Ground-truth validation of uni- and multivariate lesion inference approaches

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Abstract

Lesion analysis reveals causal contributions of brain regions to brain functions. Various strategies have been used for inferring brain functions from brain lesions. These approaches can be broadly categorized as univariate or multivariate methods. Here we analysed data from 581 patients with acute ischemic injury, parcellated into 41 Brodmann areas, and systematically investigated the inferences made by univariate and multivariate lesion analysis methods via ground-truth simulations, in which we defined a priori contributions of brain areas to assumed brain function. Particularly, we analysed single-region models, with only single areas presumed to contribute functionally, and multiple-region models, with two contributing regions. The analyses consistently showed a considerably better performance of multivariate than univariate methods in terms of accuracy and mis-inference error. Specifically, the univariate approaches of Lesion Symptom Mapping as well as Lesion Symptom Correlation mis-inferred substantial contributions from several areas even in the single-region models, and also when accounting for lesion size. Of the multivariate approaches, the game-theoretical Multi-perturbation Shapley value Analysis typically showed the best performance. Our findings suggest that multivariate approaches produce highly reliable lesion inferences, without requiring lesion size consideration, while the application of univariate methods may yield substantial mis-localizations that limit the reliability of functional attributions.

Introduction

Lesion analysis after brain damage is a traditional and powerful approach for revealing causal contributions of brain regions to mental functions. Lesion inferences aim at understanding impaired as well as normal brain function by relating lesion patterns to functional deficits (e.g., cognitive or behavioural impairments) through various strategies, which can be broadly categorized as univariate or multivariate approaches. Univariate approaches assume that the effects of lesions of individual brain region are independent from each other, while multivariate approaches take into account the physical and functional relations among lesion effects of different damaged brain sites.[1,2] Among univariate approaches are Lesion-Symptom Mapping (LSM)[3] and Lesion Symptom Correlation (LSC).[4] Most current multivariate methods are based on machine learning classification by support vector machines, such as Multivariate Pattern Analysis (MVPA)[5] and Multi-Area Pattern Prediction (MAPP).[4] Similarly, Zhang *et al.*[6] developed a multivariate lesion symptom mapping approach using a machine learning-based

multivariate regression algorithm. An alternative multivariate method is the Multi-perturbation Shapley value Analysis (MSA),[7] which is based on coalitional game theory.

Mah *et al.*[1] demonstrated that inherent physical dependencies of regions of interest might lead to substantial mis-inferences in univariate analysis methods. While some studies have suggested that univariate methods, specifically LSM, may be able to reduce false positive (mis-)inferences by accounting for total lesion size[8-10], Inoue *et al.*[11] found that LSM adjusted for lesion size actually produced a larger bias than LSM without such adjustment. Xu and colleagues[2] conceptually addressed the problem of the dimensionalities of lesion-deficit mapping, arguing that univariate methods ignore the complexity of the brain in terms of functional interactions among regions, as well as, fundamentally, in terms of anatomical interactions among regions unified by the natural patterns of brain damage. They pointed out that using lesion volume as a regressor in a mass-univariate model would penalise voxels more commonly hit by large lesions and inevitably distort lesion inference.

Given the fundamental role of lesion analysis in neurological research, these findings emphasize the need for a systematic and robust comparison between univariate and multivariate inference approaches (as advocated by Karnath and Smith[12]). In this context, Pustina *et al.*[13] compared univariate voxel LSM and a multivariate method based on sparse canonical correlation, by using synthetic behaviour as ground truth, and concluded that the multivariate approach produced systematically better accuracy than the univariate method. By contrast, Ivanova *et al.*[14] compared five univariate and eight multivariate methods (including the method suggested by Pustina *et al.*[13]) using synthetic and real data and saw no clear superiority of a multivariate against the univariate methods. Another study by Sperber *et al.*[15] found that the multivariate method of support vector regression LSM was susceptible to misplacement of statistical topographies along the brain's vasculature, as is the case for voxel LSM.

Thus, the relative merits of univariate versus multivariate lesion inferences still appear controversial, particularly in the context of large patient cohorts and using complex multivariate methods such as MSA. Therefore, we presently aimed to objectively and systematically compare a range of univariate (LSM, LSC) and multivariate (MSA, MAPP) lesion inference methods via ground-truth simulations, analysing data from a large cohort of 581 patients with acute ischemic injury.[1] Such comparisons cannot be directly performed on clinical datasets, because the true underlying functional contributions and interactions are

unknown for such data. Instead, simulations of ground truth data provide an opportunity to define these contributions and interactions *a priori* and then use a variety of inference approaches to recover the specified mechanisms and compare the accuracy of the respective inferences. The rationale of the study is summarized in Fig. 1.

--- Figure 1 about here ---

Our results confirm the substantially higher accuracy of multivariate compared to univariate inferences, also when accounting for lesion size, and particularly indicate a high reliability of the game-theoretical MSA approach.

Methods

Ground-truth simulations at region level

We analysed previously published lesion data from 581 patients with acute ischemic injury,[1] parcellated into 41 Brodmann areas (BAs), and investigated different lesion models via ground-truth simulations, by defining *a priori* the contributions of brain areas to assumed brain function. For each ground-truth setting, one or two *source regions* were selected as being responsible for a putative brain function, meaning that a theoretical performance score was derived depending on the lesion state of the source regions in each patient's lesion pattern. In different ground-truth model settings, we explored single versus multiple source region effects and analysed binary versus graded performance datasets.

