**Intracranial Hemorrhage Localization in a Population of Patients using Registration-based Techniques in CT Imaging**John Muschelli$^{1,\ast}$, Natalie L. Ullman$^{2}$, Elizabeth M. Sweeney$^{3}$, Ani Eloyan$^{4}$, Neil Martin$^{5}$, Paul Vespa$^{6}$, Daniel F. Hanley$^{5}$, Ciprian M. Crainiceanu$^{6}$**1 John Muschelli Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA2 Natalie L. Ullman Department of Neurology, Division of Brain Injury Outcomes, Johns Hopkins Medical Institutions, Baltimore, MD, USA3 Elizabeth M. Sweeney, Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA4 Ani Eloyan, Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA5 Neil Martin, Department of Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, California6 Paul Vespa, Department of Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, California7 Daniel F. Hanley Department of Neurology, Division of Brain Injury Outcomes, Johns Hopkins Medical Institutions, Baltimore, MD, USA8 Ciprian M. Crainiceanu Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA E-mail: Corresponding jmusche1@jhu.edu**

# Abstract

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**Keywords:** Intracranial Hemorrhage; CT Imaging Analysis; 3D Histograms;

# Introduction

Intracranial hemorrhage (ICH) results from a blood vessel rupturing into brain tissues and possibly the ventricles. Bleeding causes distension of brain structures and increases the likelihood of intracranial pressure (ICP) elevation. ICH accounts for 10-15% of all strokes, corresponding to approximately 80,000 annual cases , 30,000 deaths in the US , and 5 million cases worldwide . CT scanning is widely available and is the most commonly used diagnostic tool in patients with ICH . Clinicians utilize CT to define the location of bleeding, clinically assess severity, and plan patient management.

Despite robust correlation of cerebral location and functional performance in normal humans, location of ICH surpisingly is not an important factor in predicting severity of injury or prognosis . Furthermore, recent clinical trials do not demonstrate an important role for location as a factor associated with beneficial clinical outcome .

## Problems with Visual Inspection

The classification of hemorrhage location is complicated for even the best-trained neuroimage scientists. For example, a hemorrhage may extend into multiple brain areas, distend tissues altering anatomic relationships, and may break through the ventricular wall. Evaluating these anatomic possibilities challenges even the best clinicians, thus routine practice identifies a single location as the primary affected anatomic region (e.g. caudate, putamen, etc.) or describes the location of the edge of the hemorrhage in relation to a given landmark . Outcome is strongly associated with hemorrhage volume; importantly, the modulation of the relationship between volume and location has not been studied. To investigate these anatomic issues, detailed localization information can be obtained by registering scans to a common template to provide refined anatomical localization information.

## Previous CT Registration Work

Registration to template space is a crucial first step for any across-patient analysis; this allows each patient’s scan to be located in the same stereotaxic space so information may be combined spatially across scans. Moreover, brain atlases with spatially-defined anatomic structures are available in template space. Recently, released the first publicly available CT template of healthy adults in MNI (Montreal Neurological Institute) space. We propose to utilize CT images from patients enrolled in our clinical trials which have been acquired in a standardized manner via the MISTIE (Minimally Invasive Surgery plus recombinant-tissue plasminogen activator (rtPA) for Intracerebral Evacuation) trial protocol and register them to template space. This design provides a simple registration of the reference and template images in a single imaging modality as opposed to more complex referencing systems .

## Hypothesis

We propose to use CT images from the MISTIE and ICES (Intraoperative CT-Guided Endoscopic Surgery) trials to investigate the benefit or lack thereof in utilizing anatomic location as a biologically plausible predictor of ICH severity. Thus, we propose to test the hypothesis that routine clinical anatomic localization was no different than quantitative localization derived from registered-to-template images with atlas-based labeling for prediction of severity of injury.

