Comparison of Univariate and Multivariate Lesion Symptom Mapping Methods for the Analysis of Brain-Behavioral Relationships in Stroke

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Introduction

Mass-univariate lesion symptom mapping methods (ULSM), such as the original voxel-based lesion symptom mapping (VLSM), provide statistical comparisons of behavioral performance in brain-injured patients with and without a lesion on a voxel by voxel basis.¹-² New multivariate lesion-symptom mapping (MLSM) methods have been developed that consider the entirety of all lesion patterns (all measurement units) simultaneously in one model.³-⁴ Advantages and disadvantages of ULSM and MLSM techniques have been discussed in the literature, but little work has been done to empirically test these claims.⁴ In the current study, we directly compared ULSM and MLSM methods by analyzing their performance on both artificial and real datasets of brain-behavioral relationships (BBRs).

Procedures: Simulated Data & Real Data

Synthetic Data:
1. Single parcel, proportional BBR conditions (% of target lesioned ~% of behavioral deficit) in the left middle cerebral artery (MCA) territory over a fully crossed design:
   - 16 or 30 parcels of Left MCA as BBR targets
   - lesion masks from our site (n=209) and another site (n=131)
   - 13 lesion symptom mapping methods (8 MLSM)
   - 4mm lesion mask smoothing vs. none
   - 7 different patient sample sizes: n=2, 48, 64, 80, 96, 112, 128
   - multiple spatial accuracy measures (6 distance & 2 overlap)
   - 3 behavioral noise levels
2. Procedure above was repeated with two-parcel networks, testing redundant, dependent, and extended networks.

Real Data:
Western Aphasia Battery language data from LH stroke patients: repetition subtests (verbal repetition of words, phrases, comprehension subtest (auditory comprehension), and fluency subtest).

Procedures: Lesions Methods Tested

Multivariate LSM:
- ICA-L1 - ICA, independent component analysis
- LPCA-L1 - LPCA – Logistic principal component analysis
- LPCA-L2 - LPCA – Linear principal component analysis
- SVL-L1 - SVL – Singular value decomposition
- SVL-L2 - SVL – Singular value decomposition
- PLS - Partial least squares (dense)
- SVR - Support Vector Regression

Univariate LSM:
- T-max - Maximum t value
- Tu=125 - 125th highest t value (Mimran)
- T<0.0001 - cluster size when p<0.0001
- T<0.001 - cluster size when p<0.001
- T<0.01 - cluster size when p<0.01
- T<0.1 - cluster size when p<0.1
- T<0.5 - cluster size when p<0.5

Results: Single Anatomical BBR Target

Results: Two Parcell BBR Target (Network)

Lesion Coverage Map

Overlay of stroke patients’ lesions from our site, showing voxels included in the real LSA analyses. Color bar shows the degree of lesion overlap:
- T<0.0001: single chronic left stroke (36 female)
- mean post-stroke: 51 months (range 12-271)
- mean age: 51 (range 31-86)
- excludes both aphasic (n=125) and non-aphasic patients (n=48)

Results: LSM Output with Real Language Data

Summary

Modern ULSM techniques provide a robust solution for detecting single targets, and required a smaller sample size than MLSM to achieve a similar level of power and spatial accuracy.

- With certain metrics, some (but not all) MLSM methods have advantages for detecting two-target networks, but cluster-size based ULSM methods can also provide insight into this case.
- Noise level has a modest impact on ULSM and MLSM results, mostly affecting LSM power.
- ULSM methods do better with noiseless data, but certain distance metrics reduce LSM cluster spatial sensitivity to behavioral noise.
- Smoothing at 4mm improves accuracy of localization across all metrics for both ULSM and MLSM methods, despite there being no anatomical impression in the synthetic models.
- Weighted center-of-mass (wCOM) and peak statistical value (Max) locations of obtained MLSM clusters provide the most robust accuracy results across all methods.
- Dice overlap scores were unacceptably low for all methods (for single targets as well), but distributional comparisons (inside vs. outside target(s)) proved useful for method evaluation.

References

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