Stroke Lesions in a Large Upper Limb Rehabilitation Trial Cohort Rarely Match Lesions in Common Preclinical Models

Matthew A. Edwardson, *Georgetown University*
Ximing Wang, *University of Southern California*
Brent Liu, *University of Southern California*
Li Ding, *University of Southern California*
Christianne Lane, *University of Southern California*
Caron Park, *University of Southern California*
Monica A. Nelsen, *University of Southern California*
Theresa A. Jones, *University of Texas Austin*
Steven L Wolf, *Emory University*
Carolee J. Winstein, *University of Southern California*

Only first 10 authors above; see publication for full author list.

Stroke Lesions in a Large Upper Limb Rehabilitation Trial Cohort Rarely Match Lesions in Common Preclinical Models

Matthew A. Edwardson, MD[1,2], **Ximing Wang, MS**[3], **Brent Liu, PhD**[3], **Li Ding, MD**[4], **Christianne J. Lane, PhD**[4], **Caron Park, MS**[4], **Monica A. Nelsen, DPT**[5], **Theresa A Jones, PhD**[6,7], **Steven L Wolf, PhD**[8,9], **Carolee J Winstein, PhD**[5,10], and **Alexander W. Dromerick, MD**[2,1,11]

[1]Georgetown University, Department of Neurology, Washington, DC, USA

[2]Center for Brain Plasticity and Research, Department of Rehabilitation Medicine, Georgetown University and MedStar National Rehabilitation Hospital, Washington, DC, USA

[3]University of Southern California, Department of Biomedical Engineering, Los Angeles, CA, USA

[4]University of Southern California, Keck School of Medicine, Department of Preventive Medicine, Division of Biostatistics, Los Angeles, USA

[5]University of Southern California, Division of Biokinesiology and Physical Therapy, Herman Ostrow School of Dentistry, Los Angeles, USA

[6]Department of Psychology, University of Texas at Austin , Austin, Texas

[7]Institute for Neuroscience, University of Texas at Austin , Austin, Texas

[8]Emory University School of Medicine, Emory Rehabilitation Hospital, Division of Physical Therapy, Departments of Rehabilitation Medicine, Medicine and Cell Biology, Atlanta, GA, USA

[9]VA Center on Visual and Neurocognitive Rehabilitation, Decatur, GA, USA

[10]University of Southern California, Department of Neurology, Keck School of Medicine, Los Angeles, CA

[11]VA Medical Center, Washington, DC

Abstract

Background—Stroke patients with mild-moderate upper extremity (UE) motor impairments and minimal sensory and cognitive deficits provide a useful model to study recovery and improve rehabilitation. Laboratory-based investigators use lesioning techniques for similar goals.

Objective—Determine whether stroke lesions in an UE rehabilitation trial cohort match lesions from the preclinical stroke recovery models used to drive translational research.

Methods—Clinical neuroimages from 297 participants enrolled in the Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE) study were reviewed. Images were characterized based on lesion type (ischemic or hemorrhagic), volume, vascular territory, depth

Corresponding Author: Matthew A. Edwardson, Department of Neurology, Georgetown University, 4000 Reservoir Rd. NW, Building D Room 207, Washington, DC, USA. Phone: (202) 687-2184; Fax: (202) 687-7378; mae97@georgetown.edu.

(cortical gray matter, cortical white matter, subcortical), old strokes, and leukoaraiosis. Lesions were compared with those of preclinical stroke models commonly used to study upper limb recovery.

Results—Among the ischemic stroke participants, median infarct volume was 1.8 mL, with most lesions confined to subcortical structures (61%) including the anterior choroidal artery territory (30%) and the pons (23%). Of ICARE participants, <1 % had lesions resembling proximal MCA or surface vessel occlusion models. Preclinical models of subcortical white matter injury best resembled the ICARE population (33%). Intracranial hemorrhage participants had small (median 12.5 mL) lesions that best matched the capsular hematoma preclinical model.

Conclusions—ICARE subjects are not representative of all stroke patients, but they represent a clinically and scientifically important subgroup. Compared to lesions in general stroke populations and widely-studied animal models of recovery, ICARE participants had smaller, more subcortically-based strokes. Improved preclinical-clinical translational efforts may require better alignment of lesions between preclinical and human stroke recovery models.

Introduction

Motor rehabilitation investigators typically select participants based on neurological impairments, not stroke lesion characteristics[1,2]. These investigators typically enroll stroke patients with mild-moderate hemiparesis and few other neurologic deficits; this subgroup represents about 2–6% of the general stroke population[2–4]. This reductionist approach of focusing on UE motor impairment decreases heterogeneity and thus increases statistical power and precision. Investigators have identified these individuals as being particularly promising for motor recovery interventions, and likely to provide useful mechanistic information.

Investigators studying preclinical stroke recovery also focus on motor impairment, but in addition strive to create lesions that are highly reproducible with regard to size and location. The most studied ischemic stroke models include focal cortical injury with photocoagulation[5–7] or injection of vasoconstricting substances[8,9] and middle cerebral artery occlusion (MCAO)[10,11]. The most common intracranial hemorrhage (ICH) model[12–18] produces hematomas in the striatum. Lesions in these preclinical models do not align perfectly with the general stroke population[19], but do capture some of the main stroke syndromes. For example, half of all strokes in the general population are in the MCA territory[20–22], and MCAO models helped lead to successful development of acute therapies for stroke[23,24]. What remains unclear is how well the lesions in these preclinical models mimic the lesions in participants recruited into stroke motor recovery trials. Major lesion differences between preclinical and clinical motor recovery studies could potentially hinder translational efforts.

There is a longstanding but unproven theory that lesion location and size are determinants of recovery and response to rehabilitation therapy[25]. Evidence in support of this theory comes from recent stroke recovery studies in humans suggesting that deep white matter lesions affecting the corticospinal tract (CST) cause much of the hemiparesis following stroke[26,27]. This evidence was somewhat corroborated by neuroimaging data from patients with lower extremity weakness enrolled in a recent multicenter trial that showed high rates of lacunar infarction[28]. Lesion size may affect motor outcome in those with subcortical stroke[29]. It follows that if lesion size and location are truly important for recovery, then lesion differences between clinical trial samples and animal models may lead to discordant findings and impair translational efforts.

The stroke lesion attributes from large multicenter trials of upper extremity (UE) motor recovery have never previously been characterized, possibly because of the cost and complexity of adding research-quality imaging to Phase 3 rehabilitation trials. We developed a method to overcome this challenge by using images obtained during routine clinical care to characterize the stroke lesions in participants enrolled in the Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE) study. We then matched the stroke lesions from participants in ICARE to the animal stroke models most commonly used to study motor recovery of the upper limb. We theorized that a population selected for primarily motor impairments and few cognitive deficits would have small stroke lesions largely confined to subcortical locations, and therefore, not align well with common preclinical models of motor recovery.