# Materials and Methods

To address this hypothesis, we will 1) create a 3-dimensional (3D) density map of hemorrhages occurring in a population of patients with ICH; 2) provide detailed quantification of hemorrhage engagement of individual neuroanatomic regions within the brain; 3) determine if differences in location relate to two common disability scores: the National Institutes of Health Stroke Scale (NIHSS) and the modified Glasgow Coma Scale (GCS) ; and 4) generate a stroke region of engagement that is likely to be associated with stroke severity as well as test its predictive performance using within-sample validation.

All statistical analysis was done in the R statistical programming language (<http://cran.r-project.org/>).

## Subjects and Demographics

The population studied consists of 111 patients from MISTIE recruited from 26 centers. For inclusion criteria, see . CT and clinical data were collected as part of the Johns Hopkins Medicine IRB-approved MISTIE research studies with written consent from participants.

The NIHSS and GCS scores were recorded at enrollment; patients did not have a recorded NIHSS score, patient did not have a recorded GCS score. These patients were excluded from the analyses associating NIHSS and GCS scores and location, respectively. All patients were included in the construction of the 3D histogram image. Descriptive demographic of age, sex, race, baseline ICH and IVH volume, and NIHSS and GCS scores are shown in Table [t:dem]. The NIHSS score reflects stroke-related impairment (higher is worse), while the GCS score reflects a patient’s level of consciousness (higher is better).

[Table [t:dem] here.]

## Imaging Data

The study protocol was executed with minor, but important, differences across the 26 sites. Scans were acquired using GE (), Siemens (), Philips (), and Toshiba () scanners. Gantry tilt was observed in 87 scans. Slice thickness of the image varied within the scan for 14 scans, referred to as variable slice thickness. For example, a scan may have 10 millimeter (mm) slices at the top and bottom of the brain, where no hematoma is present, but with 5mm slices in the middle where the hematoma is seen (see Supplemental Figure [f:reg]). Therefore, the scans analyzed had different voxel (volume element) dimensions and image resolution prior to registration to the template. These conditions represent how scans are presented for evaluation in many diagnostic cases.

## Hemorrhage Segmentation and Location Identification

ICH was manually segmented on CT scans using the OsiriX imaging software by expert readers (OsiriX v. 4.1, Pixmeo; Geneva, Switzerland). Readers employed a semiautomated threshold-based approach using a Hounsfield unit (HU) range of to to select potential regions of ICH ; these regions were then further quality controlled and refined by readers using direct inspection of images. Readers identified the specific anatomic location most engaged by the ICH (Table [t:dem]).

## Image Registration

The DICOM (Digital Imaging and Communications in Medicine) data was preprocessed to obtain a 3D brain image (see Supplemental Section [sec:processing] for details). The image was then spatially registered to the CT template using the Clinical toolbox , which employs the unified normalization-segmentation routine from the statistical parametric mapping (version 8, SPM8, Wellcome Trust Centre for Neuroimaging, London, United Kingdom) software in MATLAB (The Mathworks, Natick, Massachusetts, USA). The binary hemorrhage mask was transformed into the template space.

## Assessing Registration

Determining the quality of registration was determined by visual inspection by expert CT readers. Visual inspection is subjective, but currently no automatic computer-based gold standard exists for assessing registration results nor agreed-upon standards for assessing registration quality in scans with large deformations of tissue as in patients with ICH.

No scans were excluded due to inadequate registration.

## Histograms of ICH in the Brain

To visualize and describe the localization of ICH, we first combined information from registered masks of 111 patients. Using these ICH masks, we obtained the -dimensional (3D) histogram of ICH localization for the study population. More precisely, for every voxel in the template space, we calculated the proportion of patients who have an ICH at that particular voxel. We used the R package brainR to create an 3D interactive map of the 3D histogram . The interactive map is located at <http://muschellij2.github.io/CT_Pipeline/index.html>.