Single versus multiple region lesion models

We analysed *single source region* effects, in which only a single area contributed to a presumed brain function as well as *double source region* effects, with two contributing regions. In the single-region setting, a specific lesion model was generated for each of the 41 BA regions selected as a source that was assumed to be solely responsible for a hypothetical brain function. The dataset derived for each of the 41 lesion models was composed of the lesion information for the 581 patients (the same across all models) and the corresponding performance scores, differing from one single-source model to another, depending on which of the 41 BAs was selected as the source of presumed brain function. Differentiating further, the hypothetical performance scores for the 581 patients were derived either in proportion to the intact voxels,

or the binary, thresholded state of the specific single or multiple source regions (see subsequent section *Binary versus graded lesion models* for details on the computation of the performance scores). In the double-region models, we focused on pairs of randomly chosen source regions, as well as two specific BAs (BA 39 and BA44) that may be putative loci for visuospatial neglect (cf. Mah *et al.*[1]).

Binary versus graded lesion models

We explored lesion models that differed in the computation of the performance score in a binary or graded fashion. In the *graded lesion models*, for each ground-truth setting the functional score was defined in proportion to the level of intactness of the source region. In the *binary lesion models*, the binary functional score was defined with respect to a binarization threshold computed as median value of the non-zero lesion size for each region (*median threshold lesion models*), but other thresholds may be used as well (cf. Zavaglia *et al.*[16] for details on threshold choice).

Specifically for the graded lesion models, intactness for every BA was defined as a relative measure of the intact voxels graded from *0* (complete lesion) to *1* (region completely intact). In the case of double region effects, the performance score was computed in three possible ways: (i) assuming *synergistic* operation, performance was the product of the intactness levels of both source regions; or (ii) assuming *redundant* operation, performance was computed as the average level of intactness of both source regions; or (iii) assuming operation by *mutual inhibition*,[17] performance was calculated as $\frac{2xy}{x^2+y^2}$, with x and y the intactness levels of two source regions (performance was set to 1 if the two source regions were completely lesioned (*0*)).

In the binary lesion models, the binary functional score for each ground-truth setting was defined as *0* (pathological) if the source region was damaged, or *1* (normal) if the source region was intact, as determined by the threshold. In the case of double-region effects, as for the graded lesion models, the performance score was defined in three possible ways: (i) assuming synergistic operation, performance was *1* (normal) only, if both source regions were intact, according to the threshold; (ii) assuming redundant operation, performance was *0* (pathological) only, if both source regions were lesioned, according to the threshold; or (iii)

assuming mutual inhibition, performance was *1* (normal) only, if both source regions were lesioned or if both source regions were intact, according to the threshold.

Lesion inference methods

In order to systematically compare univariate and multivariate lesion inference methods, we selected two representative approaches for each category. Specifically, for each generated lesion model (41 single-region lesion models and 50 double-region lesion models), we employed Lesion Symptom Correlation (LSC) and Lesion Symptom Mapping (LSM) as univariate, and Multi-Area Pattern Prediction (MAPP) and Multi-perturbation Shapley value Analysis (MSA) as multivariate analysis methods.

In LSC,[4] the contributions of the 41 BAs were computed as Spearman rank correlations between all patterns of relative (graded) lesion size and the performance scores (binary or graded, depending on the setting of the models). We used Spearman rank correlations in line with the ordinal nature of the present data.

The second approach, LSM, was originally introduced at voxel level.[3] As for LSC, we here applied it at the regional level (i.e., for Brodmann Areas). The LSM approach makes use of binary information about the impairment of each BA. The binary dataset was obtained by using a median threshold as explained above. In LSM, we computed the functional contributions of the 41 BAs by statistically comparing via t-test the performance values (graded or binary, depending on the ground-truth setting of the models) of all cases in which a particular area was lesioned versus the performance of the cases where the area was intact.

In the MAPP approach,[4] which is based on machine learning, the contributions of the 41 BAs were obtained by computing the leave-one-out cross-validation via a prediction algorithm with 41 different datasets, obtained respectively by removing each single BA one at a time. The contribution to the prediction error for each BA was obtained as the difference between the Root Mean Square Error (RMSE) computed in the leave-one-out cross validation without the particular BA and the RMSE computed with the complete set of BAs. We used bootstrap[18] to ensure the robustness of the obtained contributions. Specifically, from the available dataset, we chose 100 random samples with replacement, with the size of the original dataset. We then performed the MAPP approach as outlined above on each of these 100 samples. Finally, the contributions were averaged across the set of 100 samples. Thus, the approach, which is

computationally expensive, indicates the 'importance' of each BA for the prediction, by quantifying its individual contribution to the prediction error. MAPP makes use of the binary or graded dataset and corresponding binary or graded performance scores depending on the ground-truth settings of the models.