Methods

Participants

Clinical post-stroke neuroimages from participants prospectively enrolled in ICARE were collected and analyzed retrospectively. ICARE was a multi-center, single-blind, controlled trial which randomized participants with mild stroke and moderate upper extremity impairment to one of three outpatient rehabilitation therapy programs at 14–106 days post-stroke[3]. The study was approved by the Institutional Review Board at each site and all participants provided written informed consent. The ICARE population was 56% male and 42% African-American; mean age was 60.7 years, with a mean UE Fugl-Meyer score 42/66 (range 19–58) and a mean NIH Stroke Scale Score 3.6 (SD 1.8). All had some ability to release a grasp on the affected side and no significant neglect, aphasia or other cognitive impairments. The ICARE participants were representative of participants enrolled into other upper limb rehabilitation trials based on severity of upper extremity impairment and exclusion of cognitive deficits[2,4,30]. The primary outcome measure was the change in the log-transformed Wolf Motor Function Test (WMFT) time score 1 year post-randomization. Mean improvement in motor performance score was substantial (54%), but ICARE found no significant differences in the primary outcome measure between groups at 1 year[3].

Neuroimaging / Clinical Lesion Characterization

Participants were enrolled in ICARE from 7 rehabilitation hospitals in the greater metropolitan area of Los Angeles, Atlanta, and the District of Columbia; these participants

came from 55 acute care hospitals. Images were uploaded into the ICARE Neuroimaging Viewer[31], a custom web-based system allowing the user to view multiple imaging sequences, draw regions of interest (ROIs), calculate lesion volumes, overlay lesion location templates (see below), and store lesion characteristics in an electronic database. Lesion characterization was performed by 2 vascular neurologists, ME who read all scans and AD who independently read 25 randomly chosen scans for interrater reliability. One imaging study was analyzed for each participant. Ischemic stroke lesions were identified on diffusion weighted imaging (DWI) if 7 days from stroke onset, fluid-attenuated inversion recovery (FLAIR) if > 7 days, or CT when DWI or FLAIR was unavailable. Primary intracerebral hemorrhages (ICH) were identified on CT; gradient echo (GRE) sequences were used when CT was not available. Lesion volume was estimated using the ABC/2 method[32] and by manually drawing ROIs on each axial slice to determine planimetric volume. Intraventricular hemorrhage was not included in ICH volume determinations. Stroke lesions were characterized as involving the cortical gray matter (1st 2–4 mm along the cortical surface), cortical white matter (deep to cortical gray matter, superficial to basal ganglia), subcortical region, or a combination of these structures. Due to the heterogeneity of imaging studies, including the need for the same method to characterize both MRI and CT, lesion location analysis was performed using templates established for CT localization[33,34]. The templates were slightly modified to combine smaller template subdivisions into larger divisions and to include the basilar and vertebral artery vascular territories in the posterior circulation using MIPAV software and anatomical maps[35] (see supplementary figs 1–5 online http:// nnr.sagepub.com/content/by/supplemental-data). Figure 1 provides a description of template analysis procedures. The predominant area was chosen to reflect the template subdivision located in the 3-dimensional center of the stroke lesion. To further localize posterior circulation lesions, we determined whether lesions were centered in the midbrain, pons, medulla, cerebellar hemisphere, or cerebellar vermis. Old strokes > 1 cm in diameter were identified on FLAIR or CT. Leukoaraiosis severity was determined using the age-related white matter changes (ARWMC) scale[36]. To capture typical vascular neurology nomenclature, clinical vascular territory analysis was also performed separate from the template localization only for the ischemic strokes.

Preclinical Model Comparisons

To estimate the percentage of the ICARE population reflected by preclinical ischemic stroke models, we selected the preclinical models most commonly used to study upper limb recovery. For ischemic stroke, this entailed selection of models from all forelimb training studies in a recent meta-analysis[37] with the exception of the temporary MCAO models[38,39]. The wide variability in lesion size in temporary MCAO models depending on occlusion time did not facilitate direct comparisons with our clinical population. For ICH, we included models from all of the studies in a recent meta-analysis[40] that assessed forelimb recovery and measured hematoma volumes 3 days after stroke. In addition to the preclinical models included from the meta-analyses above, we added subcortical ischemic[41–45] and hemorrhagic[46] stroke models that create lesions localized to subcortical areas controlling the forelimb. These capsular stroke models were mostly developed later than the models in the above cited meta-analyses and were felt to be particularly relevant given the large percentage of subcortical strokes discovered in the ICARE population. All preclinical studies used for

comparison, including the capsular models, were of intermediate or high quality according to the methods of Schmidt and colleagues[37].

We then matched the preclinical and clinical lesions based on relative size and location. For lesion size comparisons, total MCA infarct volume in humans was estimated at 300 mL[47]. The total hemispheric brain volume was estimated at 200 cubic mm[48] for mice, 500 cubic mm[49] for rats and 600 cubic cm[50] for humans. Relative lesion size in the mouse and rat were therefore estimated at 1/3000 and 5/6000 the lesion size in humans respectively. Location comparisons were performed as follows. Because preclinical models using electrocautery of surface vessels produce isolated cortical gray matter infarction[51], they were matched to the number of ICARE participants with isolated cortical gray matter lesions. Although there is some heterogeneity in lesion size depending on technique, preclinical models that cause focal injury to sensorimotor cortex via injection of vasoconstricting substances[52,53] or photocoagulation[54,55] most often create a large cortical lesion that spares subcortical structures; they were matched to the number of participants with both cortical gray and cortical white matter injury. To match the lesions from animal models causing focal ischemia to the subcortical white matter controlling the forelimb[41–45] we chose the number of participants with stroke confined to subcortical structures that also overlap the anterior choroidal subtemplate area, which contains the motor fibers passing through the posterior limb of the internal capsule (PLIC). For ICH, the most widely used model – injection of collagenase into the striatum[12–18] – was compared to the number of ICH participants with hematomas centered in the lenticulostriate region. The lesser used ICH model of collagenase injection into the internal capsule[46] was compared with the number of ICH participants with hematomas centered in the anterior choroidal template region.

Statistical Analysis

Means and standard deviations for normally distributed continuous variables, and median and interquartile ranges for non-normally distributed continuous variables were computed. The percentages described in lesion comparisons are descriptive in nature. Interrater reliability was assessed using the Weighted Kappa statistic for the categorical variables, and Spearman's correlation and Bland-Altman limits of agreement for continuous variables. Weighted Kappa calculations were performed using R version 3.1.2; all other analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Eighty-two percent of the ICARE participants had interpretable neuroimaging with stroke lesions identified. Two hundred fifty-eight ischemic strokes (186 DWI / 53 CT / 19 FLAIR) and 39 primary ICHs (31 CT / 8 GRE) were analyzed. Median infarct volume was small for both the ischemic stroke (1.8 mL) and ICH (12.5 mL) participants. Lacunar infarcts made up 46% of the ischemic stroke population based on a strict definition for which the stroke diameter could not exceed 20 mm in axial diameter[56]. There was high correlation between the two raters for planimetric volume (Spearman = 0.98, P <0.001), template predominant area (K = 0.98) and clinical vascular territory (K = 0.95). Figure 2 shows the predominant area incidence map, representing the percentage of ischemic stroke and ICH participants

with lesions centered in each of the template subdivisions. For the ischemic stroke participants, lesions were centered in the anterior choroidal (35%), basilar (25%), MCA (22%), ACA (7%), lenticulostriate (3%), insular branch (3%), vertebral (2%), thalamoperforating (2%), and PCA (1%) template subdivisions; most of the posterior circulation lesions were in the pons (84%). For the ICH participants, lesions were centered in the anterior choroidal (46%), thalamoperforating (26%), lenticulostriate (13%), basilar (5%), ACA (5%), MCA (3%), and insular branch (3%) template subdivisions.