## Prediction of Severity Score Based on Hemorrhage Location

In the study population, 1045174 voxels had at least one patient with ICH. We limited our analysis to voxels in the template space where at least 10 patients exhibit ICH (166202 voxels) to optimize the models for a substantial proportion of the population. We tested the association between hemorrhage location and stroke severity as measured by the NIHSS score and GCS score running a series of models, accounting for confounders. At each voxel, we ran a linear regression model:

$\label{eq:nihss\_regression}
{\rm Y}\_i=\beta\_0+\beta\_1(v) {\rm ICH}\_i(v)+ \gamma X\_i + \epsilon\_{i}(v),$

where ${\rm Y}\_i$ was either the NIHSS or GCS score for patient , ${\rm ICH}\_i(v)$ is a binary indicator where ${\rm ICH}\_i(v) = 1$ if patient ’s ICH mask has a at voxel , and ${\rm ICH}\_i(v) = 0$ otherwise. is a vector of patient-specific confounders with effects and are assumed independent homoscedastic errors. The confounders, , either were excluded for “unadjusted” voxel-level model, or contains a combination of patient-specific confounders: age, sex, and total baseline ICH volume (TotalVol) in the “adjusted” models. We used the unadjusted Wilcoxon rank-sum test on at every voxel to confirm that results are robust to the choice of test statistic.

P-values of each voxel-wise model were calculated, testing the null hypothesis , or in the case of the Wilcoxon rank-sum test: where denotes the distribution of severity scores of patients. Figure [f:mods] displays the voxel-wise p-values from NIHSS score models (see Supplemental Figure [f:gcsmods] for GCS). The p-value images displayed were not corrected for multiple comparisons since the purpose is investigate regional brain anatomy where ICH engagement could relate to severity score.

We did investigate whether individual locations are predictive of severity score after accounting for multiple comparisons using a Bonferonni correction with a family wise error rate of . At this stringent level no location was found to be significantly associated with the scores.

### Highest Predictive Region Generation and Analysis

Although no voxel passed this strict correction, voxels with low p-values indicate candidate regions which may improve prediction of severity scores. In order to create a patient-level covariate that summarizes ICH location information, we created a sequence of nested regions of interest by selecting voxels based on the smallest p-values obtained from the undadjusted linear model, i.e. from a model where only the voxel-level ICH indicator was used, but no other covariates. We call these regions “highest predictive regions” (HPR) because they contain the locations of those voxels that are most predictive of the severity scores. We obtained different HPR, based on the smallest , , or lowest p-values and three based on p-values thresholds of , , and . For each HPR, we calculated the HPR “coverage" which represents the percentage of the voxels in the HPR that were classified as hemorrhage in the subject-specific image: $\text{Coverage}\_i = \frac{\text{\# Voxels classified ICH in HPR for scan } i}{\text{\# Voxels in HPR}} \times 100\% \nonumber$ For example, if a patient’s ICH covers the entire HPR, the coverage is , whereas if there is no overlap between the patient’s ICH and HPR then coverage is 0%. This subject-specific covariate is then used as a predictor of the severity score in the adjusted model:

${\rm Y}\_i = \beta\_0 + \beta\_1 {\rm Coverage}\_i + \gamma\_1{\rm Age}\_i +\gamma\_2{\rm Gender}\_i +\gamma\_3{\rm TotalVol}\_i + \epsilon\_{i} \label{eq:cov}$

We compared model  to one using a categorical indicator of the expert-specified ICH location, with categories: Thalamus (), Globus Pallidus (), Putamen (), and Lobar (). Prediction performance and model fit were assessed using , adjusted , Akaike information criterion (AIC) , and root mean squared error (RMSE).

## ICH Localization and Engagement

[sec:engage] Although prediction of severity score is of interest, standard practice conveys information based on known neuroanatomic regions. We automatically calculated spatial ICH engagement by neuroanatomic region using brain atlases with defined segmentations. We used the “Eve" atlas , which segments gray matter (GM) and white matter (WM) regions. Ventricular regions were not explicitly segmented; any region not classified as GM or WM were classified as cerebrospinal fluid (CSF).

From this atlas, we estimated for each patient scan: 1) the percent of the ICH engaged by region and 2) the percent of each region engaged by the ICH (see Supplemental Section [sec:calcperc] for further details). These summaries of ICH engagement provide a much finer description of location than what can currently be done by expert human readers. For example, instead of classifying a region as a putaminal bleed, we may indicate that an ICH engages 78% of the putamen. We did not directly compare reader-classified regions and the most-engaged region classified by the atlas, as the atlas labels do not directly map to the reader-classified categories.

