Image-based Stroke Assessment for Multi-site Preclinical Evaluation of Cerebroprotectants

Ryan P. Cabeen1, Joseph Mandeville2, Fahmeed Hyder3,4, Basavaraju G. Sanganahalli4, Daniel R. Thedens5, Ali Arbab6, Shuning Huang7, Adnan Bibic8, Erendiz Tarakci1, Jelena Mihailovic3, Andreia Morais9, Jessica Lamb11, Karisma Nagarkatti11, Marco A. Dinitz12, Andre Rogatko12, Arthur W. Toga1, Patrick Lyden10,11, and Cenk Ayata9

1Laboratory of Neuro Imaging, USC Mark and Mary Stevens Imaging and Informatics Institute, Keck School of Medicine of USC; Los Angeles, CA USA, 2Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, and Harvard Medical School, Charlestown, Massachusetts, USA, 3Departments of Biomedical Engineering, 4Departments of Radiology and Biomedical Imaging, Yale University, New Haven, CT USA, 5Carver College of Medicine, and Department of Epidemiology, University of Iowa, 6Medical College of Georgia, Augusta University, Augusta, GA, USA, 7Department of Diagnostic and Interventional Imaging, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, 8Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University; Baltimore, MD USA, 9Department of Radiology, Department of Neurology, Harvard Medical School, Massachusetts General Hospital, Charlestown, MA, United States, 10Department of Neurology, 11Department of Physiology and Neuroscience, Zilkha Neurogenetic Institute, Keck School of Medicine at USC; Los Angeles, CA USA 12Biostatistics and Bioinformatics Research Center, Samuel Oschin Comprehensive Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, United States. *Corresponding author: rcabeen@loni.usc.edu

Abstract. Ischemic stroke is a leading cause of death worldwide, but there has been little success translating putative cerebroprotectants from preclinical trials to patients. We investigated computational image-based assessment tools for practical improvement of the quality, scalability, and outlook for large scale preclinical screening for potential therapeutic interventions. We developed, evaluated, and deployed a pipeline for image-based stroke outcome quantification for the Stroke Preclinical Assessment Network (SPAN), which is a multi-site, multi-arm, multi-stage study evaluating a suite of cerebroprotectant interventions. Our fully automated pipeline combines state-of-the-art algorithmic and data analytic approaches to assess stroke outcomes from multi-parameter MRI data collected longitudinally from a rodent model of middle cerebral artery occlusion (MCAO), including measures of infarct volume, brain atrophy, midline shift, and data quality. We tested our approach with 1,368 scans and report population level results of lesion extent and longitudinal changes from injury. We validated our system by comparison with manual annotations of coronal MRI slices and tissue sections from the same brain, using crowdsourcing from blinded stroke experts from...
the network. Our results demonstrate the efficacy and robustness of our image-based stroke assessments. The pipeline may provide a promising resource for ongoing preclinical studies conducted by SPAN and other networks in the future.

**Keywords**: stroke · preclinical MRI · quantitative imaging · neuroinformatics · machine learning · rodent model · multi-site · longitudinal

1 Introduction

Stroke is a leading cause of death and disability worldwide. Ischemic stroke occurs when a cerebral blood vessel is blocked, and hemorrhagic stroke occurs when a cerebral vessel ruptures, leading to mortality or long-term deficits such as sensory impairment, paralysis, and difficulty walking, speaking, or understanding [18]. Hundreds of proposed stroke treatments have been tested in clinical trials, often with support from preclinical data from animal models [19]; however, there have been few successful translations of putative cerebroprotectants to patients [3]. While a variety of new candidate treatments have emerged, technical and procedural challenges that contributed to the failures of preclinical translation persist, particularly the lack of reliability and reproducibility [2]. Several ways to address these challenges include: a multi-site network approach with large sample sizes, central randomization and blinding, strict adherence to standard operating procedures (SOPs), and employing state-of-the-art imaging and data analytic tools [7] [5]. These solutions are within reach but require substantial planning, coordination, cooperation, and technical development, as well as funding.