The final approach, MSA,[7] is a mathematically rigorous method based on game theory for assessing causal function localization from perturbation data. The approach computes an unbiased estimator of the contribution of each brain region from a dataset of multiple lesions. These values represent the regions' overall contributions to function across all possible brain states. Specifically, the contribution value of a region, formalized as the Shapley value,[19] represents the importance of the region for the overall behavioral function and it is defined as the difference between the worth of coalitions which contain the region and the worth of coalitions which do not contain it. The MSA variant used here, termed estimated MSA,[20] is computationally convenient in comparison to the conventional MSA which requires 2^N (N = *number of regions*) performance scores corresponding to the 2^N binary configurations. The estimated MSA can sub-sample orderings and is useful in studies where the number of system elements is too large to enumerate all configurations in a straightforward manner.[20] We used bootstrap[18] as described above for MAPP, see Malherbe *et al.*[21] for using bootstrap with estimated MSA. MSA makes use of a prediction algorithm trained on the available set of configurations, binary or graded, and corresponding performance scores, also binary or graded (depending on the ground-truth setting of the models) to derive performance scores of unknown configurations. For this purpose, in both MAPP and MSA simulations, we used a regression tree predictor (with parameters set to default values). For details on the prediction methodology see Zavaglia *et al.*[16]. Most of the analyses were faced with imbalanced data, meaning that the different classes were not represented equally in the dataset (e.g., Megahed *et al.*[22]). If a classifier is trained on a dataset in which one of the response classes is rare, it can underestimate the probability of observing a rare event, inducing a bias in the results. To mitigate this imbalance, we trained the binary models for MSA in two ways and used the results with the higher accuracy, performing (i) the bootstrap procedure as usual, or (ii) rebalancing the data by forcing the bootstrap to choose 200 cases in the minority class and the remainder in the majority class. The same procedure was used for the MAPP analysis in each analysis. For the graded models, we used the results with the highest accuracy for the MSA of three possibilities of obtaining the training dataset: (i) the usual bootstrap, (ii) the bootstrap procedure by using 10 classes for the scores instead of the fully graded scores, (iii) the resampling in 10 classes of the

score and rebalancing the data during the bootstrap by forcing the bootstrap to choose 200 cases of the minority class and the others in the remaining data. The same procedure was used for the MAPP analysis in each analysis.

Ideally, a perfect lesion inference method should infer only one regional contribution in the single region model or two contributions in the double region models, respectively, corresponding to the preselected functional sources. As a measure of comparison between the different lesion methods, we computed the accuracy and the weighted accuracy from the sensitivity and specificity and, in addition, the normalized mis-inference error by summing all mis-inferences for a given target (i.e., all inferred regional contributions beyond the ones of the target). All simulations were implemented in MATLAB (The MathWorks Inc.).

Data availability

All scripts and data for the method part are available upon reasonable request.

Results

Fig. 2A presents the location of BAs whose lesions were simulated in single and double target lesion models, and shows the lesion overlap across all 581 cases. Fig. 2B displays the correlation of lesion sizes of the different Brodmann areas across all cases, indicating that many of these areas were affected by the vascular injuries in a related manner.

--- Figure 2 about here ---

We performed several evaluations in order to compare lesion inference methods across the various lesion models. Specifically, we compared lesion inferences in terms of accuracy, sensitivity, specificity and mis-inference error, as shown in Table 1 ans Table 2. The four inference methods were compared first for the single-region lesion models, both binary and graded (results shown in Fig. 3). Then, we focused on the double-region binary and graded lesion models, both with synergistic, redundant and mutual inhibition performance scores (results shown in Fig. 4 only for BA39 and BA44, the others listed in Table 1 and Table 2).

--- Table 1 about here ---

--- Table 2 about here ---

Fig. 3 represents the results of the single-region lesion models. Specifically, the panels show the comparison between univariate methods (Fig. 3 A, B, E and F) and multivariate methods (Fig. 3 C, D, G and H), for a single-region median threshold lesion model (binary lesion model) and a single-region graded lesion model. Each column in these confusion matrices represents the 41 contributions of the inferred regions obtained from each ground-truth lesion model (i.e., for each source region which defines a lesion model). Ideally, if a method infers contributions only of the pre-chosen source regions and there are no mis-inferences, the matrices should only have elements on the leading diagonal. The contributions of LSM and LSC were sorted in order to locate the highest values close to the leading diagonal.

--- Figure 3 about here ---

The results systematically showed a better performance of multivariate than univariate methods in terms of normalized inference error (reported in percent in Fig. 3, Table 1 and Table 2). Among univariate methods, LSM (accuracy = 48%, specificity = 47%, sensitivity =100% and *err = 80%* for median threshold lesion model and accuracy = 46%, specificity = 45%, sensitivity = 100% and *err = 87%* for graded lesion model) performed better than LSC (accuracy = 33%, specificity = 31%, sensitivity = 100% and *err = 92%* for median threshold lesion model and accuracy = 29%, specificity = 27%, sensitivity = 100% and *err = 91%* for graded lesion model), but both methods mis-inferred substantial contributions from many areas as shown by the clusters outside the leading diagonal. These mis-inferences were attributed to BAs located within the same infarct territory. Both multivariate approaches performed perfectly (accuracy = 100%, specificity = 100%, sensitivity = 100% and *err = 0%*) in the median threshold lesion model and almost perfectly in the graded lesion model (MSA: accuracy = 95%, specificity = 95%, sensitivity = 100% and err = 7%; MAPP: accuracy = 96%, specificity = 95%, sensitivity = 100% and err = 2%).