We further summarized neuroanatomic engagement at the population level (see Supplemental Section [sec:calcperc] for details).

# Results

## Histograms of ICH in the Brain

The non-spatial distribution of the prevalence of hemorrhages over all voxels (Figure [fig:StrokeHist]) shows the majority of voxels have a low prevalence of ICH engagement; the median number of patients with ICH at a given voxel is 3 (3%), though a small group of voxels () have a high prevalence of of the sample population. Figure [fig:StrokeHist] represents the 3D histogram of hemorrhage prevalence, where colors represent the percentage of patients with ICH engagement at that given area. This image indicates that ICH is distributed medially in the brain in this cohort, with a lower concentration at the cortical surface and higher on the left side of the brain. Figure [fig:StrokeHist] also indicates that the prevalence of strokes in the extreme anterior and posterior areas of the brain are very low. These observation may be a result of the inclusion criteria, but the inclusion criteria did not specifically prefer some spatial locations over others.

Overall, population maps such as these provide location information, allow researchers to sharpen their hypotheses about ICH location, and allow for such hypotheses to be tested. While this 3D histogram may not generalize to other populations, it will be crucial to obtain such maps for other studies and compare the degree of similarity to ours.

[Figure [fig:StrokeHist] here.]

Combining areas of engagement from the left and right sides of the brain may be worthwhile, though combination of these areas may not be straightforward for those by ICH that cross the mid-sagittal plane.

## Prediction of Functional Score Based on Hemorrhage Location

To study the association between localization and stroke severity scores, we have fit model ([eq:nihssregression]) using a sequence of potential confounding adjustments. More precisely, the five voxel-wise linear models fit were:

rll & $ {\rm Y}\_i =$ &

$\beta\_0+\beta\_1(v) {\rm ICH}\_i(v) + \epsilon\_{i}(v), $ & $ {\rm Y}\_i = $ &

$ \beta\_0+\beta\_1(v) {\rm ICH}\_i(v) + \gamma\_1(v){\rm Age}\_i + \epsilon\_{i}(v), $ & $ {\rm Y}\_i = $ &

$ \beta\_0+\beta\_1(v) {\rm ICH}\_i(v) + \gamma\_2(v){\rm Gender}\_i + \epsilon\_{i}(v), $ &$ {\rm Y}\_i = $ &

$ \beta\_0+\beta\_1(v) {\rm ICH}\_i(v) + \gamma\_3(v){\rm TotalVol}\_i + \epsilon\_{i}(v),$ &$ {\rm Y}\_i = $ &

$ \beta\_0+\beta\_1(v) {\rm ICH}\_i(v) + \gamma\_1(v){\rm Age}\_i +\gamma\_2(v){\rm Gender}\_i +\gamma\_3(v){\rm TotalVol}\_i + \epsilon\_{i}(v),$

where denotes a model. For consistency of notation (as it is not an explicit model) we will refer to Wilcoxon rank-sum test as .

No voxels were significantly related to NIHSS score or GCS score in any model after using the Bonferroni correction. The p-values from the models, with NIHSS score as the outcome, are presented in Figure [f:mods], overlaid on a MRI T1 image for spatial localization of structures ( and are not shown, and appear similar to Figure [f:mods]).

The estimated association of location and NIHSS can easily be visualized by comparing the relative location of high and low p-values. Figure [f:mods] indicates that the strongest associations are clustered together in the immediate vicinity of the medial plane both for the GCS (Supplemental Figure [f:gcsmods]) and NIHSS scores. The p-values are higher (more blue) in the models adjusted for age (not shown), baseline ICH volume (not shown), and both age and baseline ICH volume (Figure [f:mods]) compared to the unadjusted model .

[Figure [f:mods] here.]