This paper describes the development of a fully automated image analysis pipeline for the Stroke Preclinical Assessment Network (SPAN) [20], which is an effort to meet these emerging preclinical study needs. SPAN is funded by the National Institutes of Neurological Disorders and Stroke (NINDS) and was created to address critical issues of rigor, transparency, and reproducibility. The network includes six research universities and a coordinating center (CC) who manage enrollment of animals, experimental stroke, and blinded and randomized treatment with several candidate cerebroprotectants. Data are uploaded from each site to a centralized repository alongside the CC, processed and analyzed in a blinded fashion, and disseminated to the CC and statistics team. The study started with a pilot phase which defined SOPs for data collection across sites, and now involves multiple stages which progressively refine the set of candidate treatments. SPAN examines both behavioral and tissue readouts of stroke outcome, and we focus here on the tissue readouts obtained from magnetic resonance imaging (MRI).

Most published preclinical studies of putative cerebroprotectants measure tissue-based outcomes with triphenyltetrazolium chloride (TTC) stained brain sections [11] [8]; however, this approach has several major weaknesses, i.e. morphometric changes with tissue handling, variation in preparation and staining intensity across labs, availability at only a single time point, limited options for
subsequent tissue analysis, and high inter-rater variability [14]. MRI is a promising alternative to adopt in large scale preclinical trials because (i) it has a direct translational path to human diagnostic imaging with multiple biologically and clinically relevant readouts, (ii) it can be repeated longitudinally in the same animal and readily standardized across sites, and (iii) preserves brain morphology. A variety of algorithms have been proposed for MRI-based stroke lesion delineation, including [24], deformable models [10], artificial neural networks [15], semi-automated threshold-based procedure [23], atlas registration [17], convolutional deep neural networks [27] [9]. These works demonstrate the feasibility and potential value of MRI in preclinical stroke studies, but an important next step is to build computational imaging tools that meet the emerging needs to scale up for preclinical stroke network imaging studies outlined above.

Towards this goal, we developed a fully automated pipeline for image-based stroke assessment for SPAN that is designed for robust processing and continuous reporting of data from multiple time points after injury at multiple imaging centers working in conjunction to evaluate putative cerebroprotectants. Our work builds on previous computational imaging efforts with several notable differences. First, we focus on providing a robust end-to-end solution that includes a suite of metrics beyond just lesion volume, including measures of brain atrophy, ventricular volume, and indices of midline shift. Second, our approach was developed to robustly handle multi-site data, including steps for parameter harmonization and robust segmentation. Third, the scale of the data tested here is beyond any previous preclinical MRI study of ischemic stroke (N = 1,368). Lastly, we provide the validation of our approach with blinded and randomized human labeling of TTC tissue staining, as well an additional experiment validating against from human labeling of MRI sections. In the following sections, we describe the design, implementation, and optimization of our system, present basic outcomes from the analysis, and report the results of evaluation experiments.

2 Methods

This section focuses on the design and implementation of our image analysis pipeline (Fig. 1), which was created primarily with the Quantitative Imaging Toolkit (QIT) [6], with image registration performed using ANTs [1], and R 4.1.0 for plotting and statistical analysis. The pipeline includes steps for image acquisition, preprocessing, quality assessment, harmonization, brain and lesion segmentation, midline shift quantification, and analytic reporting, and the details are described as follows.

**Imaging protocol and data collection:** Data were collected from a mouse model with experimental middle cerebral artery occlusion (MCAO) at day 2 and day 30 after injury. With respective ethics approval, imaging was performed across six imaging centers on Bruker scanners with variable field strengths including 7T, 9.4T, 11.7T, with one site using a surface coil and all others using a volume coil. The multi-parameter imaging protocol included multi-echo T2, and diffusion-weighted MRI (DWI), which were collected at 150 \( \mu \text{m}^2 \) coronal in-plane...
resolution and 500 μm slice thickness. All sites used three b-values for DWI (0, 500, 1000 s/mm²) and the T2 protocol used either three echoes (0, 45, 75 ms) or ten echoes (equally spaced from 0 to 100 ms). 100 mice were scanned in an initial pilot phase of SPAN to establish SOPs. Following this, SPAN Stage One proceeded to acquire MRI data from 780 animals with a total of 1,368 scanning session, accounting for mortality after injury. All data were routinely uploaded by each site in the DICOM format to the LONI Image Database Archive [12] for long term storage and analytics.

