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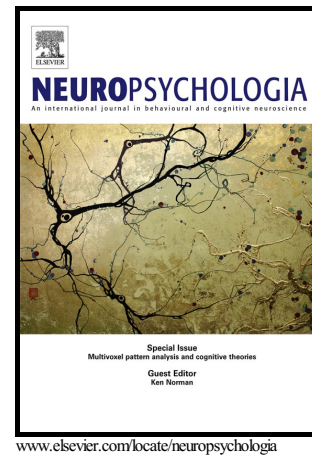
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The impact of sample size on the reproducibility of voxel-based lesion-deficit mappings

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Abstract

This study investigated how sample size affects the reproducibility of findings from univariate voxel-based lesion-deficit analyses (e.g., voxel-based lesion-symptom mapping and voxel-based morphometry). Our effect of interest was the strength of the mapping between brain damage and speech articulation difficulties, as measured in terms of the proportion of variance explained. First, we identified a region of interest by searching on a voxel-by-voxel basis for brain areas where greater lesion load was associated with poorer speech articulation using a large sample of 360 right-handed English-speaking stroke survivors. We then randomly drew thousands of bootstrap samples from this data set that included either 30, 60, 90, 120, 180, or 360 patients. For each resample, we recorded effect size estimates and p values after conducting exactly the same lesion-deficit analysis within the previously identified region of interest and holding all procedures constant. The results show (1) how often small effect sizes in a heterogeneous population fail to be detected; (2) how effect size and its statistical significance varies with sample size; (3) how low-powered studies (due to small sample sizes) can greatly over-estimate as well as under-estimate effect sizes; and (4) how large sample sizes ($N \geq 90$) can yield highly significant p values even when effect sizes are so small that they become trivial in practical terms. The implications of these findings for interpreting the results from univariate voxel-based lesion-deficit analyses are discussed.

Keywords

voxel-based; lesion-symptom; lesion; deficit; reproducibility; stroke; speech production

1 1. Introduction

2 There is a great deal of evidence showing how both false positive and false
3 negative results increase as sample size decreases (Bakker et al., 2012; Button et
4 al., 2013a; Chen et al., 2018; Cremers et al., 2017; Ingre, 2013; Ioannidis, 2008) and
5 how inadequate statistical power can lead to replication failures (Anderson et al.,
6 2017; Bakker et al., 2012; Perugini et al., 2014; Simonsohn et al., 2014a; Szucs and
7 Ioannidis, 2017). However, the impact of sample size on false negative and false
8 positive rates has never been quantified in mass-univariate voxel-based lesion-deficit
9 mapping (e.g., voxel-based lesion-symptom mapping and voxel-based
10 morphometry). Using data from a large sample of stroke patients, we firstly
11 estimated the magnitude of a lesion-deficit mapping of interest and then formally
12 investigated how effect size and its statistical significance varies with sample size. In
13 addition to demonstrating how small samples can result in over- and under-
14 estimations of effect size, we also highlight an issue with large sample sizes whereby
15 high statistical power dramatically increases the likelihood of detecting effects that
16 are so small that they become uninteresting from a scientific viewpoint (i.e. the
17 fallacy of classical inference; Friston et al., 2012). In other words, statistically
18 significant findings when sample sizes are large can hide the fact that the effect
19 under investigation might be of little importance in practical terms, or, even worse,
20 the result of random chance alone and thereby a false positive (Smith and Nichols,
21 2018).

22 To investigate the effect of sample size on the results of univariate voxel-
23 based lesion-deficit mapping, we randomly drew thousands of resamples (with a
24 range of sample sizes) from a set of data from 360 stroke survivors who had
25 collectively acquired a wide range of left hemisphere lesions and cognitive
26 impairments. By using a single patient population and holding all procedures and
27 analyses constant, we ensured that variability in the results across thousands of
28 random resamples cannot be explained by methodological confounds - such as the
29 use of dissimilar recruitment strategies and/or behavioural assessments - that are
30 likely to influence the findings of studies that aggregate data from multiple
31 independent sources (e.g., meta-analyses; Müller et al., 2018). Furthermore, by
32 performing our statistical analyses on actual data, rather than running simulations on

33 synthetically-generated data, we attempt to recreate real-world scenarios that could
34 be encountered by researchers conducting lesion-deficit mapping studies.

35 The goal of our resampling procedure was to estimate the degree to which the
36 magnitude and statistical significance of the exact same lesion-deficit mapping (i.e.
37 brain areas where damage is associated with difficulties articulating speech)
38 changed with sample size. We report the frequency of significant and non-significant
39 effects (using standard significance thresholds) for 6 different sample sizes: $N = 30$,
40 60, 90, 120, 180 and 360. In a real world situation where only one sample is typically
41 analysed, results are far more likely to be published when they reach statistical
42 significance (i.e. the associated p values are below a certain alpha threshold) than
43 when they fail to produce any evidence in favour of the tested hypothesis. This is
44 known as “publication bias” (e.g., Fusar-Poli et al., 2014; Ioannidis et al., 2014;
45 Johnson et al., 2017; Simonsohn et al., 2014a). For example, the prevalence of
46 “positive” (i.e. statistically significant) findings across a wide range of publication
47 outlets, including neuroscience and psychology, has been shown to be well over
48 80% (Fanelli, 2010, 2012), which suggests that the vast majority of studies that yield
49 “negative” findings are left unpublished. This is known as “the file drawer problem”
50 (Franco et al., 2014; Simonsohn et al., 2014b). Moreover, the number of “positive”
51 results in the fMRI (David et al., 2013) and brain volume abnormalities (Ioannidis,
52 2011) literature has been demonstrated to be significantly greater than the number
53 expected on the basis of statistical power considerations.

54 By leaving non-significant results in the file drawer, it becomes increasingly
55 difficult to ascertain which effects are true (and would replicate in subsequent
56 studies) and which are false (and would not replicate in subsequent studies). A
57 highly significant result from a heterogeneous population could, for example, be
58 driven by random noise when a study selects, by chance, a sample that renders an
59 inflated (unstandardized) effect size and under-estimated variance. In line with this
60 rationale, it has been claimed that more than 50% of all significant effects reported in
61 cognitive neuroscience and psychology journals are likely to correspond to false
62 positives (Szucs and Ioannidis, 2017).

63 Our study therefore speaks directly to the “replication crisis” that is currently
64 being highlighted in psychology and neuroscience (Forstmeier et al., 2017; Gelman

65 and Geurts, 2017; Ioannidis, 2005; Loken and Gelman, 2017; Munafò et al., 2017;
66 Pashler and Wagenmakers, 2012). In the field of psychology, for example, a large-
67 scale collaborative initiative reported that it could only successfully replicate less
68 than 40% of original effects from a representative set of one hundred randomly
69 selected studies (Open Science Collaboration, 2015). Similar failed replication
70 attempts have also been recorded in other research areas including those
71 investigating structural brain-behaviour correlations (Boekel et al., 2015) and the
72 blood-oxygen-level-dependent response (Chen et al., 2018; Wende et al., 2017).