### Highest Predictive Region Analysis

Inspired by the inspection of Figure [f:mods], we investigated whether we can define areas of the brain that can improve prediction of stroke severity scores. To investigate this, have obtained 6 different HPR, 3 based on the smallest , , and p-values and three based on all p-values below a particular threshold. We used three thresholds: , , and , corresponding to HPR with , , and voxels, respectively, for NIHSS and , , and voxels for GCS, respectively. For illustration, panel () in Figure [f:roi] displays the region obtained by choosing all the p-values smaller than in the unadjusted NIHSS regression on voxel location. Panel () in Figure [f:roi] displays the region obtained by retaining only the smallest p-values for the unadjusted regression of GCS score on ICH location. Although we show three orthographic slices for each HPR, the entire regions are available in MNI coordinates.

While the voxel-wise p-values identify areas that are potentially highly associated with the outcome, we want to reduce the complex HPR to a simple subject-specific covariate, HPR coverage. Panel  of Figure [f:roi] displays the NIHSS score (y-axis) as a function of the coverage of the HPR from Figure [f:roi]. Similarly, Panel  of Figure [f:roi] displays the GCS score as a function of the coverage of the HPR in Figure [f:roi] of Figure [f:roi]. The blue line represents a non-parametric LOESS fit to estimate the relationship between severity and coverage, the red line represents an unadjusted linear model fit. As expected, the larger the HPR coverage the higher (more severe stroke) the NIHSS score and the lower (deeper unconsciousness) the GCS score.

[Figure [f:roi] here.]

We further investigated how these regions perform compared to an ICH location classification provided by expert readers. Table [t:allres] compares prediction performance based on the expert readers location (labeled “Location model”) and the same models using HPR coverage for NIHSS and GCS scores. Prediction performance is measured primarily using the adjusted R$^2$, though conclusions were the same using R$^2$, AIC, and RMSE. We conclude that all HPR coverage models strongly outperform reader-classified location models. Indeed, for NIHSS, the adjusted almost doubled from for the reader-classified location model compared to for the best HPR coverage model. For GCS, the adjusted more than tripled from for the reader-classified location model to for the HPR coverage model. The other HPR coverage models provide relatively similar prediction performance. This indicates that the choice of one HPR versus another may need to be based on other criteria, such as total HPR volume, ICH population prevalence, and prior biological information. The coefficients for the best HPR and location models can be seen in Supplemental Table [f:beta].

[Table [t:allres] here.]

### ICH Localization and Engagement

Table [t:breakdown] represents the 10 most-engaged regions for the population 3D histogram as well as the HPR for the GCS and NIHSS score analyses. The population ICH is engaged primarily in areas of the CSF, such as the ventricles, the insular, and putaminal regions. The HPR based on the NIHSS analysis engages primarily areas of the internal capsule and ventricular regions. The HPR based on the GCS analysis engages primarily the left thalamus and superior corona radiata.

[Table [t:breakdown] here.]

Though Table [t:breakdown] represents the empirical regions most engaged, engagement by specified regions is commonly of interest. We calculated the engagement of the thalamus, putamen and globus pallidus by the population 3D histogram and the HPR for the GCS and NIHSS score analyses (Supplemental Table [t:areabreakdown]). The population engagement represents the mean proportion of the population with ICH engagement for that brain region. The HPR columns represent the percent of voxels in that brain region that are in the HPR from NIHSS and GCS scores. On average, 23% of the putamen, 20% of the globus pallidus, and 8% of the thalmus are engaged with ICH from patients in this study. The HPR from the NIHSS analysis engages 40% of the globus pallidus, 6% of the putamen, and 9% of the thalamus. The HPR from the GCS analysis engages only 2% of the thalamus, but not the putamen nor the globus pallidus; the GCS HPR again is only 1000 voxels. All engagement is higher on the left side compared to the right.

# Discussion

## Semi-Automated Localization of ICH

We have characterized the localization of ICH in a population of stroke patients by a 3D histogram of a population with ICH from prospective clinical trials. We found, in this study, more patients had ICH engagement on the left side of the brain and both left and right sided ICHs are located towards the middle of the brain. We can use this process to create a 3D histogram based on different studies or subgroups of this population. As the values in the 3D histogram represent proportions, these images can then be used to test differences between the groups using standard proportion tests. This process allows us to directly compare ICH location in 2 groups at a finer scale than currently available.