In order to assess the source of the error introduced by univariate approaches, specifically LSM, we quantified the *displacement* from the true location, by computing the total mis-inferences for every ground-truth lesion model across all the inferred BAs, both for graded and median threshold lesion models, and correlated it with (1) the median of *relative* lesion size per area across all cases, (2) the median of *absolute* lesion size per area across all cases and (3) the absolute size per area (details in Supplementary Material). The results suggested that it is the absolute lesion size of regions that matters for the misinference, but not the size of the regions as such. In this context, we also implemented a control for lesion size, as proposed by Sperber

and Karnath.[10] Specifically, we regressed the total absolute lesion size for every case across all BAs on the performance scores. The average correlation between total absolute lesion size and performance scores (across all ground-truth models) was $\rho = -0.34, p = 0.0045$ for the median threshold lesion model and $\rho = -0.41$ $p = 0.0044$ for the graded lesion model. We performed a linear regression for the graded lesion model and a logistic regression for the median threshold lesion model. We then used the residuals to re-compute the LSM. After adjusting for lesion size (LSM_vc, see Table 1), the accuracy increased to 71 % for the median threshold lesion model and to 62% for the graded lesion model, being larger than in the original LSM analysis, but still substantially smaller than in the multivariate inference approaches.

Fig. 4 represents the same quantities as in Fig. 3, but obtained with the double-region median threshold lesion model and double-region graded lesion model, with redundant performance scores (see also Table 1 and Table 2). The sources chosen for the two regions were BA39 and BA44 (two putative loci for visuospatial neglect[23,24]). The two columns in the matrices represent the 41 contributions of the inferred regions for the two lesion models (i.e., for the two source/target regions). As for the single-region models, among the univariate approaches, LSM (*err = 88%* for median threshold lesion model and *err = 89%* for graded lesion model) performed better than LSC (*err = 92%* for median threshold lesion model and *err = 90%* for graded lesion model), but both methods showed strong mis-inferences. Of the multivariate methods, MSA showed the best performance on the graded lesion model (MSA_*err = 20%* and *MAPP_err = 10%*), generally producing highly reliable lesion inferences, and perfect performance for both MSA and MAPP for median threshold lesion model (err = 0%).

--- Figure 4 about here ----

In the double-region models, in addition to the simulations results reported in Table 1 and Table 2, we also performed simulations by randomly selecting pairs of regions within a group with similar lesion patterns (i.e., with high correlations of lesion size) and within a group with dis-similar lesion patterns (i.e., low correlation of lesion size), to explore the effect of linked lesion patterns of the reliability of lesion inferences. The results in term of accuracy, sensitivity, specificity and mis-inference error are reported in Table S1 (Supplementary Material) and suggest that univariate methods produce mis-inferences independently of whether two areas have similar lesion patterns or not.

All results reported in Table 1 and Table 2 suggest that multivariate inference methods always perform better (in term of accuracy and mis-inference error) than univariate methods, across all variants of lesion models. MAPP and MSA in most of the cases performed similarly, with a higher computational cost of MAPP than MSA.

Discussion

Various strategies have been used for inferring brain function from brain lesions in stroke patients. In this study, we systematically compared univariate and multivariate lesion inference approaches via objective ground-truth simulations, by defining *a priori* the contributions of brain areas to assumed brain function. The results systematically showed a better performance of multivariate than univariate methods in terms of inference error. LSC and LSM inferred substantial contributions for multiple areas even in the single-region models and the mis-inferences were distributed in regions across the infarct territory. Specifically, the strongest mis-inferences were located in BA21, BA22, BA41, BA42 and BA39, corresponding to the lower parietal lobe or temporal lobe, where the largest overlap of lesion cases and correlation of lesion patterns occurs (Fig. 2). The mislocalization across the brain depends on the complex interaction between the multivariate lesion distribution and brain functional architecture, as also suggested by Mah *et al.*[1]. Double-region simulations of two putative loci for visuospatial neglect (BA39 and BA44) showed substantial erroneous displacement of the inferred critical regions with univariate methods, while no mis-localization was present for the multivariate methods. These results are relevant for correctly attributing functions to neural substrates, such as in the case of inferring the real causal injury location underlying neglect. Mah *et al.*[1] showed that, with univariate methods, there is a large mis-inference of lesion patterns to the superior temporal gyrus, which might be erroneously considered as critical region for neglect. This region comprises BA22, which is also strongly mis-inferred by the univariate approaches of LSM or LSC in our study.

Following recent discussions on the options for decreasing the false positive rate in LSM (c.f. Sperber and Karnath[10]), we also computed LSM contributions after accounting for lesion size, and found a substantial improvement for the median threshold lesion model, but not for the graded lesion model. Generally, however, the mis-inference error with LSM after regressing out total absolute lesion size was still much larger than the errors produced by multivariate approaches (and the accuracy still much smaller than the accuracy for multivariate approaches).

Adding lesion size as covariate is a contested point in the literature. Whereas some authors routinely incorporate lesion size regressions,[10,14] Xu and colleagues[2] pointed out the infelicity of adding lesion size as a covariate on principled grounds, as regions of the brain showing strong correlations with lesion volume (i.e., those at the edges of vascular boundaries) will generally be penalised, while others are favoured. Our empirical analyses underline the fact that lesion size regression is not an automatic cure for the imperfections of univariate lesion inference.