73 **2. Materials and Methods**

74 *2.1. Participants*

75 Data from all participants were retrieved from the Predicting Language
76 Outcome and Recovery After Stroke (PLORAS) database (Price et al., 2010; Seghier
77 et al., 2016). At a minimum, the data available for each patient included: a full
78 assessment of speech and language abilities and a 3D lesion image, in standard
79 space, created from a T1-weighted high resolution (1 mm isotropic voxels)
80 anatomical whole-brain volume, using our automated lesion identification software
81 (Seghier et al., 2008). The study was approved by the Joint Research Ethics
82 Committee of the National Hospital for Neurology and Neurosurgery and the Institute
83 of Neurology. All patients gave written informed consent prior to participation and
84 were compensated for their time.

85 Our patient selection criteria included all adult stroke survivors who: (i) had a
86 left-hemisphere lesion (as attested by a clinical neurologist: co-author A.P.L.) that
87 was greater than 1 cm³ (as measured by our automated lesion identification tool;
88 Seghier et al., 2008); (ii) had no history of neurological or psychiatric illness that was
89 not related to their stroke; (iii) were right-handed (pre-morbidly); and, (iv) were native
90 speakers of English. Additionally, individuals who had missing scores on the tasks of
91 interest (see below for details) were excluded from the study. These criteria were
92 met by a total of 363 stroke patients whose data were collected between April 2003
93 and December 2016. To ensure that our full sample could be divided evenly into
94 smaller resampled data sets (see below for details), we additionally excluded from
95 any further analyses the 3 patients with the smallest lesions (i.e. 1.2, 1.3 and 1.4 cm³

96 in size). See Table 1 for demographic and clinical details of the full sample of 360
97 stroke patients.

98 2.2. *Behavioural assessment*

99 All patients recruited to the PLORAS database are assessed on the
100 Comprehensive Aphasia Test (CAT) (Swinburn et al., 2004). The CAT is a fully
101 standardised test battery, which consists of a total of 27 different tasks. For ease of
102 comparison across tasks, the authors of the CAT encourage the conversion (through
103 a non-linear transformation) of raw scores into T-scores, which represent how well
104 the patient performed relative to a reference population of 113 patients with aphasia,
105 56 of whom were tested more than once. For example, a T-score of 50 indicates the
106 mean of the patient sample used to standardise the CAT, whereas a T-score of 60
107 represents one standard deviation above the mean. Most people without post-stroke
108 aphasia would therefore be expected to score above the average of the patient
109 standardisation sample on any given task from the CAT. The threshold for
110 impairment is defined relative to a second reference population of 27 neurologically-
111 normal controls. Specifically, it is the point below which the score would place the
112 patient in the bottom 5% of the control population (Swinburn et al., 2004). Lower
113 scores indicate poorer performance. Importantly, the two standardisation samples
114 referred to before (i.e. 113 patients with aphasia and 27 neurologically-normal
115 controls) are completely independent of the data we report in the current paper (for
116 more details on the standardisation samples, see Swinburn et al., 2004).

117 As stated in the CAT manual (p. 71), the main advantages of converting raw
118 scores into T-scores is that this allows: (i) scores from different tasks to be compared
119 because they have been put on a common scale; and (ii) the use of parametric
120 statistics given that T-scores are normally distributed scores with a mean of 50 and a
121 standard deviation of 10.

122 The current study focused exclusively on a total of 5 tasks from the CAT. Task
123 1 used nonword repetition to assess the patient's ability to articulate speech. Task 2
124 used written picture naming to test the patient's ability to find the names of objects
125 (lexical/phonological retrieval). Tasks 3-5 tested the patient's ability to recognise,
126 process and remember the semantic content of pictures and auditory words. Task
127 details were as follows:

128 **Task 1:** The CAT nonword repetition (Rep-N) task aurally presents five nonsense
129 words (e.g., gart), one at a time, with instructions to repeat them aloud. Immediate
130 correct responses were given a score of 2; incorrect responses were given a score
131 of 0; correct responses after a self-correction or a delay (> 5 seconds) were given a
132 score of 1. Articulatory errors (e.g., dysarthric distortions) not affecting the perceptual
133 identity of the target were scored as correct. Verbal, phonemic, neologistic and
134 apraxic errors were scored as incorrect. T-scores equal to or below 51 constitute the
135 impaired range.

136 **Task 2:** The CAT written picture naming (Writt-PN) task visually presents five
137 pictures of objects (e.g., tank), one at a time, with instructions to write their names
138 down. Letters in the correct position were given a score of 1 each. Substitutions,
139 omissions and transpositions were given a score of 0. One point was deducted from
140 the total score if one or more letters were added to the target word. T-scores equal to
141 or below 54 constitute the impaired range.

142 **Task 3:** The CAT semantic associations (Sem-A) task visually presents five pictures
143 of objects simultaneously. The instructions were to match the picture at the centre
144 (e.g., mitten) with one of four possible alternatives according to the strongest
145 semantic association (e.g., hand, sock, jersey, and lighthouse). The inclusion of a
146 semantically related distractor (e.g., sock) encouraged deeper levels of semantic
147 processing/control. There are a total of ten test trials plus a practice one at the
148 beginning. Correct responses were given a score of 1; incorrect responses were
149 given a score of 0. T-scores equal to or below 47 constitute the impaired range.

150 **Task 4:** The CAT recognition memory (Recog-M) task visually presents each of the
151 ten central items from the CAT semantic associations task (one at a time) along with
152 three unrelated distractors. The instructions were to indicate which of the four
153 pictures on display had been seen before. There are a total of ten test trials plus a
154 practice one at the beginning. The scoring system for this task was identical to that
155 used in the semantic associations task. T-scores equal to or below 43 constitute the
156 impaired range.

157 **Task 5:** The CAT auditory word-to-picture matching (A_W -P) task involves hearing a
158 word produced by the examiner and selecting the picture among four possible
159 alternatives that best matches the meaning of the heard word. There are a total of

160 fifteen test trials plus a practice one at the beginning. Immediate correct responses
161 were given a score of 2; incorrect responses were given a score of 0; correct
162 responses after a self-correction or a delay (> 5 seconds) were given a score of 1. T-
163 scores equal to or below 51 constitute the impaired range.

164 2.3. MRI data acquisition, pre-processing and lesion identification

165 T1-weighted high resolution anatomical whole-brain volumes were available
166 for all patients ($n = 360$). Four different MRI scanners (Siemens Healthcare,
167 Erlangen, Germany) were used to acquire the structural images: 167 patients were
168 imaged on a 3T Trio scanner, 131 on a 1.5T Sonata scanner, 57 on a 1.5T Avanto
169 scanner, and five on a 3T Allegra scanner. For anatomical images acquired on the
170 1.5T Avanto scanner, a 3D magnetization-prepared rapid acquisition gradient-echo
171 (MPRAGE) sequence was used to acquire 176 sagittal slices with a matrix size of
172 256×224 , yielding a final spatial resolution of 1 mm isotropic voxels (repetition
173 time/echo time/inversion time = 2730/3.57/1000 ms). For anatomical images
174 acquired on the other three scanners, an optimised 3D modified driven equilibrium
175 Fourier transform (MDEFT) sequence was used to acquire 176 sagittal slices with a
176 matrix size of 256×224 , yielding a final spatial resolution of 1 mm isotropic voxels:
177 repetition time/echo time/inversion time = 12.24/3.56/530 ms and 7.92/2.48/910 ms
178 at 1.5T and 3T, respectively (Deichmann et al., 2004).