Moreover, the pipeline described is semi-automated allowing for more reproducible and objective analyses. The only non-automated steps in our pipeline are the ICH segmentation and the export of ICH masks from OsiriX.

## Voxel-wise Analysis of Severity Scores

Voxel-wise hypothesis tests were performed using linear models and Wilcoxon rank-sum tests for NIHSS and GCS scores. The resulting p-values from these tests indicate that ICH at locations near the ventricles may be related to severity scores.

None of the voxels passed the stringent Bonferonni correction due to the large number of voxels being tested. As each voxel is not independent of the other voxels as ICH is commonly a contiguous region of hemorrhage, this correction is inappropriate. Other methods that attempt to account of the smoothness properties, such as random field theory, may be more powerful.

These maps allow us to explore the relationship of ICH location and severity scores, which can be used for hypothesis generation and testing. More importantly, these maps can be used as a potential diagnostic clinical marker or guide surgical interventions. In addition, we have shown the voxel-wise p-values provide a voxel screening procedure to generate a HPR for patient-level analysis.

## Highest Predictive Region Analysis

The HPR analysis rejects our hypothesis that routine clinical anatomic localization was no different than quantitative localization derived from registered-to-template images with atlas-based labeling for prediction of severity of injury. Although prediction performance was quite low even for the best models, prediction performance doubled or tripled, depending on the severity score. These measures showed demonstrable gains over using the reader-based categories commonly used in analysis.

This analysis focused on NIHSS and GCS scores as these were available at enrollment, but the process may be applied to long-term functional scores. As these populations had groups with different interventions, we aimed to analyze outcomes that were prior to any separation of the groups induced by the intervention. This procedure can be used for any patient outcome, such as the modified Rankin scale score at long-term followup visits.

## Estimation of ICH Engagement with Neuroanatomic Regions

Although 3D spatial maps are worthwhile for viewing, many clinicians want description of location in terms of known neuroanatomic regions. We demonstrate how a segmented atlas (Eve) can be used to automatically describe ICH engagement by neuroanatomic regions at a patient or population level. These measures are more interpretable for clinical relevance and may translate to better determination of disability. Additionally, these measures can be used to objectively compare different groups or populations without the requiring expert readers to determine ICH engagement.

## Conclusion

The summaries of ICH engagement presented provide a much finer description of location than currently done by expert human readers. We also have shown that using image-based measurements can substantially better predict severity scores compared to using location determined by experts.

## Limitations

Although this set of patients represent a large proportion (%) of the entire population () of the MISTIE and ICES trials, the sample size is relatively small. The framework does not impose a restriction on the number of patients to be processed; it is extendable to much larger populations with thousands of patients.

The current description of hemorrhages and all subsequent analyses are reliant on one specific registration technique. It is probably desirable to try multiple registration approaches and compare results across registrations.

One of the problems with the HPR is that they are obtained by using the data twice: once to find the voxels that are most associated with the outcome and the second time to obtain the region by selecting (screening) the voxels with the smallest p-values. Cross-validation can be used for internal validation and consists of splitting the data into a training group used to generate the HPR and a testing group to estimate model performance. Another approach is to externally validate by studying the performance of the HPR on a subset of the MISTIE and ICES patients not analyzed here. We will investigate external validation in our future studies.