**Pre-processing and quality assessment:** While the sequences are similar across sites, there are subtle differences in the image data structure that we first reconcile by parsing DICOM tags, sorting by imaging parameters, fixing image coordinates, converting using dcm2nii, and finally producing a set of matching NIfTI files for each case. We applied adaptive non-local means denoising [22] with voxelwise noise estimation, and to account for differences in image grids between scans, we also uniformly resample the images at 150 μm isotropic resolution using tricubic interpolation. We then perform image quality assessment for each modality by first segmenting foreground and background using Otsu thresholding and computing the signal-to-noise ratio, contrast-to-noise ratio, and signal variance-to-noise variance ratio. We then performed relaxometry to derive quantitative parameter maps, which included a signal baseline and rate of decay for the multi-echo T2 scan (T2{\text{base}} and T2{\text{rate}}) and DWI (ADC{\text{base}} and ADC{\text{rate}}) scans (Figs. 2.A1,2.A2) For simplicity of presentation, we report all T2{\text{rate}} values as the inverse relaxation rate (R2).

**Brain segmentation and spatial normalization:** We performed brain extraction using a deep learning neural network approach with a U-net architecture (Fig. 2.A3) implemented in PyTorch [25] similar to several previous rodent imaging studies [16] [13]. We bootstrapped our model using a semi-automated conventional brain extraction approach applied to the ADC{\text{base}} (because it showed the least lesion contrast); this process involved edge-preserving smoothing, gradient computation, thresholding, and morphological operations to isolate the brain. We selected training examples from 180 cases and hold-out testing and
validation examples from 30 cases; each was split roughly evenly between imaging centers and time points. Our network took all four parameter maps as input (128x128x4 resolution), used a kernel size of 64 and a batch size of 20, and included albulmentations-based data augmentation for translation, rotation, scaling, contrast, and deformations [4]. We trained a single 2D U-nets with data from each image plan, and then at inference time, we applied the model to each image slice direction and computed the average prediction. We trained for 10 epochs on an Nvidia 1080 Ti 12GB GPU for two hours and ten minutes. Following this, we performed linear registration of each case to the MBAT mouse brain atlas [21] using the R2\text{rate} parameter map.

Harmonization and lesion segmentation: We found that image parameters differed significantly across sites (Figs. 2.B1, 2.B3), likely due to variety in imaging hardware and physiological factors, so we performed global intensity harmonization of each individual scan (Figs. 2.B2, 2.B4). We used a simple procedure which computed a smoothed histogram of the intensity distribution within the brain mask, identified the peak value (the mode), and then scaled the entire image by that value to bring the most likely value to one. We chose the mode, as opposed to the mean, because it is less affected by distributional skew due to the presence of lesion. We then performed lesion segmentation using a multiple threshold image processing approach applied to these harmonized parameters (Fig. 2.B4). We first defined an initial lesion map by applying an inverted sigmoidal soft threshold of 0.8 to the R2\text{rate} map and a threshold of 1.5 to the ADC\text{rate} map. We applied a median smoothing filter to regularize the lesion map, and we then applied a hysteresis threshold to extract a lesion mask, with a strong threshold of 0.55 and a weak threshold of 0.45. We then performed a morphological opening operation to refine the mask and reduce spurious voxel labels. We then applied an atlas-defined restriction mask to exclude lesion labels on the contralateral side to injury. We applied a similar procedure to segment cerebrospinal fluid (CSF) with a R2\text{rate} threshold of 0.75 and ADC\text{rate} threshold of 1.25 (not inverted). Hence, we identified lesion as areas with both dark T2 and ADC, and CSF as areas with dark R2 and bright ADC. We then took the remainder of the brain to be a third segment for “normal appearing tissue”. This thresholding approach was jointly chosen by the network’s imaging team with the strict goal of having an interpretable and understandable lesion definition, which is why we chose not to use a black-box neural network approach as in the brain segmentation step.