179 The T1-weighted anatomical whole-brain volume of each patient was
180 subsequently analysed with our automated lesion identification toolbox using default
181 parameters (for more details, see Seghier et al., 2008). This converts a scanner-
182 sensitive raw image into a quantitative assessment of structural abnormality that
183 should be independent of the scanner used. The procedure combines a modified
184 segmentation-normalisation routine with an outlier detection algorithm according to
185 the fuzzy logic clustering principle (for more details, see Seghier et al., 2007). The
186 outlier detection algorithm assumes that a lesioned brain is an outlier in relation to
187 normal (control) brains. The output includes two 3D lesion images in standard MNI
188 space, generated at a spatial resolution of $2 \times 2 \times 2 \text{ mm}^3$. The first is a fuzzy lesion
189 image that encodes the degree of structural abnormality on a continuous scale from
190 0 (completely normal) to 1 (completely abnormal) at each given voxel relative to
191 normative data drawn from a sample of 64 neurologically-normal controls. A voxel

192 with a high degree of abnormality (i.e. a value near to 1 in the fuzzy lesion image)
193 therefore means that its intensity in the segmented grey and white matter deviated
194 markedly from the normal range. The second is a binary lesion image, which is
195 simply a thresholded (i.e. lesion/no lesion) version of the fuzzy lesion image. All our
196 statistical analyses were based on the fuzzy images. The binary images were used
197 to delineate the lesions, to estimate lesion size and to create lesion overlap maps.

198 2.4. *Lesion-deficit analyses*

199 We used voxel-based morphometry (Ashburner and Friston, 2000; Mechelli et
200 al., 2005) to assess lesion-deficit relationships (Mummery et al., 2000; Tyler et al.,
201 2005), performed in SPM12 using the general linear model. The imaging data
202 entered into the voxel-based analysis were the fuzzy (continuous) lesion images that
203 are produced by our automated lesion identification toolbox.

204 The most important advantage of utilising the fuzzy lesion images (as in Price
205 et al., 2010) over alternative methods is that they provide a quantitative measure of
206 the degree of structural abnormality, at each and every voxel of the brain, relative to
207 neurologically-normal controls. In contrast to fuzzy lesion images, (i) binary lesion
208 images do not provide a continuous measure of structural abnormality and will be
209 less sensitive to subtle changes that are below an arbitrary threshold for damage
210 (e.g., Fridriksson et al., 2013; Gajardo-Vidal et al., 2018); (ii) normalised T1 images
211 do not distinguish between typical and atypical (abnormal) variability in brain
212 structure (e.g., Stamatakis and Tyler, 2005); and (iii) segmented grey or white matter
213 probability images when used in isolation (as in standard VBM routines) do not
214 provide a complete account of the whole of the lesion (e.g., Mehta et al. 2003).

215 In Analysis 1, the fuzzy lesion images were entered into a voxel-based
216 multiple regression model with 6 different regressors (5 behavioural scores and
217 lesion size); see Fig. 1. The regressor of interest was nonword repetition scores that
218 are sensitive to difficulties articulating speech. In addition, the following regressors
219 were included to factor out other sources of variance: written picture naming scores
220 (which are sensitive to name retrieval abilities), semantic associations scores (which
221 are sensitive to visual recognition and semantic processing), auditory word-to-picture
222 matching scores (which are sensitive to auditory recognition and lexical-semantic
223 processing), recognition memory scores (which are sensitive to picture recognition

224 and memory) and lesion size (to partial out linear effects of lesion size). For the
225 voxel-based lesion-deficit analysis (with 360 patients), the search volume was
226 restricted to voxels that were damaged in at least five patients (as in Fridriksson et
227 al., 2016; for rationale, see Sperber and Karnath, 2017). For this purpose, a lesion
228 overlap map based on the binary lesion images from all 360 patients was created,
229 thresholded at five, and used as an inclusive mask before estimating the model (see
230 Fig. 2A). Our statistical voxel-level threshold was set at $p < 0.05$ after family-wise
231 error (FWE) correction for multiple comparisons (using random field theory as
232 implemented in SPM; Flandin and Friston, 2015) across the whole search volume
233 (for alternative approaches, see Mirman et al., 2018).

234 Having identified a significant lesion-deficit mapping, we quantified the
235 strength of the association between lesion and deficit by: (i) extracting the raw signal
236 (which indexes the degree of structural abnormality) from each statistically significant
237 voxel; (ii) averaging the signal across voxels (i.e. a single value per patient); and,
238 finally, (iii) computing the partial correlation between lesion load in the region of
239 interest and nonword repetition scores, after adjusting for the effect of the covariates
240 of no interest (i.e. 4 behavioural scores and lesion size). Our measure of effect size
241 was the proportion of variance ($= R^2$) in nonword repetition scores explained
242 uniquely by lesion load in the region of interest (i.e. the best estimate of the true
243 population effect that we have).

244 In Analysis 2, we investigated how sample size affected the reproducibility of
245 the lesion-deficit mapping within the region of interest identified in Analysis 1.
246 Specifically, we generated 6000 bootstrap samples of the following sizes: 360, 180,
247 120, 90, 60 and 30 (i.e. 36000 resamples in total). These sample sizes were
248 selected to follow as closely as possible those observed in the vast majority of
249 published voxel-based lesion-deficit mapping studies (e.g., Dressing et al., 2018;
250 Fridriksson et al., 2013, 2016; Halai et al., 2017; Schwartz et al., 2011, 2012). For
251 each iteration of the resampling procedure, individuals were drawn randomly from
252 the full set of 360 patients with replacement, meaning that the probability of being
253 chosen remained constant throughout the selection process (i.e. the procedure
254 satisfied the Markovian, memory-less, property). For each bootstrap sample, the
255 partial correlation between nonword repetition scores and lesion load (averaged
256 across voxels in the region of interest from Analysis 1) was computed. The resulting

257 R^2 and p values were recorded, after regressing out the variance accounted for by
258 the covariates of no interest. Of note, when we re-ran the resampling procedure
259 outlined above with the replacement feature disabled (i.e. sampling without
260 replacement), virtually the same results were obtained (for more details, see
261 Supplementary Material).

262 In addition, to rule out the possibility that variability in the results could simply
263 be explained by differences in the distribution of damage across the brain, we
264 quantified statistical power in the region of interest from Analysis 1 for a
265 representative subset of bootstrap samples. Specifically, only those resamples that
266 produced an R^2 value which fell exactly at a particular decile (i.e. 0th, 10th,
267 20th...100th) of the distribution of effect sizes were considered. This resulted in the
268 selection of a total of 66 bootstrap samples (i.e. 11 for each sample size); see Table
269 2. Critically, our power calculations show where in the brain there was sufficient
270 statistical power to detect a significant lesion-deficit association at a threshold of $p <$
271 0.05 after correction for multiple comparisons. The statistical power maps were
272 generated using the “nii_powermap” function of NiiStat
273 (<https://www.nitrc.org/projects/niistat/>), which is a set of Matlab scripts for analysing
274 neuroimaging data from clinical populations.

