

Voxel based lesion symptom mapping for the identification of critical regions for motor recovery after stroke

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Introduction: Stroke remains the third leading cause of death in the United States and the leading cause of long term disability worldwide. Recovery from stroke is varied and often results in deficits that can affect daily living. Because of this incomplete recovery, it is extremely important to have a comprehensive prognosis for patients so they understand the level of recovery to expect and which treatments may be applicable for their condition. This study attempts to overcome this limitation by using voxel-based lesion symptom mapping (VLSM) to identify specific anatomical regions required for preservation of motor function.

Methods: One-hundred-and-fifty moderate to moderately-severe chronic (minimum >6months; mean 63 months) stroke subjects (Upper Extremity Fugl-Meyer = 28-50, Arm Motor Ability Test > 35) were imaged with a 1mm isotropic T1-weighted volumetric sequence and their motor performance assessed. The data were collected over 26 sites across all MR vendors and at 1.5T and 3T field strengths. All data were transferred via Dicom data format. The T1 volume images were normalized to a symmetric template using SPM5. All right hemisphere lesions were maintained in the native space and also oriented so the lesion appeared in the left hemisphere to facilitate comparisons of handedness, and hemisphere location.

Voxel-based Lesion Symptom Mapping (VLSM) is able to statistically assess the lesion's effect on behavioral scores on a voxel-by-voxel basis (Bates 2003). In each lesioned voxel a statistical test is conducted to determine if a difference in the behavioral measures exists between the lesioned and non-lesioned group. The groups are assigned at each new voxel location based on the presence of the lesion. A t-test produces a statistical map overlaid on the lesioned voxels. This voxel-by-voxel analysis produces high resolution statistical maps (1 mm³), rather than a large region of interest analysis or lesion categories as seen in prior lesion studies. VLSM analysis is not limited by tissue type as in voxel based morphometry or BOLD functional MRI which only assesses blood flow changes in gray matter. VLSM interrogates any type of brain tissue included in the lesion maps. The lesioned areas were manually segmented on the normalized T1 image. All 3D lesion maps were entered into VLSM analysis. Areas showing significant correlations with functional performance measures were identified using the false discovery rate corrected at $p \leq 0.05$.

Results: VLSM analysis was performed on the entire data set (e.g. lesions flipped so that they would all be oriented in the left hemisphere) and then pursued on stratified data in the native space (right-hemisphere and left-hemisphere; dominant-hemisphere lesion and non-dominant hemisphere lesion). A right-hemisphere lesion is defined as a lesion appearing in the right-hemisphere of the brain. A dominant-hemisphere lesion is defined as a lesion that appears in the hemisphere contralateral to the dominant hand (e.g. right-handed individual with a lesion in the left hemisphere). Lesions which appeared in both hemispheres were eliminated in these strata.

	Flipped (n=140)	R-hemisphere (n=50)	L-hemisphere (n=89)	Dominant (n=85)	Non-Dominant (n=52)
UEFM	insignificant	insignificant	insignificant	insignificant	insignificant
AMAT	significant	significant	significant	significant	insignificant
Box&Block	significant	insignificant	significant	significant	insignificant

Discussion: This project is an extension of the work published by Lo et al. who completed a pilot investigation on a group of forty-one subjects from a single center [1]. The results from this study are consistent and indicate that the findings may be extended to the population at large. The fact that the areas identified using VLSM correlate with loss of motor performance emphasizes the importance of the anatomical structures (e.g. the junction of the corona radiata and the corticospinal tract).

More importantly, the larger population size afforded the ability to perform additional statistical analysis; this in turn provided answers to important questions concerning earlier findings. For example, in order to reach statistical significance, the protocol for previous studies required orientation of all lesions such that they appeared in the left hemisphere. This study justifies that assumption by showing that left-hemisphere lesions and right-hemisphere lesions are significant when analyzed alone and that these results are similar.

Interestingly however, stratifying the data by dominant and non-dominant hemisphere lesions did not produce the expected similar results. In particular, while analysis of the dominant-hemisphere lesions provided statistically significant results that matched previous findings, analysis of the non-dominant hemisphere lesions did not produce statistically significant results. This effect cannot be explained by small sample size alone as the sample size of non-dominant lesions (n=52) was greater than that of right-hemisphere lesions (n=50), another strata of similar size that did produce statistically significant results. What this analysis suggests is that the mechanisms underlying recovery from stroke may be different between dominant and non-dominant hemisphere lesions. Evidence for this includes the observation that in normal individuals, movement of the non-dominant hand activates the ipsilateral premotor cortex to a higher degree than movement of the dominant hand [2]. In addition, this difference in activation (e.g. increased reliance on the ipsilateral hemisphere in movement of non-dominant hand) is increased in patients after stroke [3]. Thus, one may propose that following stroke of the non-dominant hemisphere, reorganization of the dominant hemisphere may occur to a greater degree than the reorganization of the non-dominant hemisphere following a dominant lesion. In other words, the motor deficits observed following a non-dominant hemisphere lesion may be expected to be more mild due to an increase in restructuring of the dominant hemisphere. This would explain the observed lack of statistical significance when analyzing the non-dominant lesions alone. There have been some fMRI studies that show evidence of this difference in reorganization following dominant and non-dominant hemisphere lesions [4].

1. Lo R, et al., Identification of critical areas for motor function recovery in chronic stroke subjects using voxel-based lesion symptom mapping.. *Neuroimage*, 49(1):9-18, 2009. 2. Kim, S.-G., et al., *Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness*. *Science*, 1993. **v261**(n5121): p. p615(3). 3. Cramer, S.C., et al., *A Functional MRI Study of Subjects Recovered From Hemiparetic Stroke*. *Stroke*, 1997. **28**(12): p. 2518-2527. 4. Zemke, A.C., et al., *Motor Cortex Organization After Stroke Is Related to Side of Stroke and Level of Recovery*. *Stroke*, 2003. **34**(5): p. e23-26.