Generally, our findings confirm the presence of substantial mis-inferences of locations in univariate lesion analysis approaches, and demonstrate that multivariate approaches consistently produce highly reliable lesion inferences, with MSA typically showing the best performance (in terms of accuracy and computational cost), without requiring lesion size correction. Nonetheless, future work ought to expand these findings by testing even more intricate models of brain function[17] and lesion effects, in order to derive a comprehensive understanding of lesion inference approaches.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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Tables and figures

Inference method	Accuracy %	Accuracy weighted %	Sensitivity %	Specificity %	Misinference error %
Single source binary					
LSC (Fig. 2A)	33	5	100	31	92
LSM (Fig. 2B)	48	11	100	47	80
LSM_vc	71	54	100	70	26
MAPP (Fig. 2C)	100	100	100	100	0
MSA (Fig. 2D)	100	100	100	100	0
Single source graded					
LSC (Fig. 2E)	29	5	100	27	91
LSM (Fig. 2F)	46	8	100	45	87
LSM_vc	62	13	100	61	83
MAPP (Fig. 2G)	96	94	100	95	2
MSA (Fig. 2H)	95	89	100	95	7
Double source binary synergistic					
LSC	22	22	100	18	90
LSM	34	34	100	31	80
MAPP	100	100	100	100	0
MSA	100	100	100	100	0
Double source binary redundant					
LSC	39	39	88	37	91
LSM	50	50	85	48	86
MAPP	98	98	99	98	1
MSA	93	92	100	92	12
Double source binary mutual inhibition					
LSC	41	41	90	40	92
LSM	55	55	85	55	89
MAPP	95	95	98	95	1
MSA	95	95	96	95	7
Double source graded synergistic					
LSC	19	19	100	15	89
LSM	33	33	100	30	87
MAPP	53	53	100	50	8
MSA	59	59	100	52	18
Double source graded redundant					
LSC	19	19	100	15	89
LSM	33	33	100	30	87

MAPP	52	52	100	50	9
MSA	64	64	100	62	19
Double source graded mutual inhibition					
LSC	23	23	99	20	89
LSM	45	45	89	43	89
MAPP	79	79	68	79	17
MSA	94	93	85	94	21

Table 1: **Accuracy and misinference errors of uni- and multivariate evaluations of ground-truth models of brain function of single source region and double source regions**. **LSM_vc**: LSM volume corrected; **TP**: true positive; **TN**: true negative; **FP**: false positive; **FN**: false negative. **Accuracy** = *(TP+TN)/(TP+TN+FP+FN)*; **Accuracy_weighted** = *(TP*(1-var(diag))+TN*(1-sum(off_diag)))/(TP+TN+FP+FN)*. **Sensitivity** = *TP/(TP+FN)*; **Specificity** = *TN/(TN+FP)*; **Mis-inference error** = sum of all inferred regional contributions beyond the ones of the target/s. All the quantities are computed on the normalized significant values in the matrices (figures instead show all the values in the matrices, without excluding the nonsignificant values). For all simulations, we used a regression tree predictor (default parameters).

Inference method	Accuracy %	Accuracy weighted %	Sensitivity %	Specificity %	Misinference error %
Double source binary redundant (BA39 and BA44)					
LSC (Fig. 3A)	22	22	100	18	92
LSM (Fig. 3B)	34	34	100	31	88
MAPP (Fig. 3 C)	100	100	100	100	0
MSA (Fig. 3D)	100	100	100	100	0
Double source graded redundant (BA39 and BA44)					
LSC (Fig. 3E)	22	22	100	18	90
LSM (Fig. 3F)	29	29	100	26	89
MAPP (Fig. 3G)	26	26	100	22	10
MSA (Fig. 3H)	33	33	100	30	20
Double source binary mutual inhibition (BA39 and BA44)					
LSC	27	27	100	23	90
LSM	49	48	100	46	83
MAPP	98	98	100	97	0
MSA	100	100	100	100	0
Double source graded mutual inhibition (BA39 and BA44)					
LSC	22	22	100	18	90
LSM	44	44	100	41	90
MAPP	63	63	100	62	11
MSA	92	93	100	92	16

Table 2: **Accuracy and misinference errors of uni- and multivariate evaluations of ground-truth models of brain function for a concrete choice of double source regions: BA39 and BA44**. **LSM_vc**: LSM volume corrected; **TP**: true positive; **TN**: true negative; **FP**: false positive; **FN**: false negative. **Accuracy** = *(TP+TN)/(TP+TN+FP+FN)*; **Accuracy_weighted** = *(TP*(1-var(diag))+TN*(1-sum(off_diag)))/(TP+TN+FP+FN)*. **Sensitivity** = *TP/(TP+FN)*; **Specificity** = *TN/(TN+FP)*; **Mis-inference error** = sum of all inferred regional contributions beyond the ones of the target/s. All the quantities are computed on the normalized significant values in the matrices (figures instead show all the values in the matrices, without excluding the nonsignificant values). For all simulations, we used a regression tree predictor (default parameters).