275 Importantly, we have chosen to assess in-sample effect sizes, i.e. without
276 validating in a separate data set (Friston, 2012). In this context, the effect size is
277 providing an estimate of the strength of the particular effect identified by our analysis
278 in our data. It may be that an out-of-sample prediction - on new data - would indicate
279 a smaller effect size. However, this would not invalidate the logic of our reasoning,
280 particularly since the essential point we are making here is that our effect size
281 estimate (i.e. approximately 11% in R^2 terms) is very small. If there is inflation in this
282 estimate, it could only mean that the out-of-sample effect size would be even less.
283 Therefore, we have been able to show that even for an over-estimated effect size (if
284 it would turn out to be), there are serious problems that arise from small sample
285 sizes, the fallacy of classical inference, and publication bias. The impact of these
286 issues on the reliability of the findings would only be worse if the effect size were to
287 come down.

288 Furthermore, we have first statistically selected an ROI in a large sample of
289 patients, with a “left-hemisphere” analysis, and then used smaller and smaller
290 bootstrap samples that focused on the identified ROI. In this sense, we are

291 performing (non-orthogonal) statistical tests in a previously selected ROI, which
292 could potentially inflate false positive rates (Brooks et al., 2017). Consequently, the
293 results derived from the analysis of smaller samples should not be taken as robust
294 findings: they are being presented to make important methodological points. Our
295 best statistical estimates of the effect considered are those obtained from the full
296 data set.

297 **3. Results**

298 *3.1. Analysis 1: identifying a region of interest*

299 Poorer speech articulation was significantly associated with greater lesion
300 load (after controlling for written picture naming, recognition memory, semantic
301 associations and auditory word-to-picture matching scores in addition to lesion size)
302 in 549 voxels (= 4.4 cm³ in size; see Table 3). These voxels became our region of
303 interest (ROI) for all subsequent analyses. They were located in parts of the left
304 ventral primary motor and somatosensory cortices (i.e. tongue, larynx, head and face
305 regions), anterior supramarginal gyrus, posterior insula and surrounding white matter
306 (see Fig. 2B).

307 This highly significant lesion-deficit relationship accounted for 11% of the
308 variance (95% credible interval calculated using a flat prior: 0.06-0.18; Morey et al.,
309 2016); see Fig. 3. In the following analyses, we ask how sample size affects the
310 reproducibility of the identified effect.

311 *3.2. Analysis 2: effect size variability and replicability*

312 Although the mean/median effect sizes were similar across sample sizes, the
313 mean/median p values changed considerably with sample size (see Fig. 4), because
314 there was wide sample-to-sample variability in the extent to which the original effect
315 was replicated. For instance, less than 40% of the random resamples where $N = 30$
316 generated significant p values, while this raised to virtually 100% for the resampled
317 data sets where $N \geq 180$. Overall, R^2 values ranged between 0.00 and 0.79, whereas
318 p values ranged between $6 \cdot 10^{-27}$ and 1 (see Fig. 5A and B). Additionally, our
319 analyses showed that, as sample size increased, R^2 values tended to fall closer to
320 the mean of the effect size distribution, although a not inconsiderable degree of
321 uncertainty regarding R^2 estimation remained (even for $N = 180$ and 360). In other

322 words, the dispersion of the R^2 values tended to be larger with smaller sample sizes
323 (see Fig. 5A), resulting in less precision in the estimation of the magnitude of the true
324 population effect.

325 3.2.1. Low-powered resamples can inflate effect sizes

326 Since studies that obtain statistically non-significant results (i.e. typically $p \geq$
327 0.05) are hardly ever published (also known as the file drawer problem or study
328 publication bias), we focused directly upon the resampled data sets that produced
329 significant p values. For $N = 30$, the mean and median effect sizes of these
330 significant resamples (i.e. roughly 37%) were 0.26 and 0.24 (range = 0.16-0.79).
331 Conversely, the mean and median effect sizes for the $N = 30$ resamples where the
332 lesion-deficit mapping did not reach statistical significance (roughly 63%) were 0.07
333 and 0.06 (range = 0.00-0.16); see Table 4 for similar findings when $N = 60$. Critically,
334 using a more stringent statistical threshold would only aggravate the problem (for
335 more details, see Table 4). With larger sample sizes ($N \geq 90$), however, effect size
336 inflation is counteracted since both over- and under-estimations of the true effect
337 size surpassed the threshold for statistical significance, resulting in relatively
338 accurate mean estimates (0.13, 0.12, 0.12, and 0.11 respectively).

339 3.2.2. High-powered resamples are sensitive to trivial/small effects

340 The frequency with which a significant association was observed between
341 lesion load in the ROI and nonword repetition scores increased dramatically with
342 sample size. For example, whereas roughly 37% of the effects for $N = 30$ would be
343 typically regarded as statistically significant (i.e. $p < 0.05$), more than 85% of the
344 lesion-deficit mappings for $N \geq 90$ generated equally low or even lower p values (see
345 Table 4). More importantly, effects as small as 0.05 in R^2 terms (i.e. that only
346 accounted for 5% of the variance) reached statistical significance for $N = 90$; and this
347 phenomenon was even more pronounced in the presence of larger sample sizes:
348 0.02 for $N = 180$ (see Table 4 and Fig. 5A). Reporting point and interval estimates of
349 effect sizes is therefore essential for assessing the importance or triviality of the
350 identified lesion-deficit mapping, which is particularly relevant when the study uses
351 large sample sizes.

352 4. Discussion

353 The goal of this study was to examine how sample size influences the
354 reproducibility of voxel-based lesion-deficit mappings. First, we identified a significant
355 lesion-deficit association and estimated its magnitude using data from a very large
356 sample of 360 patients who were all right-handed, English speaking stroke survivors
357 with unilateral left hemisphere damage. By repeating the same analysis on
358 thousands of bootstrap samples of different sizes we illustrate how the estimated
359 effect size, and its statistical significance, varied across replications. This allowed us
360 to index the degree of uncertainty in the estimation of the true population effect as a
361 function of sample size. As expected, effect sizes were more likely to be over-
362 estimated or under-estimated with small sample sizes (i.e. variability in the results
363 increased as sample size decreased). Conversely, we demonstrate how highly
364 significant lesion-deficit mappings can be driven by a negligible proportion of the
365 variance when the sample size is very large.

366 4.1. *Estimating the true effect size*

367 The first part of our investigation identified a region of interest (ROI) where
368 damage was reliably associated with impairments in speech articulation. We then
369 calculated what proportion of the variance in nonword repetition scores could be
370 accounted for by the degree of damage to the identified region after factoring out
371 confounds from auditory and visual perception, speech recognition, lexical/semantic
372 processing and word retrieval abilities. The ROI included anatomical brain structures
373 that have been associated with speech production in many previous lesion studies.
374 These include the insula (Ogar et al., 2006), the precentral gyrus, the postcentral
375 gyrus, the supramarginal gyrus and surrounding white matter (Baldo et al., 2011;
376 Basilakos et al., 2015). It did not involve the inferior frontal gyrus/frontal operculum
377 as reported in Hillis et al. (2004) and Baldo et al. (2011), even though our full sample
378 incorporated plenty of patients with damage to these regions (see Fig. 2A). We do
379 not attempt here to adjudicate whether this discrepancy was a consequence of a
380 false negative in our study or a false positive in prior studies. Our focus was on how
381 well the identified lesion-deficit mapping could be replicated across thousands of
382 bootstrap samples drawn randomly from the original data set of 360 patients. For
383 each resample, we estimated how much of the variance in nonword repetition scores
384 could be accounted for by lesion load in the ROI (after adjusting for the effect of the
385 covariates of no interest). These effect sizes and their statistical significance were

386 then compared to our best estimate of the “true” population effect size, which was
387 found (from our full sample of 360 patients) to be 11%.

