difference between the US and Finland cohorts in age, gender, and infarct volume.

The agreement between examiners in assigning a NIHSSS to each designated brain region was excellent (weighted \(k = 0.98\)). The correlation coefficient between infarct volume and NIHSSS was 0.65. The correlation between EXPERT scores and clinically measured NIHSSS was \(r = 0.78\). This correlation was significantly higher than the correlation using volume alone to estimate NIHSSS \((r = 0.62\) using VOLUME scores, \(P = 0.047\) comparing the 2 correlation coefficients; Figures 1 and 2). The correlation between the data-driven atlas’ estimates and clinically measured NIHSSS was \(r = 0.69\), an improvement over volume that did not reach statistical significance for this sample size (\(n = 80\)). The correlation between HYBRID scores and NIHSSS, \(r = 0.79\) (Figure 1), was slightly better than EXPERT and significantly higher than the volume-based correlation \((P = 0.032)\).

Left-hemisphere deficits were better estimated by volume \((r = 0.71\) for VOLUME scores versus NIHSSS) than right-hemisphere deficits \((r = 0.51\), analyzed separately. HYBRID scores outperformed VOLUME scores in both hemispheres (Figure 3), but this did not reach statistical significance for the given sample sizes.

Discussion
The current study is the first to quantitatively account for lesion location anywhere in the brain to predict stroke severity through the generation of atlases. Incorporation of infarct location in a volume-based determination of stroke severity significantly improved the correlation between imaging and NIHSSS. Whereas infarct volume accounted for 38% \((r^2)\) of the variation in stroke severity, the combination of volume and location accounted for 62% of the variation (using HYBRID). Given a larger sample size, a data-driven atlas developed using the methodology outlined here may surpass the current results. This is especially likely if this larger sample includes more infarcts outside of the middle cerebral artery. Most patients in the current study had middle cerebral artery infarcts, and so there was considerably less data available to inform the data-driven atlas.
for brain regions outside of the middle cerebral artery (ie, those within the anterior cerebral artery, posterior cerebral artery, etc).

In the current study, there was left-to-right asymmetry in which voxels in the left hemisphere were associated with higher atlas values than those in the right hemisphere. This is attributable to the fact that left (dominant) hemisphere functions are more heavily weighted by the NIHSS and underscores that accounting for the impact of volume or location on clinical deficit severity is inextricably linked to the scale used. Despite these limitations, the NIHSS is the most widely used neurological scale in clinical research studies. However, the atlas methodology outlined here does not have to be used in conjunction with the NIHSS; it can be used with other scales. By substituting more targeted neurological or cognitive measures for the NIHSS, the atlas methodology can help identify the relative impact that different anatomical regions have on specific neurological functions.

The choice of a time at which to perform structural or functional correlation is inherently challenging. The current study used the subacute timepoint to perform structure-function correlations because the damage pattern seen on imaging presumably closely corresponds to the measured neurological deficit. The impact of this study, though, lies in the ability to translate the results to the acute timeframe, in which final outcome prediction can affect treatment decisions. In this respect, the atlas technique developed here can be combined with tissue outcome predictive models, which aim to identify potentially salvageable tissue based on acute MRI data, so that the potential clinical impact of salvaging or not salvaging the ischemic brain tissue in a given patient can be assessed acutely.

Although the location of a lesion clearly plays a role in its neurological impact, many brain functions are not anatomically distinct. Activation studies have confirmed that normal brain functions often require an intact network of anatomically distinct areas working in concert. Improved estimation of functional outcome requires knowledge of the sophisticated networks that connect different brain regions. Future

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**Figure 1.** Comparison of predictions to measured scores: (a) VOLUME scores, (b) EXPERT scores, and (c) HYBRID scores.

**Figure 2.** An anatomical MR image is shown (left), depicting an axial brain slice. This slice is deformed vertically to reflect different compartmentalization strategies (ie, atlases): EXPERT (middle) and HYBRID (right). The vertical dimension (colorized) indicates relative impact in units of NIHSS such that regions that appear redder correspond to greater deficits than regions that appear bluer.
work with larger data sets could address these issues by incorporating knowledge of functional networks. Such studies in different patient cohorts would also address reproducibility and reliability of the current findings.

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Disclosures
None.

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