We used lesion size and location data (tables 1&2) to estimate the percentage of ischemic stroke and ICH participants that align with various preclinical stroke models (table 3). With regard to lesion size, only 1 participant had a stroke lesion approaching the volume of a complete MCA infarct (Fig 3). The median volume for ischemic stroke in the ICARE human cohort corresponds to a 0.8 mm^3 lesion in the mouse and a 1.5 mm^3 lesion in the rat; the median ICH volume corresponds to a 4.2 mm^3 lesion in the mouse and a 10.4 mm^3 lesion in the rat. For frame of reference, preclinical ICH volume from the control groups of the 7 striatal models[12–18] and the capsular model[46] was 21 mm^3 and 7.1 mm^3 respectively (note that all of these studies were in rats).

For ischemic stroke lesion location, only 1 participant had a lesion confined to the cortical gray matter, suggesting that models employing electrocautery of surface vessels[51] reflect < 1% of the ICARE population. Two preclinical models that have come into widespread use in recovery studies, photocoagulation[5–7] or endothelin-1 injection[8,9] to sensorimotor cortex, capture a modest subset of the ICARE population - 40 participants (16%). Preclinical models that inject vasocontricting agents or target photocoagulation at the subcortical white matter controlling the forelimb[41–45] best reflected the ICARE cohort. This subcortical stroke model would capture 85 of the ICARE participants (33%). For ICH location, the striatum injection model[12–18] reflected 13% of the ICARE population, whereas the lesser used capsular injection model[46] matched 46% of the ICARE sample. In summary, more recent subcortical models of ischemic and hemorrhagic stroke best matched our clinical trial population with regard to lesion size and location.

Discussion

The relationships between brain lesion characteristics, recovery, and response to rehabilitation intervention remain controversial. One path towards resolution of the controversies is to study both animal and human models of stroke recovery, often in analogous interspecies studies[57]. This approach may be strengthened by aligning the models as much as possible to resolve whether lesion location, size, timing and other variables are determinants of recovery or treatment response. Since many clinical investigators choose to study stroke patients with relatively isolated UE motor impairments, we asked to what extent the lesions in this human sample resemble and differ from the animal models. We argue that this information is useful in translating the results of preclinical modeling into human studies, and to translate results from clinical trials back to the bench. To the extent that lesion location and size drive mammalian brain recovery and response to rehabilitation, misaligned animal and human models risk yielding incorrect or imprecise translation of findings between species. Should future studies show that lesion location and size do not

drive clinical stroke recovery, then preclinical investigators interested in studying motor recovery can simply focus on motor phenotype with less regard for lesion characteristics.

First, while differences in lesion characteristics between this mild-moderately impaired subgroup from the general stroke population were expected, the extent of these differences is striking. Compared to the general stroke population, lesion volume was much smaller for both ischemic stroke (1.8 mL vs. 9–35 mL)[58,59] and ICH (12.5 mL vs. 27 mL)[60,61] participants. There was a higher percentage of lacunar infarction than typically seen in general stroke samples, (46% vs. 13–25%)[20,62,63]. Most of the strokes in ICARE were subcortical, and there was approximately half the incidence of MCA stroke reported in population-based studies (31% vs. 45–65%)[20–22]. ICARE participants had a much higher incidence of ischemic stroke in the anterior choroidal artery territory (30% vs. 2–8%)[64–66] and the pons (23% vs. 5–11%)[20,21,65,67], which corroborates reports that strokes causing motor impairment commonly overlap the CST[26,27]. Note that there is a large literature of prior studies not cited above assessing lesion volumes in general stroke populations[32,68–72], but methodological concerns hindered proper comparison to our patient cohort. Though these prior studies all showed larger stroke volumes than the lesions seen in ICARE, they had inclusion / exclusion criteria that would select for larger or smaller strokes and were therefore not true population-based samples. Our findings demonstrate that participants recruited into upper extremity motor rehabilitation trials are markedly different with respect to lesion size and location than those in true general stroke populations, skewed toward those with small subcortical infarcts.

Second, we found that the lesions in the ICARE population rarely resembled the most common preclinical stroke models. Thus, to the extent that lesion location and size matter, animal model-based generalization about mammalian motor recovery may not apply to the typical human candidates currently enrolled in UE motor recovery intervention trials. Permanent MCAO in rodents creates lesions that are proportionally orders of magnitude larger than the majority of the lesions seen in ICARE participants[10,11]. Models employing more focal lesions, such as the classic motor plasticity studies in squirrel monkeys[51] or photocoagulation of sensorimotor cortex in rodents[5–7], are the right size; however, unlike the strokes in ICARE, the lesions are primarily confined to the cortex. For ICH, the striatum injection model typically creates hematomas that are larger and more anterolateral than those typical for ICARE participants[12–18]. The discrepancies in infarct size and location described above may have significant consequences, similar to those discussed in the current STAIR committee guidelines, which outline methods to improve preclinical stroke studies in an effort to improve translation[19].

If lesion characteristics drive recovery and response to therapies, then more effort to converge the clinical trial samples and animal models would be needed. One approach could be to devote greater efforts to developing subcortical preclinical stroke models – particularly those targeting white matter tracts that control the forelimb. This important endeavor has begun[73]. A rodent model of anterior choroidal artery infarction exists[74], but is complicated by variable infarct size and concurrent hypothalamic injury. The structures supplied by the anterior choroidal artery in humans include the medial temporal lobe, posterior putamen, PLIC, lateral thalamus, periventricular tail of the caudate nucleus, optic radiations, lateral

geniculate nucleus, and the cerebral peduncle[64]. Injecting vasoconstricting agents[41,42] or targeting photocoagulation[43,45] directly at structures supplied by the anterior choroidal artery that contain the white matter tracts controlling the forelimb such as the PLIC may be the most straightforward approach to recreating ICARE-like ischemic stroke lesions in animals. There is also a preclinical model for ICH that targets the internal capsule[46]. This capsular injection model in the rat produces motor weakness with hematoma volumes (~10 mm^3) similar to the relative lesion volume in the ICARE cohort and may therefore be preferred over the striatal model for testing motor rehabilitation strategies.

In developing these subcortical models, differences in brain and behavior between rodents and humans must be considered. Rodent brains contain 15% white matter by volume compared to 50% for humans[75]. In addition, rodents do not rely on the CST to control skilled forelimb movements, but rather the corticoreticulospinal tract (CRST) which runs parallel to the CST through the internal capsule[76,77]. Capsular rodent models therefore explore a different cellular environment with behavioral measures that reflect disynaptic (CRST) rather than monosynaptic (CST) control pathways. As a result, subcortical models may require either larger lesions by volume or more sensitive measures of motor function to effectively study motor recovery. One might argue that creating pure lesions of the motor tracts more distal to the PLIC, such as with pyramidotomy[78] might effectively mimic the lesions seen in ICARE. We do not favor this approach, however, because brain ischemia itself induces endogenous repair mechanisms[79] that might be lost with such a model.