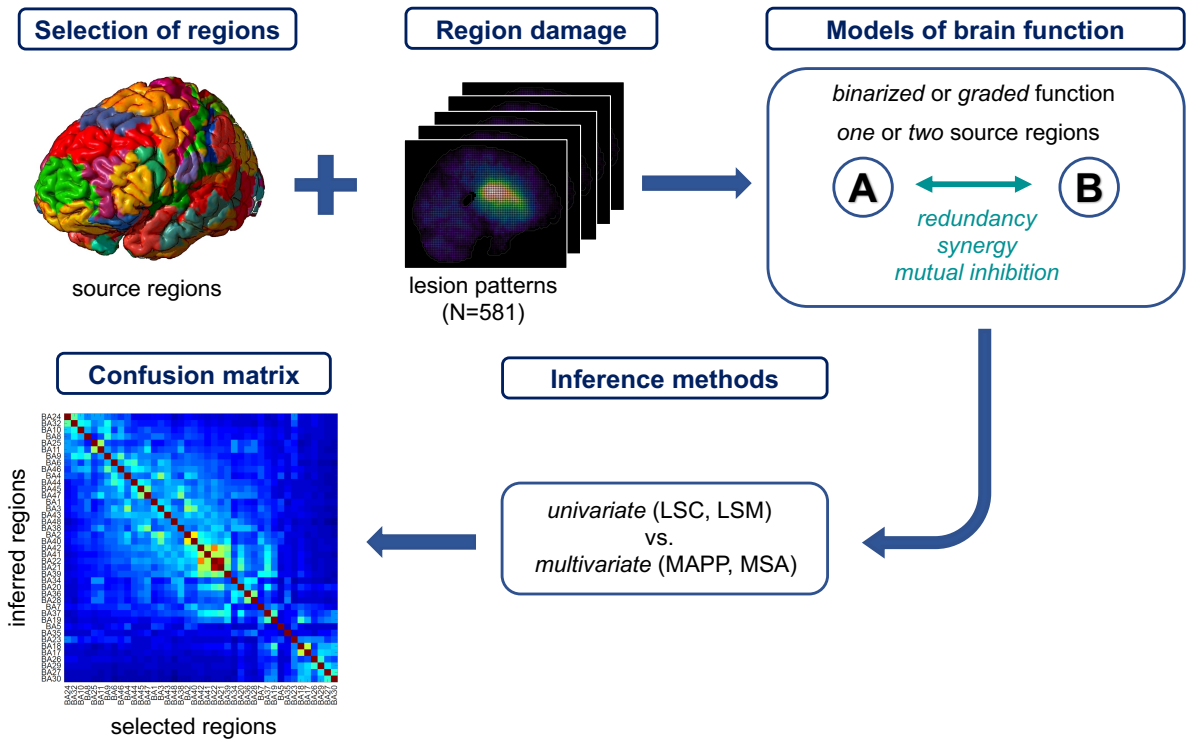

Figure 1: **Validation of univariate and multivariate lesion inference methods by ground truth models of brain function.** Function was assumed to arise at the regional level, from contributions and interactions of one or two source regions, here selected *a priori* from the set of 41 Brodmann Areas. Region damage was modelled with empirical stroke lesion data (N=581). Damage was assumed to have a categorical or gradual impact on regional function, and regions could interact by synergy, redundancy or mutual inhibition to produce a hypothetical brain function. Lesion patterns and the associated simulated function values were passed to two univariate (Lesion Symptom Correlation, LSC, and Lesion Symptom Mapping, LSM) and two multivariate (Multi-Area Pattern Prediction, MAPP, and Multiperturbation Shapley value Analysis, MSA) lesion inference methods. Finally, the regions inferred by these methods to be functionally contributing were compared with the originally selected regions, determining the accuracy, sensitivity and specificity for each inference method and ground truth model.