388 4.2. *Variability in the estimated effect size and its statistical significance*

389 The second part of our investigation showed that the probability of finding a
390 significant lesion-deficit association in the ROI from the first analysis (with 360
391 participants), depended on the size of the sample. For larger samples ($N \geq 180$), the
392 effect of interest was detected in virtually 100% of resamples. Whereas for smaller
393 samples ($N = 30$), it was detected in less than 40% of resamples (see Table 4). We
394 can also show that p values decrease as N increases, even when effect sizes are
395 equated (see Fig. 4 and 50th percentile in Table 2). This observation is in line with
396 prior reports that p values exhibit wide sample-to-sample variability (Cumming, 2008;
397 Halsey et al., 2015; Vsevolozhskaya et al., 2017), particularly in the presence of
398 small sample sizes (Hentschke and Stüttgen, 2011).

399 When considering the central tendency of effect size estimates, the difference
400 between larger and smaller resamples is dramatically reduced compared to that
401 seen for p values (see mean/median effect sizes in Fig. 4). Nevertheless, even if p
402 values were completely abandoned (e.g., Trafimow and Marks, 2015), there is still a
403 great deal of uncertainty in the accuracy with which effect sizes can be estimated
404 when small samples are used. This highlights the importance of reaching a better
405 balance between null-hypothesis significance testing and effect size estimation
406 (Chen et al., 2017; Cumming, 2014; Morey et al., 2014). Indeed, p values only
407 indicate the likelihood of observing an effect of a given magnitude (when the null
408 hypothesis is true). As such, they cannot convey the same information provided by
409 point and interval estimates of effect sizes (Steward, 2016; Wasserstein and Lazar,
410 2016), particularly since the relationship between p values and effect sizes is non-
411 linear (Hentschke and Stüttgen, 2011; Simonsohn et al., 2014a, 2014b).

412 There are several potential reasons why the magnitude and statistical
413 significance of the same effect varies so markedly across resamples. For example,
414 high sample-to-sample variability could reflect (i) sampling error due to heterogeneity
415 in the lesion-deficit association across participants (Button, 2016; Stanley and
416 Spence, 2014), (ii) outliers that are confounding the effects (Rousselet and Pernet,
417 2012) or (iii) measurement error (Button, 2016; Loken and Gelman, 2017; Stanley

418 and Spence, 2014). In this context, the field needs to adopt informed sampling
419 strategies that ensure representative samples and maximise the probability of
420 identifying generalizable lesion-deficit mappings (Falk et al., 2013; LeWinn et al.,
421 2017; Paus, 2010).

422 4.3. *Unreliable effect sizes in smaller samples*

423 High variance in the results of our lesion-deficit mappings with smaller
424 samples ($N = 30$ and 60) demonstrates how effects can be over- as well as under-
425 estimated (e.g., Cremers et al., 2017; Ioannidis, 2008). Indeed, we show that 85% of
426 all significant random data sets for $N = 30$ yielded effect size estimates that were
427 larger than the upper bound of the credible interval (see Table 5). This is consistent
428 with prior observations that low-powered studies (with small sample sizes) can only
429 consistently detect large deviations from the true population effect (Szucs and
430 Ioannidis, 2017). Put another way, even when effect sizes are accurately estimated
431 from small samples, they are unlikely to attain statistical significance; particularly
432 when the magnitude of the effect under investigation is small or medium. In our data,
433 for example, we found that more than half the analyses with $N = 30$ that did not
434 reach statistical significance produced effect sizes that fell within the credible interval
435 (i.e. accurate estimations of effect sizes resulted in false negatives). Even worse,
436 analyses of small sample sizes can invert the direction of the effect (Gelman and
437 Carlin, 2014) as seen in our data where we found that 5% of all results for $N = 30$
438 were in the wrong direction. Furthermore, reporting such findings as if they were
439 accurate representations of reality would lead to misleading conclusions (Nissen et
440 al., 2016).

441 Critically, the problem was not solved but became worse when we adopted a
442 more stringent statistical threshold, which is contrary to that proposed by Johnson
443 (2013) and Benjamin et al. (2018). For example, if we were to raise the statistical
444 threshold from $p < 0.05$ to $p < 0.001$ for the $N = 30$ resamples, the statistically
445 significant effect sizes would range from 38% to 79% of the variance (compared to
446 11% in the full sample of 360 patients). Increasing sample size, however, does
447 improve accuracy, with less than 10% of significant p values associated with inflated
448 effect sizes when $N \geq 180$ (see Table 5).

449 Given that results are more likely to be published if they reach statistical
450 significance than if they do not (i.e. the file drawer problem or study publication bias),
451 our findings highlight three important implications for future lesion-deficit mapping
452 studies. First, low-powered studies (due to small sample sizes) could lead a whole
453 research field to over-estimate the magnitude of the true population effect. Second,
454 power calculations based on inflated effect sizes from studies with small samples will
455 inevitably over-estimate the statistical power associated with small sample sizes
456 (Anderson et al., 2017). Third, although the mean effect size measured over many
457 studies with small sample sizes will eventually converge on the true effect size, in
458 reality, the same study is seldom replicated exactly and null results are only rarely
459 reported. It has therefore been advocated that, contrary to current practices, it is
460 better to carry out a few well-designed high-powered studies than it is to assimilate
461 the results from multiple low-powered studies (Bakker et al., 2012; Higginson and
462 Munafò, 2016). In brief, large scale studies increase the probability that an identified
463 lesion-deficit mapping is correct (Button et al., 2013a; Szucs and Ioannidis, 2017).

464 4.4. *Trivial effect sizes in larger samples*

465 Another important observation from the current study is that, when samples
466 are sufficiently large, relatively weak lesion-deficit associations can be deemed
467 statistically significant (i.e. $p < 0.05$). For instance, effects that only accounted for as
468 little as 3% of the variance reached statistical significance when $N \geq 120$ - an
469 inferential problem known as the fallacy of classical inference (Friston, 2012; Smith
470 and Nichols, 2018). However, our findings are consistent with the view that this issue
471 can be addressed by reporting point and interval estimates of effect sizes (Button et
472 al., 2013b; Lindquist et al., 2013), which allow one to assess the practical
473 significance (as opposed to statistical significance only) of the results. In other
474 words, it can be argued that the fallacy of classical inference is specific to statistical
475 tests (e.g., t , F and/or p values), leaving effect sizes largely unaffected (Reddan et
476 al., 2017). Furthermore, there are two important advantages of conducting high-
477 powered studies: (i) they greatly attenuate the impact of study publication bias as
478 both over- and under-estimations of the true effect size will surpass the threshold for
479 statistical significance; and (ii) the precision with which the magnitude of the true
480 population effect can be estimated is substantially improved (Lakens and Evers,
481 2014; see Table 5 and Figs. 4 and 5A). Our study also indicates that, even with

482 sample sizes as large as $N = 360$, a not inconsiderable degree of uncertainty in R^2
483 estimation remained, which suggests that increasing sample size beyond this N will
484 continue to bring benefit.