Other preclinical models also warrant consideration. Temporary MCAO models could capture a significant fraction of the lesions in our clinical trial population. Direct comparison between published studies and the ICARE cohort was made difficult, however, by the wide variability in lesion size depending on occlusion time. For ICARE, 31% of our participants had MCA strokes. Temporary MCAO models would not capture this entire fraction, however, because this technique does not create the small cortical lesions that one sees with distal MCA strokes in humans. Short occlusion times for temporary MCAO may best match the relative lesion volumes from the ICARE sample. We also acknowledge that other preclinical stroke models that do not represent a large proportion of lesions in rehabilitation trial participants remain important for studying particular aspects of motor recovery physiology. For example, cortical lesioning in squirrel monkeys[80] and the mouse[81] led to evidence of vicarious function in other cortical areas following recovery from injury. There may be cases, therefore, where preclinical investigators wish to closely match a clinical trial sample and others where motor physiology is the primary concern.

As an alternative to turning toward subcortical preclinical models, clinical rehabilitation investigators could instead perform trials that enroll participants with lesions that more closely resemble those found in the most common preclinical models. Preclinical models of MCAO eventually proved quite valuable in the general stroke population as evidenced by the remarkable efficacy shown in endovascular trials[23,82]. Yet most large recovery trials in humans to date failed to show any improvement in the primary outcome measure when compared to usual and customary care[3,83,84]. While some have argued these failures were a result of insufficient dose or timing of therapy[85], perhaps recruitment of participants with infarct characteristics matching those of the supporting preclinical studies would allow the

gains shown in preclinical models to be realized in humans. Developing clinical rehabilitation trials based on preclinical studies is challenging, but can be accomplished by mitigating some of the limitations inherent in studying human participants[57]. In this case, the challenge of selecting study participants by stroke lesions would need to be offset by enrolling persons with a wider range and combination of neurological impairments than is current practice. New outcome measures would need to be developed along with alternative statistical methods that embrace the multidimensional nature of rehabilitation and recovery[86].

Finally, while rigorous and detailed lesion data about stroke rehabilitation trial samples would be ideal to characterize the stroke lesions that lead to motor impairment, such data are not always necessary or feasible to collect. Additionally, there are few, if any high-quality large sample human imaging databases that include detailed motor outcomes to inform stroke rehabilitation researchers. We demonstrated a new method for stroke lesion characterization, using vascular territory templates overlaid on routinely ordered clinical images that may be adequate for studies in which research-quality MRI is unavailable or unnecessary. This method has the advantage of accommodating clinical neuroimaging obtained at different centers and times from stroke onset without adding significant study-related cost or complexity. There are, of course, limitations to this approach. In the current study, for example, we suspect ICARE participants had a high incidence of lesion overlap with the CST, but cannot carefully quantify this possibility without diffusion tensor tractography[27]. In addition, these templates may not be accurate for participants with large variation in ventricular size or displacement due to cerebral edema. On the other hand, few large stroke motor rehabilitation trials have attempted any lesion characterization, and our method provides a straightforward approach to usefully classify stroke lesion features.

Conclusions

Participants enrolled between 14 and 106 days after stroke in a large upper extremity motor restoration trial have a higher incidence of small, subcortical strokes than the general stroke population. These lesion characteristics only rarely resemble the lesions in the most common preclinical stroke models, which are either too large or too superficial. If future studies prove that lesion characteristics drive recovery and response to treatment then greater efforts will need to be made to match the stroke lesions in preclinical and clinical study populations, perhaps by further developing subcortical stroke models.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011; 10(2):123–130. [PubMed: 21216670]

2. Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006; 296(17):2095–2104. [PubMed: 17077374]

3. Winstein CJ, Wolf SL, Dromerick AW, et al. Effect of a Task-Oriented Rehabilitation Program on Upper Extremity Recovery Following Motor Stroke: The ICARE Randomized Clinical Trial. JAMA. 2016; 315(6):571–581. [PubMed: 26864411]

4. Dromerick AW, Lang CE, Birkenmeier RL, et al. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS): A single-center RCT. Neurology. 2009; 73(3):195–201. [PubMed: 19458319]

5. Diederich K, Quennet V, Bauer H, et al. Successful regeneration after experimental stroke by granulocyte-colony stimulating factor is not further enhanced by constraint-induced movement therapy either in concurrent or in sequential combination therapy. Stroke. 2012; 43(1):185–192. [PubMed: 22020031]

6. Muller HD, Hanumanthiah KM, Diederich K, Schwab S, Schabitz WR, Sommer C. Brain-derived neurotrophic factor but not forced arm use improves long-term outcome after photothrombotic stroke and transiently upregulates binding densities of excitatory glutamate receptors in the rat brain. Stroke. 2008; 39(3):1012–1021. [PubMed: 18239176]

7. Schabitz WR, Berger C, Kollmar R, et al. Effect of brain-derived neurotrophic factor treatment and forced arm use on functional motor recovery after small cortical ischemia. Stroke. 2004; 35(4):992–997. [PubMed: 14988579]

8. Fang PC, Barbay S, Plautz EJ, Hoover E, Strittmatter SM, Nudo RJ. Combination of NEP 1–40 treatment and motor training enhances behavioral recovery after a focal cortical infarct in rats. Stroke. 2010; 41(3):544–549. [PubMed: 20075346]

9. Maldonado MA, Allred RP, Felthauser EL, Jones TA. Motor skill training, but not voluntary exercise, improves skilled reaching after unilateral ischemic lesions of the sensorimotor cortex in rats. Neurorehabil Neural Repair. 2008; 22(3):250–261. [PubMed: 18073324]

10. Ploughman M, Attwood Z, White N, Dore JJ, Corbett D. Endurance exercise facilitates relearning of forelimb motor skill after focal ischemia. Eur J Neurosci. 2007; 25(11):3453–3460. [PubMed: 17553014]

11. Rasmussen RS, Overgaard K, Hildebrandt-Eriksen ES, Boysen G. D-amphetamine improves cognitive deficits and physical therapy promotes fine motor rehabilitation in a rat embolic stroke model. Acta Neurol Scand. 2006; 113(3):189–198. [PubMed: 16441250]

12. Chu K, Jeong SW, Jung KH, et al. Celecoxib induces functional recovery after intracerebral hemorrhage with reduction of brain edema and perihematomal cell death. J Cereb Blood Flow Metab. 2004; 24(8):926–933. [PubMed: 15362723]

13. Jung KH, Chu K, Jeong SW, et al. HMG-CoA reductase inhibitor, atorvastatin, promotes sensorimotor recovery, suppressing acute inflammatory reaction after experimental intracerebral hemorrhage. Stroke. 2004; 35(7):1744–1749. [PubMed: 15166393]

14. Jung KH, Chu K, Lee ST, et al. Blockade of AT1 receptor reduces apoptosis, inflammation, and oxidative stress in normotensive rats with intracerebral hemorrhage. J Pharmacol Exp Ther. 2007; 322(3):1051–1058. [PubMed: 17538008]