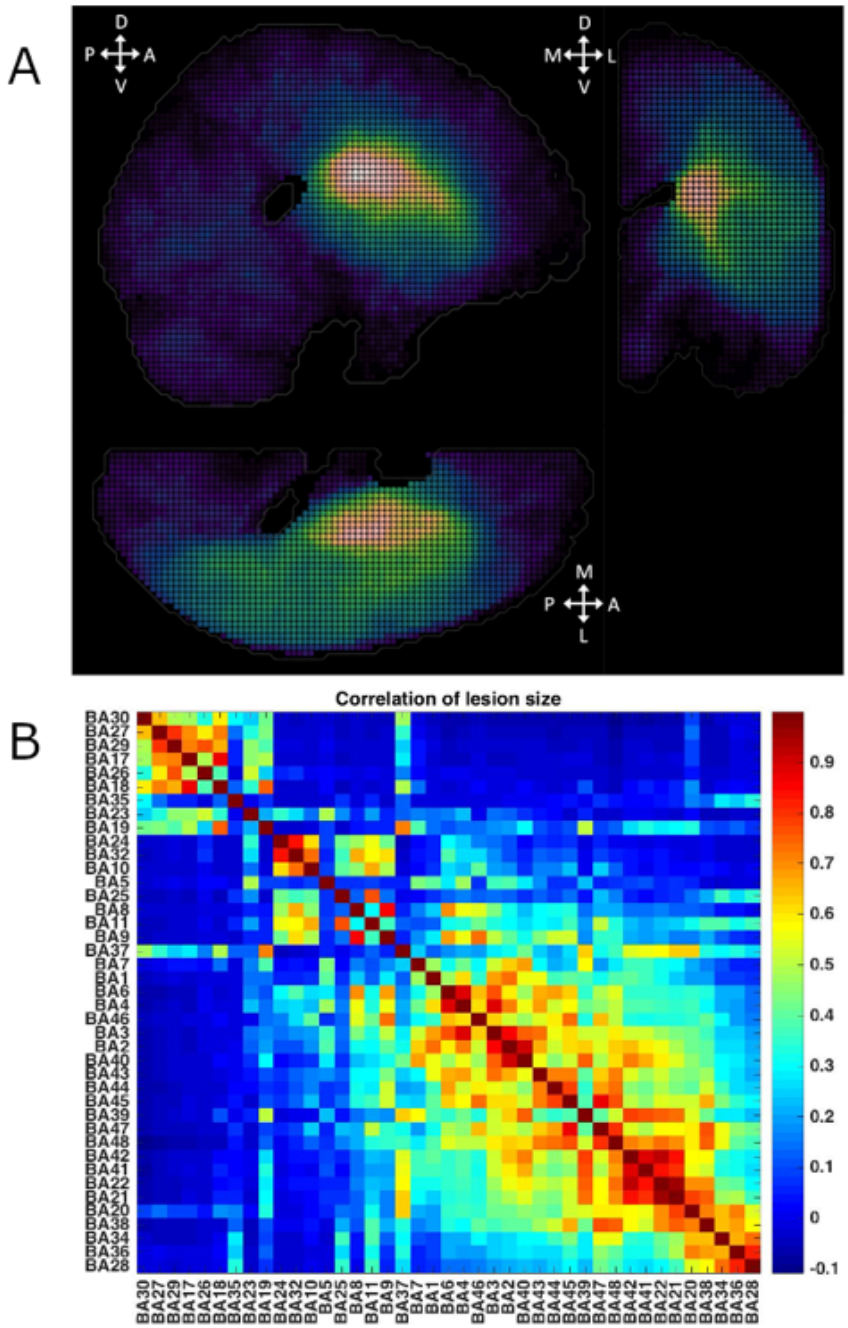

Figure 2: **Lesion distribution in the analysed cohort of 581 stroke patients.** (A) Overlay plot of stroke lesions from all patients included in the analysis (n=581). The color bar indicates lesion frequency across all patients. (B) Correlation of area lesion patterns. Areas are resorted to show the highest correlation values close to each other. The plot demonstrates that many areas are affected by damage in a similar way.

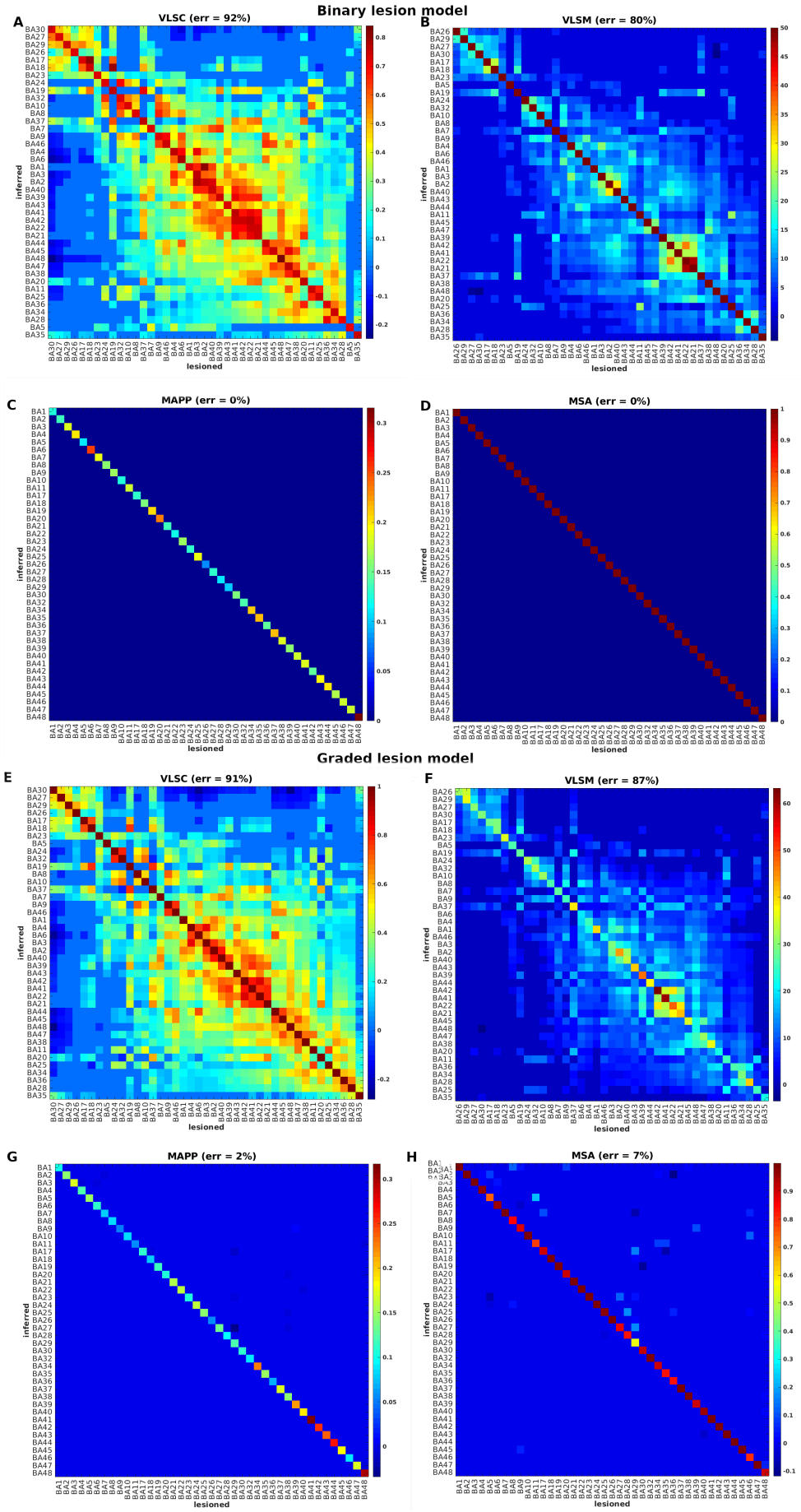
Binary lesion model
A
VLSC (err = 92%)
B
VLSM (err = 80%)
C
MAPP (err = 0%)
D
MSA (err = 0%)
Graded lesion model
E
VLSC (err = 91%)
F
VLSM (err = 87%)
G
MAPP (err = 2%)
H
MSA (err = 7%)
inferred
lesioned