485 4.5. *Study limitations*

486 The focus of the current paper has been on establishing the degree to which
487 the replicability of lesion-deficit mappings is influenced by sample size. To illustrate
488 our points, we have (i) searched for brain regions where damage is significantly
489 related to impairments in articulating speech; (ii) estimated the strength of the
490 identified lesion-deficit association; and, (iii) run the exact same analysis on
491 thousands of samples of varying size. However, we have not attempted to account
492 for all possible sources of inconsistencies in univariate voxel-based lesion-deficit
493 mapping. Nor have we investigated how our results would change if we selected
494 another function of interest (e.g., word retrieval or phonological processing). Indeed,
495 it has already been pointed out that higher-order functions might be associated with
496 smaller effects than lower-level ones (Poldrack et al., 2017; Yarkoni, 2009).

497 We also acknowledge that there are many different ways of conducting voxel-
498 based lesion-deficit analyses (for more information see de Haan and Karnath, 2018;
499 Karnath et al., 2018; Rorden et al., 2007; Sperber and Karnath, 2018). We have
500 selected one approach, using mass-univariate multiple regression on continuous
501 measures of structural abnormality, behaviour and lesion size. However, we could
502 have used other types of images or other behavioural regressors. For example,
503 several recent studies have adopted dimensionality reduction techniques, such as
504 principal component analysis (PCA), to transform a group of correlated behavioural
505 measures into a smaller number of orthogonal (uncorrelated) factors (e.g., Butler et
506 al., 2014; Corbetta et al., 2015; Mirman et al., 2015a). This PCA approach has made
507 an important contribution to finding coarse-grained explanatory variables (e.g., Halai
508 et al., 2017; Lacey et al., 2017; Mirman et al., 2015b; Ramsey et al., 2017), but some
509 of its limitations are that it: (i) involves an arbitrary criterion for factor extraction; (ii)
510 ignores unexplained variance when selecting a limited number of components; and,
511 (iii) necessitates subjective, a posteriori, interpretation as to what the components
512 might mean based on the factor loadings, which is not typically clear cut. Instead, we
513 propose that a better solution for tackling orthogonality issues is to adopt both a

514 rigorous sampling strategy as well as behavioural measures that offer an optimal
515 sensitivity-specificity balance.

516 Finally, we have highlighted that the reliance on small-sized samples of
517 patients in the presence of publication bias can undermine the inferential power of
518 univariate voxel-based lesion-deficit analyses. However, we have not attempted to
519 provide guidance on how prospective power calculations - that correct for the various
520 forms of bias present in scientific publications - can be conducted. Nor have we
521 illustrated how the presence of publication and other reporting biases in the lesion-
522 deficit mapping literature, specifically, can be ascertained. The reason simply being
523 that others have already devoted considerable effort to developing tools that identify
524 and deal with problems such as: (i) the excess of statistically significant findings
525 (e.g., Ioannidis and Trikalinos, 2007); (ii) the proportion of false positives (e.g.,
526 Gronau et al., 2017); (iii) the presence of publication bias and questionable research
527 practices (e.g., Du et al., 2017; Simonsohn et al., 2014a, 2014b); (iv) errors in the
528 estimation of the direction and/or magnitude of a given effect (e.g., Gelman and
529 Carlin, 2014); and, (v) sample size calculations that take into account the impact of
530 publication bias and uncertainty on the estimation of reported effect sizes (e.g.,
531 Anderson et al., 2017). With respect to statistical power, the situation is further
532 complicated by the fact that - in the context of univariate voxel-based lesion-deficit
533 mapping - it not only depends on the size of the sample, the magnitude of the effect
534 under study and the statistical threshold used (Cremers et al., 2017), but also on the
535 distribution of damage across the brain (which is non-uniform; Inoue et al., 2014;
536 Kimberg et al., 2007; Mah et al., 2014; Sperber and Karnath, 2017). More research
537 on the topic will be required before prospective power calculations can be fully
538 trusted. Until that moment, the recruitment of representative patient samples in
539 combination with high-powered designs seems to be the best available solution to
540 the issues discussed here.

541 4.6. *Interpreting voxel-based lesion-deficit mappings*

542 The strength of the lesion-deficit association that we identified in a large
543 sample of 360 patients illustrates that the majority of the variability in speech
544 articulation abilities was driven by factors other than the degree of damage to the
545 ROI. A clear implication of this is that the field of lesion-deficit mapping still has a

546 long way to go before it can inform current clinical practice, which is arguably one of
547 its most important goals. Future studies will need to control and understand other
548 known sources of variance (apart from lesion site and size) such as time post-stroke,
549 age and education in order to improve our ability to predict language outcome and
550 recovery after stroke at the individual patient level (Price et al., 2017). Furthermore,
551 to map all the possible ways in which brain damage can affect behaviour, it will in all
552 likelihood be necessary to use increasingly larger samples of patients (e.g., Price et
553 al., 2010; Seghier et al., 2016) and multivariate methods (e.g., Hope et al., 2015;
554 Pustina et al., 2018; Yourganov et al., 2016; Zhang et al., 2014).

555 **5. Conclusions**

556 This study investigated the impact of sample size on the reproducibility of
557 voxel-based lesion-deficit mappings. We showed that: (i) highly significant lesion-
558 deficit associations can be driven by a relatively small proportion of the variance; (ii)
559 the exact same lesion-deficit mapping can vary widely from sample to sample, even
560 when analyses and behavioural assessments are held constant; (iii) the combination
561 of publication bias and low statistical power can severely affect the reliability of
562 voxel-based lesion-deficit mappings; and, finally, (iv) reporting effect size estimates
563 is essential for assessing the importance or triviality of statistically significant
564 findings. Solutions to the issues highlighted here will, in our view, likely involve the
565 use of: (a) improved reporting standards; (b) increasingly larger samples of patients;
566 (c) multivariate methods; (d) informed sampling strategies; and, (e) independent
567 replications. Careful reflection on some deeply-rooted research practices, such as
568 biases in favour of statistically significant findings and against null results, might also
569 be necessary.

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Table 1: Summary of demographic and clinical data for full sample.

Factor		N = 360
Age at stroke onset (years)	<i>M</i>	54.4
	<i>SD</i>	12.9
	Range	17.2-86.5
Age at testing (years)	<i>M</i>	59.4
	<i>SD</i>	12.4
	Range	21.3-90.0
Time post-stroke (years)	<i>M</i>	4.9
	<i>SD</i>	5.2
	Range	0.2-36.0
Education (years)*	<i>M</i>	14.5
	<i>SD</i>	3.2
	Range	10.0-30.0
Lesion size (cm ³)	<i>M</i>	85.7
	<i>SD</i>	87.6
	Range	1.5-386.2
Gender	Males	250
	Females	110
Rep-N	Imp/Non	132/228
	<i>M</i>	54.4
	<i>SD</i>	9.1
Writt-PN	Imp/Non	105/255
	<i>M</i>	58.6
	<i>SD</i>	8.7
Recog-M	Imp/Non	37/323
	<i>M</i>	53.9
	<i>SD</i>	7.0
Sem-A	Imp/Non	36/324
	<i>M</i>	56.6
	<i>SD</i>	6.1
A _w -P	Imp/Non	77/283
	<i>M</i>	57.0
	<i>SD</i>	6.8

Imp/Non = number of patients with impaired/non-impaired performance. *Missing data: three patients.

Table 2: Statistical power in the region of interest.