15. Lee ST, Chu K, Jung KH, et al. Memantine reduces hematoma expansion in experimental intracerebral hemorrhage, resulting in functional improvement. J Cereb Blood Flow Metab. 2006; 26(4):536–544. [PubMed: 16107786]

16. Lee ST, Chu K, Sinn DI, et al. Erythropoietin reduces perihematomal inflammation and cell death with eNOS and STAT3 activations in experimental intracerebral hemorrhage. J Neurochem. 2006; 96(6):1728–1739. [PubMed: 16539688]

17. Park HK, Chu K, Lee ST, et al. Granulocyte colony-stimulating factor induces sensorimotor recovery in intracerebral hemorrhage. Brain Res. 2005; 1041(2):125–131. [PubMed: 15829221]

18. Sinn DI, Lee ST, Chu K, et al. Combined neuroprotective effects of celecoxib and memantine in experimental intracerebral hemorrhage. Neurosci Lett. 2007; 411(3):238–242. [PubMed: 17123715]

19. Fisher M, Feuerstein G, Howells DW, et al. Update of the stroke therapy academic industry roundtable preclinical recommendations. Stroke. 2009; 40(6):2244–2250. [PubMed: 19246690]

20. Bogousslavsky J, Van Melle G, Regli F. The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. Stroke. 1988; 19(9):1083–1092. [PubMed: 3413804]

21. Chung JW, Park SH, Kim N, et al. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and vascular territory of ischemic stroke lesions diagnosed by diffusion-weighted imaging. J Am Heart Assoc. 2014; :3. Published Online Aug 11, 2014. doi: 10.1161/JAHA. 114.001119

22. Paciaroni M, Silvestrelli G, Caso V, et al. Neurovascular territory involved in different etiological subtypes of ischemic stroke in the Perugia Stroke Registry. Eur J Neurol. 2003; 10(4):361–365. [PubMed: 12823486]

23. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015; 372(1):11–20. [PubMed: 25517348]

24. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995; 333(24):1581–1587. [PubMed: 7477192]

25. Chen CL, Tang FT, Chen HS, Chung CY, Wong MK. Brain lesion size and location: Effects on motor recovery and functional outcome in stroke patients. Archives of Physical Medicine and Rehabilitation. 2000; 81(4):447–452. [PubMed: 10768534]

26. Byblow WD, Stinear CM, Barber PA, Petoe MA, Ackerley SJ. Proportional recovery after stroke depends on corticomotor integrity. Ann Neurol. 2015

27. Feng W, Wang J, Chhatbar PY, et al. Corticospinal tract lesion load: An imaging biomarker for stroke motor outcomes. Ann Neurol. 2015; 78(6):860–870. [PubMed: 26289123]

28. Nadeau SE, Dobkin B, Wu SS, Pei Q, Duncan PW, Team LI. The effects of stroke type, locus, and extent on long-term outcome of gait rehabilitation: the LEAPS experience. Neurorehabil Neural Repair. 2015; doi: 10.1177/1545968315613851

29. Prabhakaran S, Zarahn E, Riley C, et al. Inter-individual variability in the capacity for motor recovery after ischemic stroke. Neurorehabil Neural Repair. 2008; 22(1):64–71. [PubMed: 17687024]

30. Kwakkel G, Winters C, van Wegen EE, et al. Effects of Unilateral Upper Limb Training in Two Distinct Prognostic Groups Early After Stroke: The EXPLICIT-Stroke Randomized Clinical Trial. Neurorehabil Neural Repair. 2016; Published Online. doi: 10.1177/1545968315624784

31. Wang X, Liu BJ, Martinez C, Zhang X, Winstein CJ. Development of a novel imaging informatics-based system with an intelligent workflow engine (IWEIS) to support imaging-based clinical trials. Comput Biol Med. 2016; 69:261–269. [PubMed: 25870169]

32. Vogt G, Laage R, Shuaib A, Schneider A, Collaboration V. Initial lesion volume is an independent predictor of clinical stroke outcome at day 90: an analysis of the Virtual International Stroke Trials Archive (VISTA) database. Stroke. 2012; 43(5):1266–1272. [PubMed: 22403046]

33. Damasio, H., Damasio, AR. Lesion Analysis in Neuropsychology. New York, NY: Oxford University Press; 1989. p. 213-220.

34. Dromerick, AW., Morris, LB. Acute ischemic stroke lesions in humans: How do they compare to animal models used to study stroke recovery? [abstract]. Program No. 358.2. 2005 Neuroscience Meeting Planner; Washington, DC: Society for Neuroscience; 2005. Online

35. Tatu L, Moulin T, Vuillier F, Bogousslavsky J. Arterial territories of the human brain. Front Neurol Neurosci. 2012; 30:99–110. [PubMed: 22377874]

36. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke. 2001; 32(6):1318–1322. [PubMed: 11387493]

37. Schmidt A, Wellmann J, Schilling M, et al. Meta-analysis of the efficacy of different training strategies in animal models of ischemic stroke. Stroke. 2014; 45(1):239–247. [PubMed: 24178915]

38. Bland ST, Pillai RN, Aronowski J, Grotta JC, Schallert T. Early overuse and disuse of the affected forelimb after moderately severe intraluminal suture occlusion of the middle cerebral artery in rats. Behav Brain Res. 2001; 126(1–2):33–41. [PubMed: 11704249]

39. Bland ST, Schallert T, Strong R, Aronowski J, Grotta JC, Feeney DM. Early exclusive use of the affected forelimb after moderate transient focal ischemia in rats : functional and anatomic outcome. Stroke. 2000; 31(5):1144–1152. [PubMed: 10797179]

40. Frantzias J, Sena ES, Macleod MR, Al-Shahi Salman R. Treatment of intracerebral hemorrhage in animal models: meta-analysis. Ann Neurol. 2011; 69(2):389–399. [PubMed: 21387381]

41. Blasi F, Whalen MJ, Ayata C. Lasting pure-motor deficits after focal posterior internal capsule white-matter infarcts in rats. J Cereb Blood Flow Metab. 2015; 35(6):977–984. [PubMed: 25649992]

42. Frost SB, Barbay S, Mumert ML, Stowe AM, Nudo RJ. An animal model of capsular infarct: endothelin-1 injections in the rat. Behav Brain Res. 2006; 169(2):206–211. [PubMed: 16497394]

43. Kim HS, Kim D, Kim RG, et al. A rat model of photothrombotic capsular infarct with a marked motor deficit: a behavioral, histologic, and microPET study. J Cereb Blood Flow Metab. 2014; 34(4):683–689. [PubMed: 24473479]

44. Rosenzweig S, Carmichael ST. Age-dependent exacerbation of white matter stroke outcomes: a role for oxidative damage and inflammatory mediators. Stroke. 2013; 44(9):2579–2586. [PubMed: 23868277]

45. Song H, Park JY, Kim HS, Lee MC, Kim Y, Kim HI. Circumscribed capsular infarct modeling using a photothrombotic technique. J Vis Exp. 2016; (112)