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# Tables

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|  |  |
| --- | --- |
| **Variable (N = 111)** | **N (%) or Mean (SD)** |
| Age in Years: Mean (SD) | 60.8 (11.2) |
| Gender: Female | 35 (31.5%) |
| NIHSS Score: Mean (SD) | 22.1 (8.7) |
| GCS Score: Mean (SD) | 10.0 (3.0) |
| ICH Volume: Mean (SD) | 37.4 (20.1) |
| IVH Volume: Mean (SD) | 3.2 (6.3) |
| Race |  |
| Caucasian not Hispanic | 59 (53.2%) |
| African American not Hispanic | 35 (31.5%) |
| Hispanic | 12 (10.8%) |
| Asian or Pacific Islander | 5 (4.5%) |
| Reader-Classified ICH Location |  |
| Putamen | 68 (61.3%) |
| Lobar | 33 (29.7%) |
| Globus Pallidus | 6 (5.4%) |
| Thalamus | 4 (3.6%) |

[t:dem]

[H]

rr|cccc & **P-value** & **Adjusted R$^2$** & **R$^2$** & **AIC** & **RMSELocation Model & & 0.129 & 0.178 & 18.60 & 8.1161000 & .0005 & 0.236 & 0.265 & 2.47 & 7.5982000 & .0009 & 0.234 & 0.263 & 2.81 & 7.6102422 & .0010 & 0.247 & 0.275 & 0.98 & 7.5453000 & .0013 & 0.244 & 0.272 & 1.46 & 7.56219047 & .0100 & 0.254 & 0.282 & 0.00 & 7.51147736 & .0500 & 0.248 & 0.276 & 0.77 & 7.538Location Model & & 0.069 & 0.120 & 20.51 & 2.9141000 & .0002 & 0.214 & 0.243 & 0.00 & 2.6772000 & .0004 & 0.213 & 0.242 & 0.09 & 2.6783000 & .0006 & 0.212 & 0.241 & 0.25 & 2.6804669 & .0010 & 0.212 & 0.241 & 0.23 & 2.68022858 & .0100 & 0.191 & 0.221 & 3.17 & 2.71652368 & .0500 & 0.166 & 0.197 & 6.44 & 2.757**

[t:allres]

[ht]

|  |  |  |  |
| --- | --- | --- | --- |
| Area | Population Prevalence | NIHSS HPR | GCS HPR |
| CSF | 7.9 | 10.9 | 4.2 |
| Insular | 7.6 |  |  |
| Superior temporal gyrus | 5.5 |  |  |
| Putamen | 4.8 | 4.3 |  |
| External capsule | 3.9 |  |  |
| Superior corona radiata | 3.7 | 11.0 | 27.9 |
| Precentral gyrus | 3.3 |  |  |
| Precentral WM | 3.1 |  | 1.3 |
| Superior temporal WM | 3.1 |  |  |
| Posterior limb of internal capsule | 3.0 | 12.0 | 3.9 |
| Thalamus |  | 10.1 | 33.9 |
| Caudate nucleus |  | 8.4 | 9.6 |
| Anterior limb of internal capsule |  | 6.8 |  |
| Globus pallidus |  | 6.0 |  |
| Superior longitudinal fasciculus |  | 4.5 | 5.9 |
| Outside brain mask |  | 3.6 |  |
| Postcentral WM |  |  | 6.7 |
| Posterior corona radiata |  |  | 3.1 |
| Supramarginal WM |  |  | 1.1 |

[t:breakdown]

# Figure Legends

[H]

[fig:StrokeHist]

[H]

[f:mods]

[H]

[f:roi]

# Supplemental Material

## Image Processing: Brain Extraction, Reorientation, Registration

[sec:processing] To register the CT scan to the CT template, the hemorrhage was excluded from the algorithm, i.e. “masked out”, using manual ICH segmentations. Binary image masks were created for the hemorrhage ROI by setting voxel intensity to if the voxel was classified as hemorrhage, and otherwise.

CT images were processed as follows:

1. Export from OsiriX to DICOM format
2. Gantry tilt corrected (if applicable) using a customized MATLAB user-written script (<http://bit.ly/1ltIM8c>)
3. Converted to the Neuroimaging Informatics Technology Initiative (NIfTI) data format using dcm2nii (2009 version, provided with MRIcro )
4. The brain extraction tool (BET) , a function of the FSL neuroimaging software (v5.0.4) extracted a brain image.
5. The data was aligned to the anterior-posterior commissure line (<http://bit.ly/1gUqMDw>) from the brain image.
6. The Clinical toolbox was applied.

