Acute lesion topography relationship with clinical admission symptoms and long-term functional outcomes in stroke patients

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Target audience: Clinician research scientists, neuroimaging researchers

Purpose: The heterogeneity of human stroke pathophysiology has been implicated in the limited success of therapeutic interventions.[1, 2] Neuroimaging markers such as acute infarct volume reduction have often been proposed as a potential surrogate for clinical outcome in the evaluation of novel stroke therapies. Many studies,[3-7],including a *post hoc* analysis of NINDS alteplase trial[8], show that lesion volume is only moderately correlated with chronic clinical outcome measures such as the NIH Stroke Scale (NIH SS) score or mortality. To account for this variability of the association between an imaging biomarker such as infarct volume and clinically meaningful endpoints, a large sample size is needed to determine any effect. Small pilot studies have shown that integration of lesion location and size to create a location-weighted volume score can estimate stroke severity better than volume alone.[9] Here we propose to build upon these early studies that focused on chronic lesion volumes by investigating the relationship between acute lesion volumes identified on diffusion-weighted MRI (DWI) with admission clinical symptoms and long-term functional outcomes.

Methods: DWI from ischemic stroke patients prospectively enrolled in the Genes Associated with Stroke Risk and Outcomes Study (GASROS) between 2007-2011 who were imaged within 48 h of last seen well were retrospectively analyzed. Eligibility criteria for GASROS included age ≥18 years, and a diagnosis of CT or MRI confirmed ischemic stroke. All patients were evaluated emergently by a neurologist at the time of admission, and clinical data from this encounter (e.g. admission NIH SS) were extracted from corresponding medical records. The long-term functional outcome was assessed using the modified Rankin Scale (mRS) which was collected over the telephone at 3-6 months post-stroke. If the subject could not be reached, the 3-6 months mRS was reconstructed from the subject's medical record. Only patients with mRS were included for this study. Lesion volumes were outlined on the acute DWI by a reader blinded to the mRS scores. All DWI data sets were co-registered to the ICBM 452 T1 atlas 1 mm^3 (MNI Autoreg[10]). Voxel-based lesion symptom mapping (VLSM) was then performed using non-parametric mapping[11] with either admission NIH SS or post-stroke mRS as the symptom score. Voxels were tested only if the voxels were damaged in at least 2% of the subjects (i.e. 10 subjects). Statistical testing was performed using Brunner-Munzel tests. 5% permutation thresholds were generated based on 1000 iterations.

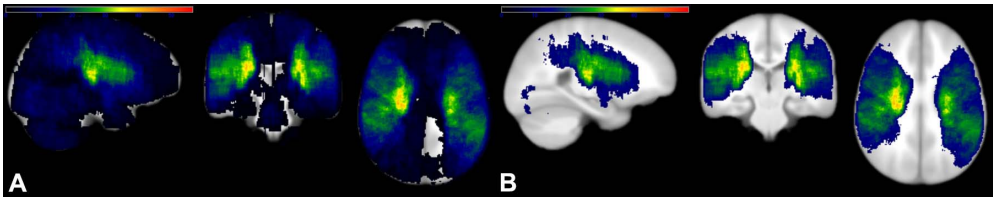

Fig 1: Number of patients with lesions within each voxel (A) using range 0 to 56 and (B) range 10 to 56. Images are shown in radiologic orientation. Color bars are from 0 to 56, the maximum number of patients with a lesion in a common voxel.

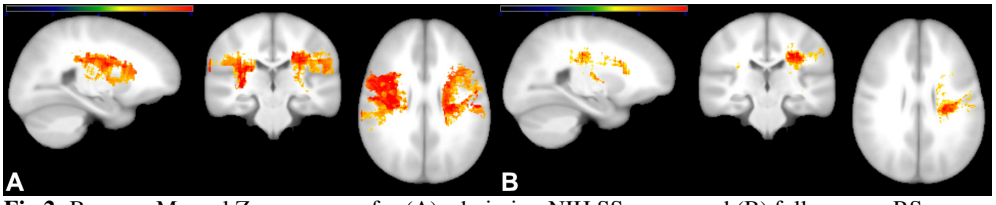

Fig 2: Brunner-Munzel Z-score maps for (A) admission NIH SS scores and (B) follow-up mRS scores. Only voxels that survived the 5% permutation thresholds (5.3 and 5.07 respectively) are shown. Images are shown in radiologic orientation. Color bars are from 0 to 8.

Results: Four-hundred eighty (480) subjects met the inclusion criteria. Of these, 465 had admission NIH SS available. Demographics were as follows: mean ±SD age 65.2±15.1 y.o, 61% were male, median [IQR] NIHSS 3 [1-8], mRS 1 [0-3], and time-to-MRI 19.7±12.9 hours. Figure 1 shows the incidence maps of lesions for all subjects, along with those with at least 2% of the patients having DWI lesions. Figure 2 shows the results of 5% permutation thresholds of (Fig 2A) Z=5.3 for NIHSS and (Fig 2B) Z=5.07 for post-stroke mRS. For the mRS results, despite comparable incidence of acute left and right lesions, acute DWI lesions involving the left MCA territory and in particular superior corona radiata, posterior limb of the internal capsule, operculum, putamen and parts of the insular cortex were associated with less favorable functional outcome at 3-6 months post-stroke. In comparison, poor admission NIH SS scores exhibited associations with regions in both left and right hemisphere.

Discussion: VLSM techniques were originally developed to better understand which regions of the brain are critical for brain functions.[12] The association between poor mRS outcomes and lesions in the left hemisphere, predominantly in the motor pathway, is expected due to the heavy weighting of the mRS score on motor recovery. Admission NIH SS score, on the other hand, reflects various symptomatology, including aphasia, dysarthria, and neglect, not captured well in the mRS score. Our results confirm the hypothesis that the location of acute stroke lesions is an important determinant of patients' clinical presentation and outcomes. Therefore, integration of VLSM methods into clinical assessment of patients with acute ischemic stroke may facilitate early identification of patients at risk for poor long-term functional outcomes and enhance significantly our current strategies for selection of patients for aggressive acute intervention and focused post-stroke rehabilitation programs.

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