46. Ishida A, Tamakoshi K, Hamakawa M, et al. Early onset of forced impaired forelimb use causes recovery of forelimb skilled motor function but no effect on gross sensory-motor function after capsular hemorrhage in rats. Behav Brain Res. 2011; 225(1):126–134. [PubMed: 21771615]

47. van der Zwan A, Hillen B, Tulleken CA, Dujovny M. A quantitative investigation of the variability of the major cerebral arterial territories. Stroke. 1993; 24(12):1951–1959. [PubMed: 8248978]

48. Kovacevic N, Henderson JT, Chan E, et al. A three-dimensional MRI atlas of the mouse brain with estimates of the average and variability. Cereb Cortex. 2005; 15(5):639–645. [PubMed: 15342433]

49. Tinsley CJ, Bennett GW, Mayhew TM, Parker TL. Stereological analysis of regional brain volumes and neuron numbers in rats displaying a spontaneous hydrocephalic condition. Exp Neurol. 2001; 168(1):88–95. [PubMed: 11170723]

50. Allen JS, Damasio H, Grabowski TJ. Normal neuroanatomical variation in the human brain: an MRI-volumetric study. Am J Phys Anthropol. 2002; 118(4):341–358. [PubMed: 12124914]

51. Barbay S, Zoubina EV, Dancause N, et al. A single injection of D-amphetamine facilitates improvements in motor training following a focal cortical infarct in squirrel monkeys. Neurorehabil Neural Repair. 2006; 20(4):455–458. [PubMed: 17082500]

52. Windle V, Szymanska A, Granter-Button S, et al. An analysis of four different methods of producing focal cerebral ischemia with endothelin-1 in the rat. Exp Neurol. 2006; 201(2):324–334. [PubMed: 16740259]

53. Roome RB, Bartlett RF, Jeffers M, Xiong J, Corbett D, Vanderluit JL. A reproducible Endothelin-1 model of forelimb motor cortex stroke in the mouse. J Neurosci Methods. 2014; 233:34–44. [PubMed: 24915635]

54. Lee JK, Park MS, Kim YS, et al. Photochemically induced cerebral ischemia in a mouse model. Surg Neurol. 2007; 67(6):620–625. discussion 625. [PubMed: 17512331]

55. Karl JM, Alaverdashvili M, Cross AR, Whishaw IQ. Thinning, movement, and volume loss of residual cortical tissue occurs after stroke in the adult rat as identified by histological and magnetic resonance imaging analysis. Neuroscience. 2010; 170(1):123–137. [PubMed: 20600639]

56. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013; 12(8):822–838. [PubMed: 23867200]

57. Dromerick AW, Edwardson MA, Edwards DF, et al. Critical periods after stroke study: translating animal stroke recovery experiments into a clinical trial. Front Hum Neurosci. 2015; 9(231):231. [PubMed: 25972803]

58. Lindgren A, Norrving B, Rudling O, Johansson BB. Comparison of clinical and neuroradiological findings in first-ever stroke. A population-based study. Stroke. 1994; 25(7):1371–1377. [PubMed: 8023352]

59. Zakaria T, Lindsell CJ, Kleindorfer D, et al. Age accounts for racial differences in ischemic stroke volume in a population-based study. Cerebrovasc Dis. 2008; 26(4):376–380. [PubMed: 18728365]

60. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001; 32(4):891–897. [PubMed: 11283388]

61. Zia E, Engstrom G, Svensson PJ, Norrving B, Pessah-Rasmussen H. Three-year survival and stroke recurrence rates in patients with primary intracerebral hemorrhage. Stroke. 2009; 40(11):3567–3573. [PubMed: 19729603]

62. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991; 337(8756):1521–1526. [PubMed: 1675378]

63. Gross CR, Kase CS, Mohr JP, Cunningham SC, Baker WE. Stroke in south Alabama: incidence and diagnostic features--a population based study. Stroke. 1984; 15(2):249–255. [PubMed: 6701932]

64. Derflinger S, Fiebach JB, Bottger S, Haberl RL, Audebert HJ. The progressive course of neurological symptoms in anterior choroidal artery infarcts. Int J Stroke. 2015; 10(1):134–137. [PubMed: 23294991]

65. Moulin T, Tatu L, Vuillier F, Berger E, Chavot D, Rumbach L. Role of a stroke data bank in evaluating cerebral infarction subtypes: patterns and outcome of 1,776 consecutive patients from the Besancon stroke registry. Cerebrovasc Dis. 2000; 10(4):261–271. [PubMed: 10878430]

66. Ois A, Cuadrado-Godia E, Solano A, Perich-Alsina X, Roquer J. Acute ischemic stroke in anterior choroidal artery territory. J Neurol Sci. 2009; 281(1–2):80–84. [PubMed: 19324377]

67. Caplan LR, Wityk RJ, Glass TA, et al. New England Medical Center Posterior Circulation registry. Ann Neurol. 2004; 56(3):389–398. [PubMed: 15349866]

68. Ay H, Arsava EM, Gungor L, et al. Admission international normalized ratio and acute infarct volume in ischemic stroke. Ann Neurol. 2008; 64(5):499–506. [PubMed: 18661516]

69. Group MRSC, Phan TG, Donnan GA, Davis SM, Byrnes G. Proof-of-principle phase II MRI studies in stroke: sample size estimates from dichotomous and continuous data. Stroke. 2006; 37(10):2521–2525. [PubMed: 16931782]

70. Rivers CS, Wardlaw JM, Armitage PA, Bastin ME, Hand PJ, Dennis MS. Acute ischemic stroke lesion measurement on diffusion-weighted imaging--important considerations in designing acute stroke trials with magnetic resonance imaging. J Stroke Cerebrovasc Dis. 2007; 16(2):64–70. [PubMed: 17689396]

71. Schaefer PW, Barak ER, Kamalian S, et al. Quantitative assessment of core/penumbra mismatch in acute stroke: CT and MR perfusion imaging are strongly correlated when sufficient brain volume is imaged. Stroke. 2008; 39(11):2986–2992. [PubMed: 18723425]

72. Shook SJ, Gupta R, Vora NA, Tievsky AL, Katzan I, Krieger DW. Statin use is independently associated with smaller infarct volume in nonlacunar MCA territory stroke. J Neuroimaging. 2006; 16(4):341–346. [PubMed: 17032384]

73. Ahmad AS, Satriotomo I, Fazal J, Nadeau SE, Dore S. Considerations for the optimization of induced white matter injury preclinical models. Front Neurol. 2015; 6:172. [PubMed: 26322013]

74. He Z, Yang SH, Naritomi H, et al. Definition of the anterior choroidal artery territory in rats using intraluminal occluding technique. J Neurol Sci. 2000; 182(1):16–28. [PubMed: 11102635]

75. Zhang K, Sejnowski TJ. A universal scaling law between gray matter and white matter of cerebral cortex. Proc Natl Acad Sci U S A. 2000; 97(10):5621–5626. [PubMed: 10792049]

76. Alstermark B, Ogawa J, Isa T. Lack of monosynaptic corticomotoneuronal EPSPs in rats: disynaptic EPSPs mediated via reticulospinal neurons and polysynaptic EPSPs via segmental interneurons. J Neurophysiol. 2004; 91(4):1832–1839. [PubMed: 14602838]