Figure 3: **Ground-truth single-region lesion models.** Comparison of univariate approaches (panels A, B, E, F) and multivariate approaches (panels C, D, G, H), for ground-truth single-region lesion models. LSC and LSM values were sorted to bring the highest contribution values close to each other. Represented quantities are not normalized.

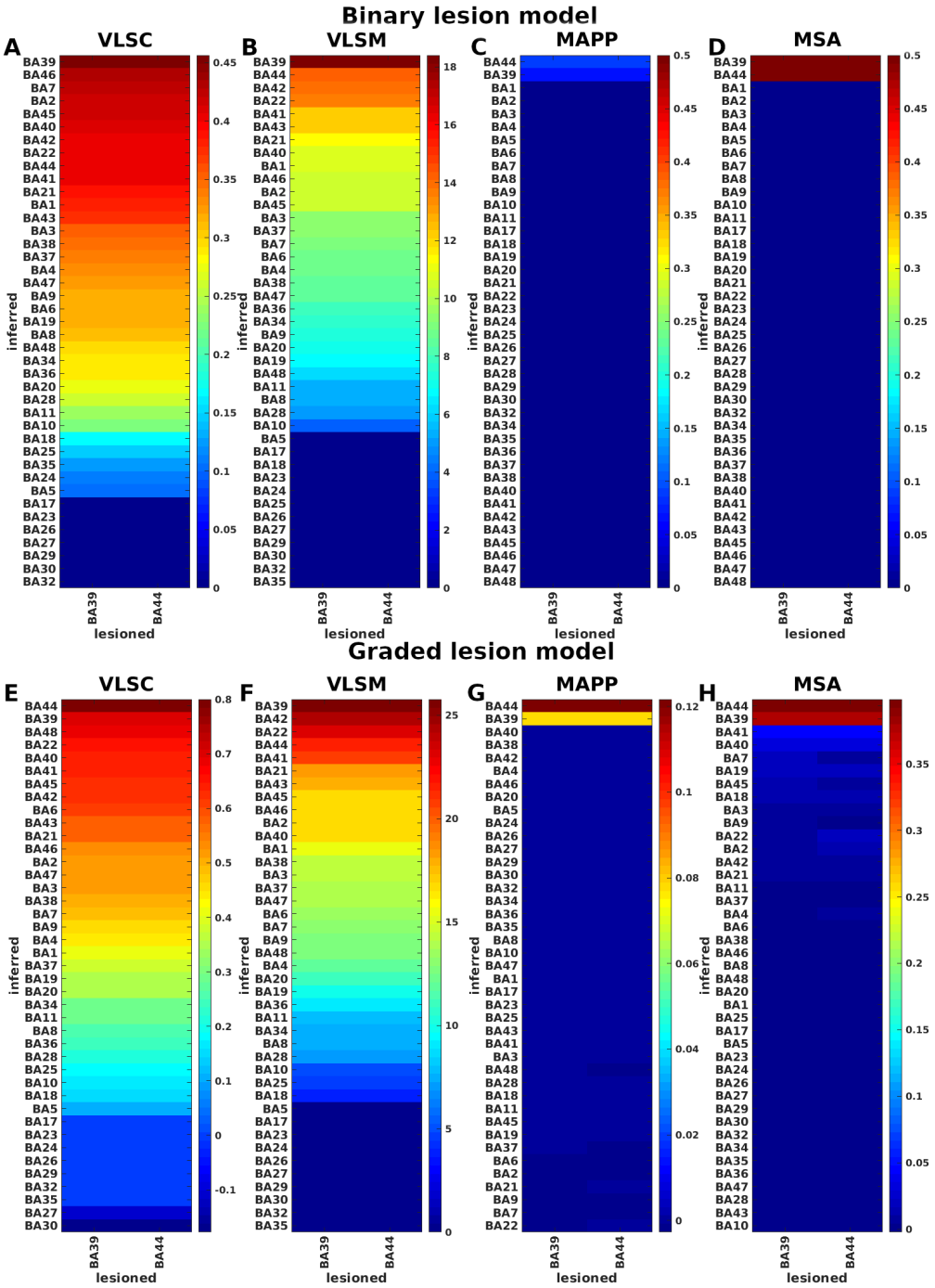

Figure 4: **Ground-truth lesion models of double regions BA39 and BA44.** Comparison between univariate (panels A, B, E, F) and multivariate (panels C, D, G, H) methods, for specific ground-truth lesion models of double regions BA39 and BA44. Represented quantities are not normalized.