%tile		Sample Size					
		30	60	90	120	180	360
0th	Power	98%	100%	100%	100%	100%	100%
	R^2	0.00	0.00	0.00	0.00	0.00	0.01
	P	0.999	0.999	0.999	0.999	0.404	0.093
10th	Power	99%	100%	100%	100%	100%	100%
	R^2	0.01	0.03	0.04	0.05	0.06	0.07
	P	0.638	0.218	0.064	0.015	0.001	0.000
20th	Power	63%	100%	100%	100%	100%	100%
	R^2	0.03	0.05	0.06	0.07	0.08	0.09
	P	0.400	0.093	0.022	0.004	0.000	0.000
30th	Power	86%	100%	100%	100%	100%	100%
	R^2	0.06	0.07	0.08	0.08	0.09	0.10
	P	0.250	0.046	0.009	0.002	0.000	0.000
40th	Power	92%	100%	100%	100%	100%	100%
	R^2	0.08	0.09	0.10	0.10	0.10	0.11
	P	0.158	0.025	0.004	0.001	0.000	0.000
50th	Power	98%	100%	100%	100%	100%	100%
	R^2	0.11	0.11	0.11	0.11	0.11	0.11
	P	0.099	0.012	0.002	0.000	0.000	0.000
60th	Power	100%	100%	100%	100%	100%	100%
	R^2	0.15	0.14	0.13	0.13	0.13	0.12
	P	0.060	0.006	0.001	0.000	0.000	0.000
70th	Power	83%	100%	100%	100%	100%	100%
	R^2	0.18	0.16	0.15	0.14	0.14	0.13
	P	0.032	0.002	0.000	0.000	0.000	0.000
80th	Power	96%	100%	100%	100%	100%	100%
	R^2	0.23	0.19	0.17	0.16	0.15	0.14
	P	0.015	0.001	0.000	0.000	0.000	0.000
90th	Power	100%	100%	100%	100%	100%	100%
	R^2	0.30	0.23	0.21	0.19	0.18	0.16
	P	0.004	0.000	0.000	0.000	0.000	0.000
100th	Power	99%	100%	100%	100%	100%	100%
	R^2	0.79	0.52	0.39	0.39	0.38	0.28
	P	0.000	0.000	0.000	0.000	0.000	0.000

The table shows that in all but one case, more than 80% of the voxels comprising the region of interest from Analysis 1 had sufficient statistical power to detect a significant lesion-deficit association at a threshold of $p < 0.05$ after correction for multiple comparisons. %tile = percentile of the effect size (R^2) distribution; Power =

percentage of voxels within the region of interest from Analysis 1 that had sufficient statistical power to detect a significant lesion-deficit association at a statistical threshold of $p < 0.05$ after correction for multiple comparisons; $R^2 = R^2$ value (at a particular decile); $P = p$ value (at a particular decile).

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Table 3: Brain regions where lesion load is associated with speech articulation abilities.

Brain region	Peak coordinates			Voxel-level		Cluster-level	
	x	y	z	Z-score	$P_{\text{FWE-corr}}$	Extent	$P_{\text{FWE-corr}}$
Post-Central	-60	-16	12	5.8	0.000	549*	< 0.001
	-52	-14	24	4.7	0.009		
	-56	-12	18	4.6	0.012		
Posterior Insula	-40	-16	8	5.3	0.001		
Anterior SMG	-66	-30	20	4.7	0.008		
WM	-48	-24	26	4.6	0.010		

The table shows representative (peak) voxels where a significant association between stroke damage and difficulties articulating speech was found. All were in the left hemisphere and the coordinates are reported in MNI space. SMG = supramarginal gyrus; WM = white matter; $P_{\text{FWE-corr}}$ = p value corrected (family-wise error correction) for multiple comparisons. *At a cluster-forming voxel-wise threshold of $p < 0.05$ FWE-corrected.

Table 4: Mean and median effect size of the significant and non-significant random data sets by sample size.

R^2	Sample Size											
	30		60		90		120		180		360	
	s	ns	s	ns	s	ns	s	ns	s	ns	s	ns
Count	2214	3786	4272	1728	5289	711	5747	253	5974	26	5999	1
	258	5742	1279	4721	2613	3387	3911	2089	5369	631	5997	3
M	0.26	0.07	0.16	0.04	0.13	0.03	0.12	0.02	0.12	0.01	0.11	---
	0.45	0.12	0.24	0.09	0.18	0.07	0.15	0.06	0.12	0.05	0.11	0.02
Mdn	0.24	0.06	0.15	0.04	0.12	0.03	0.11	0.02	0.11	0.01	0.11	---
	0.43	0.11	0.23	0.09	0.17	0.08	0.14	0.06	0.12	0.05	0.11	0.03
Min	0.16	0.00	0.07	0.00	0.05	0.00	0.03	0.00	0.02	0.00	0.03	0.01
	0.38	0.00	0.19	0.00	0.12	0.00	0.09	0.00	0.06	0.00	0.03	0.01
Max	0.79	0.16	0.52	0.07	0.39	0.05	0.39	0.03	0.38	0.02	0.28	0.01
	0.79	0.38	0.52	0.19	0.39	0.12	0.39	0.09	0.38	0.06	0.28	0.03

For each summary statistic, the upper row indicates the corresponding value when the alpha threshold was set at 0.05, whereas the lower row indicates the corresponding value when the alpha threshold was set at 0.001. Count = the number of resampled data sets that generated significant or non-significant R^2 values; s = significant (i.e. $p < \alpha$); ns = not significant (i.e. $p \geq \alpha$); M = mean R^2 value; Mdn = median R^2 value; Min = minimum R^2 value; Max = maximum R^2 value.

Table 5: Frequency of accurate and inaccurate effect size estimates by sample size and statistical significance.

<i>N</i>	Effect Size					
	Significant			Not significant		
	> 95% CI	= 95% CI	< 95% CI	> 95% CI	= 95% CI	< 95% CI
360	173	5686	140	0	0	1
180	556	4925	493	0	0	26
120	795	4430	522	0	0	253
90	1081	3887	321	0	0	711
60	1417	2855	0	0	421	1307
30	1873	341	0	0	2007	1779

The table shows, for each sample size, the frequency with which effect size estimates reached statistical significance (i.e. $p < 0.05$) and fell within (=) or outside the 95% credible interval (i.e. 0.06-0.18) of the best estimate of the “true” population effect (i.e. $R^2 = 0.11$). 95% CI = 95% credible interval; > = larger than the upper bound of 95% CI; < = smaller than the lower bound of 95% CI.