77. Alstermark B, Pettersson LG. Skilled reaching and grasping in the rat: lacking effect of corticospinal lesion. Front Neurol. 2014; 5:103. [PubMed: 24999340]

78. Brus-Ramer M, Carmel JB, Chakrabarty S, Martin JH. Electrical stimulation of spared corticospinal axons augments connections with ipsilateral spinal motor circuits after injury. J Neurosci. 2007; 27(50):13793–13801. [PubMed: 18077691]

79. Carmichael ST, Chesselet MF. Synchronous neuronal activity is a signal for axonal sprouting after cortical lesions in the adult. J Neurosci. 2002; 22(14):6062–6070. [PubMed: 12122067]

80. Nudo RJ, Milliken GW. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. J Neurophysiol. 1996; 75(5):2144–2149. [PubMed: 8734610]

81. Zeiler SR, Gibson EM, Hoesch RE, et al. Medial premotor cortex shows a reduction in inhibitory markers and mediates recovery in a mouse model of focal stroke. Stroke. 2013; 44(2):483–489. [PubMed: 23321442]

82. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015; 372(11):1019–1030. [PubMed: 25671798]

83. Bernhardt J, Langhorne P, et al. ATC group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. Lancet. 2015; 386(9988):46–55. [PubMed: 25892679]

84. Lo AC, Guarino PD, Richards LG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010; 362(19):1772–1783. [PubMed: 20400552]

85. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? Neurorehabil Neural Repair. 2012; 26(8):923–931. [PubMed: 22466792]

86. Valero-Cuevas FJ, Klamroth-Marganska V, Winstein CJ, Riener R. Robot-assisted and conventional therapies produce distinct rehabilitative trends in stroke survivors. J Neuroeng Rehabil. 2016; 13(1):92. [PubMed: 27724916]
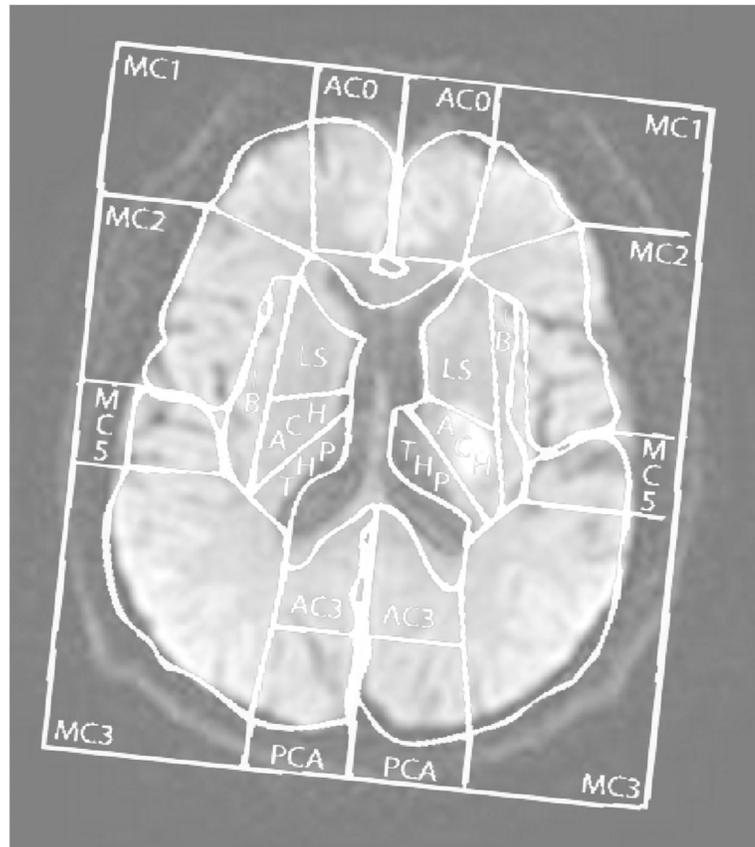
Figure 1.
Template analysis using the ICARE Neuroimaging Viewer. After identifying the group of templates corresponding to the angle at which the head was scanned, the template that best matched the axial slice was chosen and overlaid on top of the diffusion weighted image (DWI) image. The template was rotated clockwise and enlarged to match the outer border of the brain. This process was repeated for each axial slice to be sure the predominant area captured the template subdivision in the 3 dimensional center of the lesion. In this example the predominant area was scored as anterior choroidal (ACH). AC0/AC3 – anterior cerebral artery subdivisions, MC1/MC2/MC3/MC5 – middle cerebral artery subdivisions, PCA – posterior cerebral artery, IB – insular branches, LS – lenticulostriates, THP – thalamoperforating.
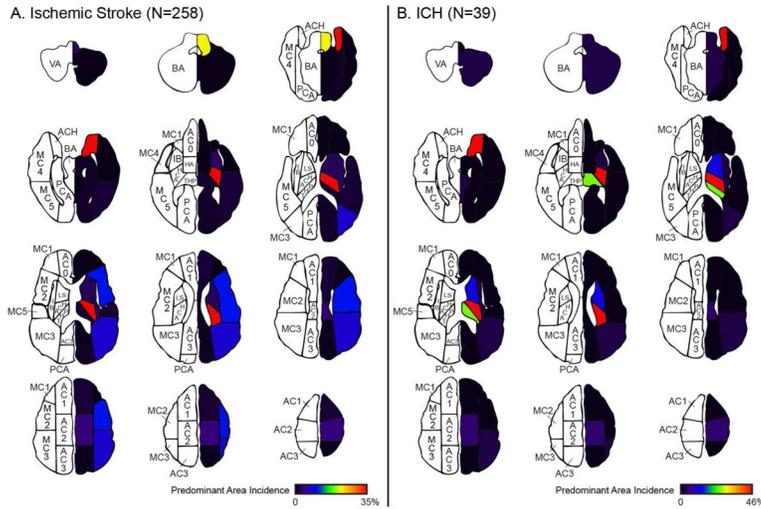
Figure 2.
Map displaying the incidence of stroke lesions centered in each template subdivision (predominant area) for (A) Ischemic stroke participants and (B) ICH participants. The incidence was normalized to the template subdivision with the highest incidence, which was the anterior choroidal (ACH) for both ischemic stroke and ICH. To better delineate lesion involvement in the posterior circulation, the vascular territory data from the template analysis was replaced by the predominant area analysis for the brainstem / cerebellum. Note that the ACH vascular distribution extends into the anteromedial region of the temporal horns, but the vast majority of ACH involvement was confined to the internal capsule / basal ganglia. AC0/AC1/AC2/AC3 – anterior cerebral artery subdivisions, MC1/MC2/MC3/MC4/MC5 – middle cerebral artery subdivisions, PCA – posterior cerebral artery, HA – Heubner's artery, IB – insular branches, LS – lenticulostriates, THP – thalamoperforating, BA – basilar artery, VA – vertebral artery.
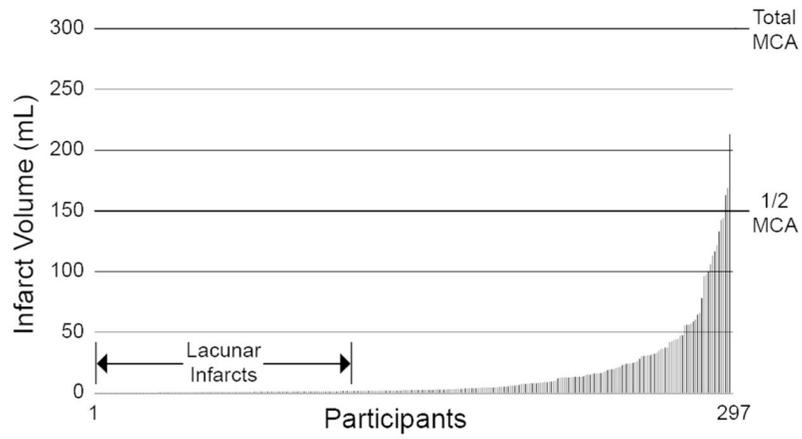
Figure 3.
Stroke lesion planimetric volumes for ICARE participants (n = 297). The y-axis on the right denotes the approximate volume of the MCA territory in humans.