An image with its brain-extracted counterpart can be seen in Supplemental Figure [f:reg].

We thresholded the smoothed hemorrhage mask: let be the smoothed image mask for person , and denotes voxel of that mask; let represents voxel for person of the thresholded image. The was thresholded using the rule : These binary ICH masks were used in analysis.

## Calculating Region Engagement from the Eve Atlas

[sec:calcperc] We also calculated the percent engagement of regions for the best-performing HPR for the NIHSS and GCS score analyses to characterize potential locations relating to these functional outcomes. More explicitly, let denote the brain region (e.g. Putamen) and let represent the sum of the voxels for an image (HPR or population ICH image) in that brain region. These represent the percent that brain region engages the ICH compared to other regions (Table [t:breakdown]): We have also calculated how much a brain region is engaged with the population ICH or HPR images (Table [t:areabreakdown]): These percentages () are at a region level rather than the , which are at an image level.

## Image Registration Results

To illustrate registration results, we present Figure [f:reg]: manually segmented blood in the original space with the hemorrhage mask in pink (panel ), this image after skull stripping (panel ), the registered image and hemorrhage mask in template space (panel ), and the ICH mask on the template (panel ). These images represent one patient with variable slice thickness with a large hemorrhage. Though variable slice thickness is present, the transformation morphs the image into the full space of the template; therefore, non-linear registration seems to reasonably account for variable slice thickness, most likely by non-uniform scaling. We also see gross brain features remain relatively unchanged, but large deformations of tissue, mainly due to ICH, appear well preserved by registration.

[Figure [f:reg] here.]

## Figures

[H] [f:reg]

[H]

[f:gcsmods]

## Tables

[!htbp]

@l@c@c|@c@c& && **HPR Coverage** & **Reader-Based** & **HPR Coverage** & **Reader-Based**Age & 0.04 (0.2, 0.1) & 0.1 (0.2, 0.1) & 0.02 (0.03, 0.1) & 0.02 (0.03, 0.1)Sex: Male vs. Female & 0.7 (3.8, 2.4) & 1.7 (5.0, 1.7) & 0.03 (1.1, 1.1) & 0.1 (1.1, 1.3)TICHVol per 10 cc & 0.8$^{}$ (0.003, 1.5) & 1.6$^{}$ (0.8, 2.4) & 0.2$^{}$ (0.5, 0.02) & 0.5$^{}$ (0.7, 0.2)HPR Coverage per 10% & 2.0$^{}$ (1.1, 2.8) & & 0.4$^{}$ (0.6, 0.2) &Reader-Based Location&&&&Globus Pallidus & & 4.5 (2.9, 11.9) & & 1.8 (4.5, 0.8)Putamen & & 4.2$^{}$ (0.3, 8.2) & & 1.2$^{}$ (2.6, 0.2)Thalamus & & 4.8 (4.1, 13.6) & & 1.0 (4.2, 2.1)Constant & 18.8$^{}$ (9.1, 28.4) & 19.6$^{}$ (7.5, 31.7) & 10.6$^{}$ (7.4, 13.7) & 11.2$^{}$ (6.9, 15.5)

[f:beta]

[ht]

|  |  |  |  |
| --- | --- | --- | --- |
| Area | Population Engagement | NIHSS HPR | GCS HPR |
| Globus Pallidus: Total | 20.3 | 40.0 | 0.0 |
| Globus Pallidus: Right | 14.8 | 34.8 | 0.0 |
| Globus Pallidus: Left | 25.2 | 44.7 | 0.0 |
| Putamen: Total | 23.3 | 6.6 | 0.0 |
| Putamen: Right | 17.5 | 3.8 | 0.0 |
| Putamen: Left | 29.2 | 9.4 | 0.0 |
| Thalamus: Total | 7.9 | 8.9 | 1.7 |
| Thalamus: Right | 6.8 | 3.1 | 0.0 |
| Thalamus: Left | 9.1 | 14.6 | 3.4 |

[t:areabreakdown]