Midline shift quantification: We estimated a variety of metrics reflecting midline shift, including the raw lateral displacement, a normalized index of shift, and ratio of ipsilesional and contralesional hemisphere volume. We first estimated the anatomical midpoint based on ventricular geometry. We used an atlas-defined restriction mask to select voxels from the lateral and third ventricles in a coronal section (seven voxels thick) located roughly at the midpoint of the corpus callosum in the anterior-posterior direction. The midpoint was estimated from the average 3D position of CSF segmented in the previous step. We then defined a surface that splits the left and right hemispheres based on this
estimated midpoint. For this, we fit an implicit quadratic surface based on points located at the inferior, superior, left, right, anterior, and posterior extremes of the individual brain of the case being analyzed. The surface was fit such that the left and right points were one and negative one and all other points lay on the surface with value zero. We then created volumetric masks labeling the left and right hemispheres based on this surface (Fig. 2B4). From this, we computed the absolute midline shift from the difference between the estimated midline and the theoretical typical midline from the atlas. We also computed a normalized midline shift index from the ratio of the absolute shift over the width of the brain, as well as left and right hemisphere volumes and their lateralization index.

**Analytic reporting and network feedback:** The final step in the pipeline creates reports summarizing these outcome measures across the study cohort. This included 3D visualizations (Figs. 2A.5, 2A.6) and mosaic plots showing a matrix of coronal sections with segmentation masks superimposed, which provides a rapid way to view multiple subjects within the network and perform additional quality assurance. We also created data tables which are shared with the statistics team within the network on a periodic basis. These are used for providing biweekly feedback to sites about lesion outcomes and whether they are within the expected range, and they are also used at the end of each stage to determine which treatments meet futility criteria and should be excluded for subsequent stages. Data was processed at the USC Neuro Imaging Computing Center (NICC) using a 4096 core Sun Grid Engine computing environment.

3 Results and Discussion

In this section, we present results from our initial steps to refine our pipeline, the primary outcomes from analysis of SPAN Stage One, and the results from validating our automated lesion segmentation measures in comparison to manual traces of MRI sections and TTC stained tissue sections.

**System refinement and testing:** In the SPAN pilot phase, we also acquired RARE and T2-star MRI, but these were excluded in subsequent phases because the former was redundant with the multi-echo T2 scan and the latter was too severely degraded by susceptibility induced geometric distortion. In training our brain segmentation network, our final model had a Dice score of 0.964 on the hold-out test dataset. We found that T2 parameters had greater inter-site variability than ADC; however, both modalities required harmonization for fully automated lesion segmentation (Fig. 2B.2, 2B.4). We found that several sites had image artifact due to the MCAO catheter and also the imaging hardware; these were sometimes misclassified as lesion, but because they were anatomically consistent, they were simply excluded by adjusting the lesion restriction mask. We experimented with a range of lesion and CSF thresholds within ±0.05 of our chosen thresholds, and the results were robust to these minor changes. We analyzed a total of 1,368 scans from SPAN Stage One, and among these there were 20 cases excluded, including one due to file transfer is-
sues, six due to missing scans, and 13 due to excessive motion. A final count of 1,348 scans passed QC with an analytics completion rate of 98.5%.

The average time to completely process an individual case was one hour and 48 minutes.

**Group-level analysis of lesion extent and longitudinal changes:** We performed a preliminary analysis of the primary outcomes from the SPAN Stage One data. We computed distributional statistics of total brain volume, lesion volume, midline shift, and atrophy in aggregate and split by site (Figs. 2.C, 2.D). We also computed lesion probability maps for the entire cohort and split by site; these were visualized on sectional anatomy of the atlas and also as 3D surface renderings (Figs. 2.A.5, 2.A.6). We then examined longitudinal changes in outcome measures by comparing day 2 lesion volume to day 30 atrophy (both whole brain and split by hemisphere). The results indicate that there exists a small but consistent differences in apparent total brain volume by site ($F_{5,1347} = 264.4$, $p < 10^{-15}$), which suggests that per-site corrections should be included in statistical models. We found the sites had some variability in lesion volume, but the anatomical location of lesion was consistent across sites. The average lesion volume was $32.26 \text{ mm}^3$. With site as a covariate, we found that day 2 volume was highly predictive of hemispheric atrophy on the side ipsilateral to the injury at day 30 ($R^2 = 0.73$, $\beta = -0.34$, $p < 10^{-15}$; Fig. 2.D.1), while there was no significant effect contralateral to injury at day 30 ($R^2 = 0.57$, $\beta = -0.01$, $p = 0.23$; Fig. 2.D.2). This supports the general understanding that MCAO leads to localized tissue atrophy, and it supports the notion that the pipeline is able to measure both lesion and lateralized atrophy with high fidelity.