TABLE 1

LESION CHARACTERISTICS

	All Participants (N=297)	Ischemic Stroke (N=258)	ICH (N=39)
Time from Symptom Onset to Scan, median (IQR), days	1 (0–3)	1 (0–2.8)	1 (0–3)
Lesion Side, No. (%)			
Left	122 (41%)	107 (41%)	15 (38%)
Right	172 (58%)	148 (57%)	24 (62%)
Midline	3 (1%)	3 (1%)	0
Lesion Size, median (IQR)			
Max Axial Diameter (mm)	23 (17–43)	22 (16–42)	33 (24–44)
ABC/2 Volume (mL)	2.9 (1–16.3)	2.1 (0.9–13.5)	14 (5.5–20.4)
Planimetric Volume (mL)	2.4 (1–12.8)	1.8 (0.9–8.5)	12.5 (4.2–16.1)
Old Stroke, No. (%)			
Yes	44 (15%)	41 (16%)	3 (8%)
No	253 (85%)	217 (84%)	36 (92%)
Leukoaraiosis, No. (%) *			
None	104 (35%)	82 (32%)	22 (56%)
Mild	129 (43%)	117 (45%)	12 (31%)
Moderate	54 (18%)	49 (19%)	5 (13%)
Severe	10 (3%)	10 (3%)	0

*Graded according to the Age-Related White Matter Disease Scale (ARWMC)[18]. Mild, moderate and severe correlate with a maximum score of 1, 2, or 3 respectively in any of the 5 ARWMC regions.

Table 2

Stroke Lesion Vascular Template Predominant Area, Depth, and Clinical Vascular Territory

	All Participants (N=297) No. (%)	Ischemic Stroke (N=258) No. (%)	ICH (N=39) No. (%)
Vascular Template Predominant Area [*]			
Anterior Cerebral Artery (ACA)	19 (6%)	17 (7%)	2 (5%)
AC0	0	0	0
AC1	4 (1%)	4 (2%)	0
AC2	14 (5%)	12 (5%)	2 (5%)
AC3	1 (0%)	1 (0%)	0
Middle Cerebral Artery (MCA)	58 (20%)	57 (22%)	1 (3%)
MC1	0	0	0
MC2	30 (10%)	30 (12%)	0
MC3	24 (8%)	23 (9%)	1 (3%)
MC4	0	0	0
MC5	4 (1%)	4 (2%)	0
Deep Hemispheric Structures	146 (49%)	112 (43%)	34 (87%)
Heubner's Artery	0	0	0
Lenticulostriates	13 (4%)	8 (3%)	5 (13%)
Insular Branches	10 (3%)	9 (3%)	1 (3%)
Anterior Choroidal	109 (37%)	91 (35%)	18 (46%)
Thalamoperforating	14 (5%)	4 (2%)	10 (26%)
Posterior Cerebral Artery	2 (1%)	2 (1%)	0
Brainstem / Cerebellum	72 (24%)	70 (27%)	2 (5%)
Basilar Artery	67 (23%)	65 (25%)	2 (5%)
Vertebral Artery	5 (2%)	5 (2%)	0
Predominant Area Subgroup Analysis - Brainstem / Cerebellum [†]	All (N=72) No. (%)	Ischemic Stroke (N=70) No. (%)	ICH (N=2) No. (%)
Midbrain	2 (3%)	2 (3%)	0
Pons	60 (83%)	59 (84%)	1 (50%)
Medulla	9 (13%)	9 (13%)	0
Cerebellar Hemisphere	1 (1%)	0	1 (50%)
Cerebellar Vermis	0	0	0
Lesion Depth	All Participants (N=297) No. (%)	Ischemic Stroke (N=258) No. (%)	ICH (N=39) No. (%)
Cortical Gray Matter (CG)	1 (0%)	1 (0%)	0
Cortical White Matter (CW)	1 (0%)	1 (0%)	0
Subcortical (SC)	172 (58%)	157 (61%)	15 (38%)
CG + CW	42 (14%)	40 (16%)	2 (5%)
CG + SC	0	0	0
CG + CW + SC	52 (18%)	48 (19%)	4 (10%)

	All Participants (N=297) No. (%)	Ischemic Stroke (N=258) No. (%)	ICH (N=39) No. (%)
CW + SC	29 (10%)	11 (4%)	18 (46%)
Clinical Vascular Territory[‡]			
Internal Carotid Artery (MCA + ACA involvement)		5 (2%)	
Anterior Cerebral Artery		7 (3%)	
Middle Cerebral Artery		80 (31%)	
M1		48 (19%)	
M2		11 (4%)	
Distal MCA		21 (8%)	
Anterior Choroidal		78 (30%)	
Posterior Cerebral Artery		9 (3%)	
Basilar		64 (25%)	
Vertebral		7 (3%)	
Watershed		8 (3%)	

[*] Predominant area reflects the area located in the 3-dimensional center of the stroke lesion. See Fig 1 for a description of template analysis procedures.

[†] Breakdown of lesions centered in the brainstem / cerebellum by common anatomical structures as opposed to vascular territory.

[‡] Vascular territory analysis as would be performed by a vascular neurologist during the course of clinical care. M1 lesions include either deep MCA or 2 of the following territories: deep MCA, inferior M2, and superior M2.

Table 3

Estimation of How Animal Models of Stroke Align with ICARE Population

Preclinical Stroke Model	ICARE Participants with Similar Lesions[*]
Ischemic Stroke	N=258, No. (%)
Electrocautery of cortical surface vessels[80] (pure gray matter stroke)	1 (< 1%)
Permanent MCAO[10,11] (total MCA)	1 (< 1%)
Cortical photocoagulation[5–7] or endothelin-1 to cortical surface[8,9] (cortical gray + white matter stroke)	40 (16%)
Injection of vasoconstricting agents into subcortical white matter[41–45]	85 (33%)
Hemorrhagic Stroke	N=39, No. (%)
Striatal hematoma[12–18]	5 (13%)
Capsular hematoma[46]	18 (46%)

[*] See methods for description of how lesions from ICARE participants were matched to those in preclinical stroke models