**Validation with manual tracing of MRI sections:** We performed an initial validation experiment to determine the accuracy of our lesion segmentation. We first selected ten typical day 2 scans with a range of lesion sizes from SPAN pilot data. Two stroke experts from the SPAN network were recruited to estimate lesion volume from manually delineated coronal sections of the $R2_{rate}$ parameter map using ImageJ. All ten cases were analyzed by both raters, and they were...
blinded to the results of our pipeline. The same ten cases were subsequently processed with our pipeline without manual intervention to obtain the lesion volume for comparison in each case. We compared the human raters and the automated approach by computing descriptive statistics, the root-mean-square error (RMSE), and Pearson’s correlation coefficient. We found the average lesion volume from manual raters was 11.56 mL and from the automated approach was 11.38 mL. The RMSE error between the two human raters was 2.22 mL, and the RMSE error between the humans and automated approach was 2.99 mL. The correlation between the human raters was 0.969 and that between the humans and automated approach was 0.957. The results indicate that the automated approach recovered similar lesion estimates as human raters, and difference in performance was practically the same as between humans.

Validation with manual tracing of TTC stained sections: We performed a subsequent validation experiment to address whether the MRI-derived lesion metrics reflect tissue-level changes as observed using the standard approach of TTC stained sections (Fig. 2A7). For this, 37 mice were randomly selected, treated with MCAO, and imaged at day 2. But unlike others enrolled in the study, these cases were sacrificed immediately after imaging and their brains were subsequently sectioned in 2 mm thick slices, stained with TTC, photographed on slides (front and back), and the images were shared with the imaging team. The cases were split among the sites to ensure the TTC stains were representative of the variation in the greater stroke field. This resulted in a total of 746 individual images, and we chose a total of six annotators (one from each site) to provide at least two annotation for each image. Due to the scale and logistics of the task, we built an online web-based annotation system based on LabelMe [26] to allow annotations to be performed remotely without installing any software. We modified LabelMe to use a restricted set of drawing operations, to anonymize the images and raters, to enable deployment across multiple isolated servers for each rater, and to provide instructions to label the brain, lesion, and any other relevant features. Once collected, we computed the lesion volume fraction from the ratio of the total lesion area over the total brain surface area. The MRI data from these 37 were processed like the other cases without manual intervention, and the lesion volume fraction was computed similarly. We estimated the reliability among human-TTC raters using the coefficient of variation (CoV = σ / μ) and measured Pearson’s correlation coefficient between the human-TTC and automated-MRI lesion volume fractions. We found human-TTC raters to be highly reliable in delineating the brain (CoV = 2.50%); however, lesion segmentations had greater variability (CoV = 18.5%). Given this, we also selected a subgroup of “high-reliability” TTC cases (N= 24 cases with CoV < 5%). The overall Pearson correlation between the automated-MRI volume fraction and the human-TTC was 0.743, and for the “high-reliability” cases, the correlation was 0.865. The results generally indicate the substantial agreement between lesion quantification gathered from both TTC tissue and automated MRI analysis. TTC staining is considered the gold-standard technique
for stroke preclinical imaging, but even so, inter-rater variability in several cases demonstrated potential limitations as well.

**Conclusions:** We developed, evaluated, and deployed a pipeline for image-based stroke outcome quantification for SPAN that combines state-of-the-art algorithmic and data analytic approaches to assess stroke outcomes from preclinical multi-parameter MRI data collected longitudinally from a rodent model of middle cerebral artery occlusion (MCAO), including measures of lesion extent, brain atrophy, midline shift, and data quality. We tested our approach with the largest preclinical cohort of mice to date and rigorously evaluated the validity of our approach with expert manual annotations of MRI and TTC-stained sections from the same specimens. Our results suggest the efficacy and robustness of our image-based stroke assessments. The opportunities ahead include increasing the imaging resolution, inclusion of additional modalities for detecting hemorrhage and water content, combined analysis with behavioral readouts, and expansion to rats, female, aged, and obese specimens. Our pipeline may provide a promising resource for ongoing preclinical studies conducted by SPAN and others in the future.

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