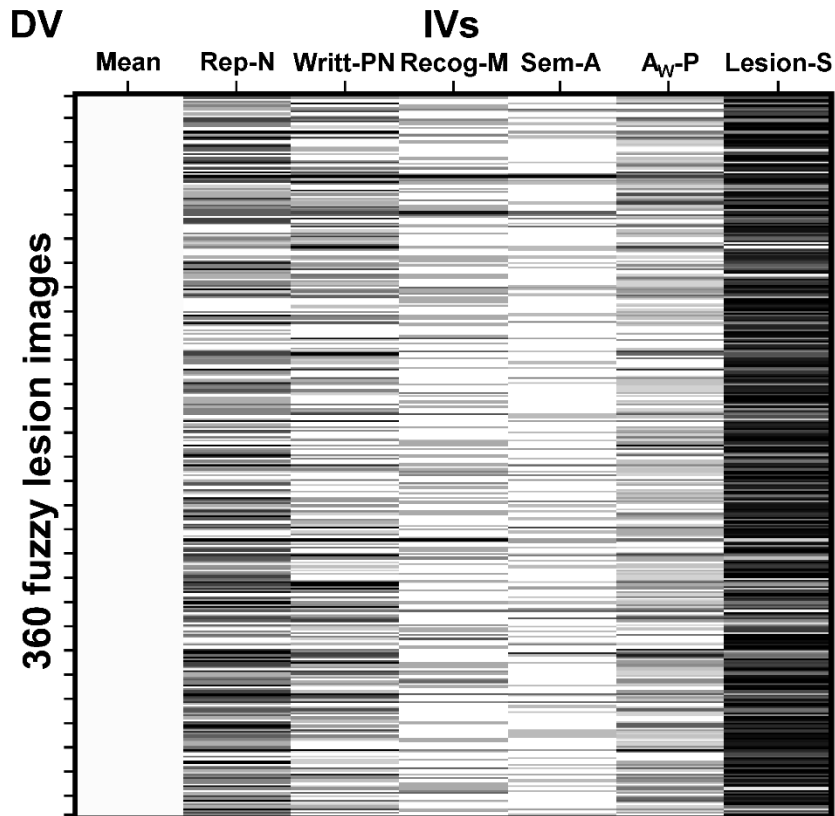


Fig. 1. Design matrix. The design matrix for Analysis 1 is shown, where the columns represent the subject-specific independent variables (IVs), with one value for each subject, and the rows correspond to the dependent variable (DV) indexing the degree of structural abnormality in the fuzzy lesion images.

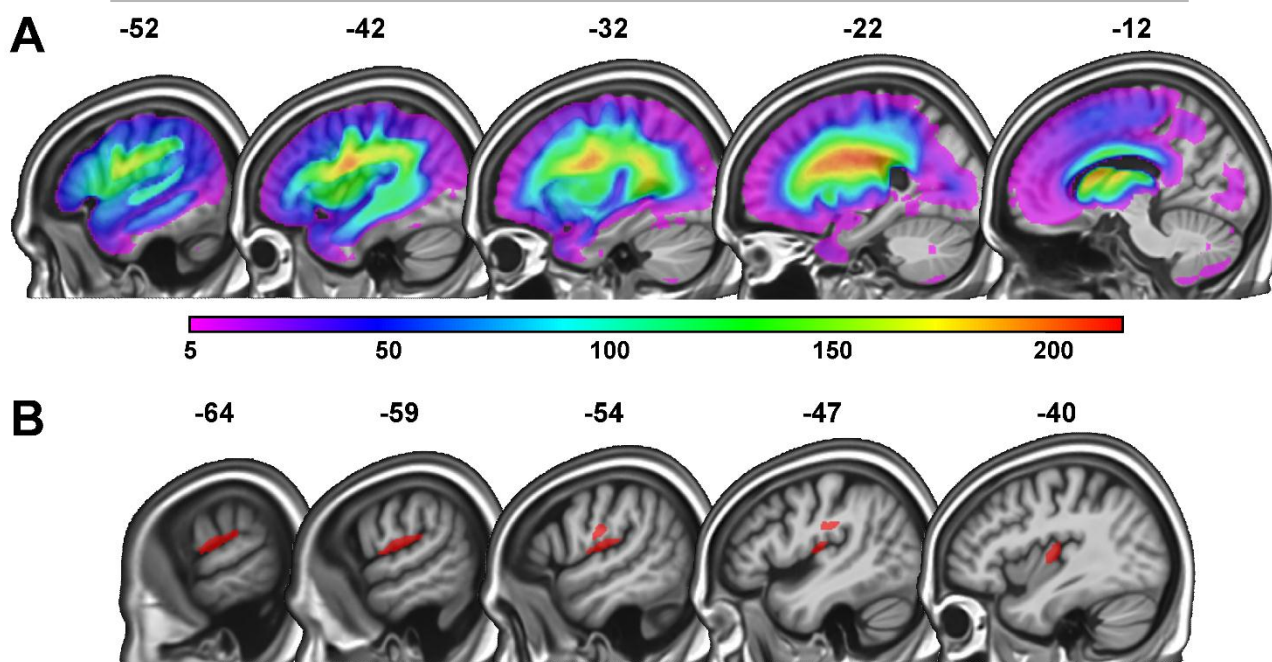


Fig. 2. Lesion overlap map and region of interest from Analysis 1. **(A)** Lesion overlap map for the full sample of 360 stroke patients, depicting voxels that were damaged in a minimum of 5 and a maximum of 215 patients. The colour scale indicates the number of patients with overlapping lesions at each given voxel. **(B)** In red, the region of interest identified in Analysis 1 (i.e. 549 voxels) where a significant association between lesion load and speech articulation abilities was found.

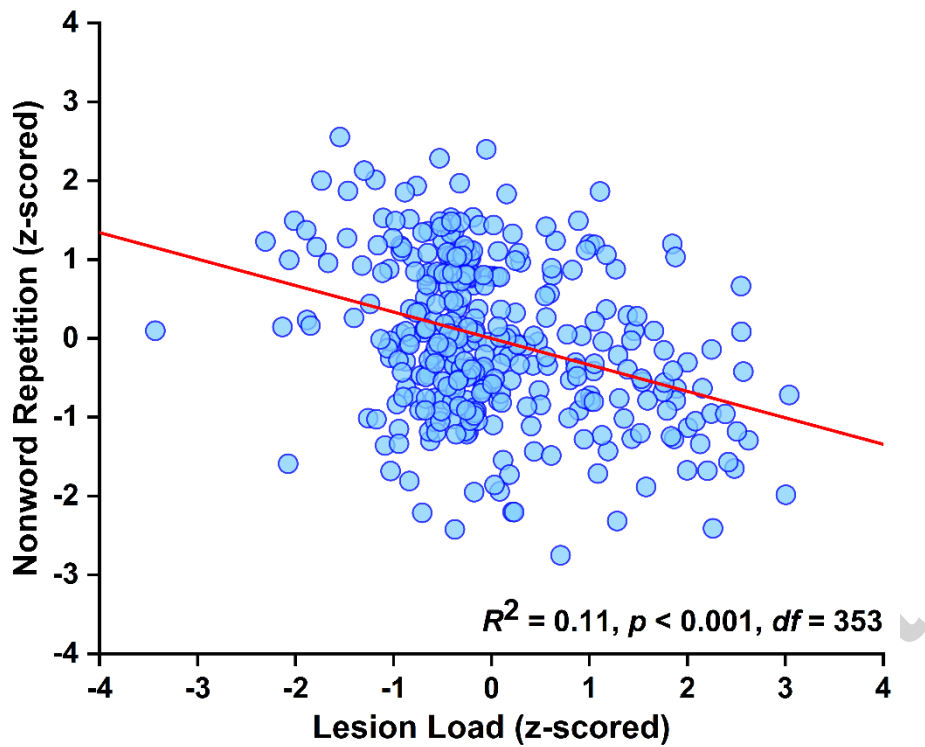


Fig. 3. Effect of interest. Visual illustration of the strength of the relationship between lesion load in the region of interest and nonword repetition scores, after factoring out variance explained by the covariates of no interest (i.e. a plot of the lesion load and nonword repetition residuals; Analysis 1).

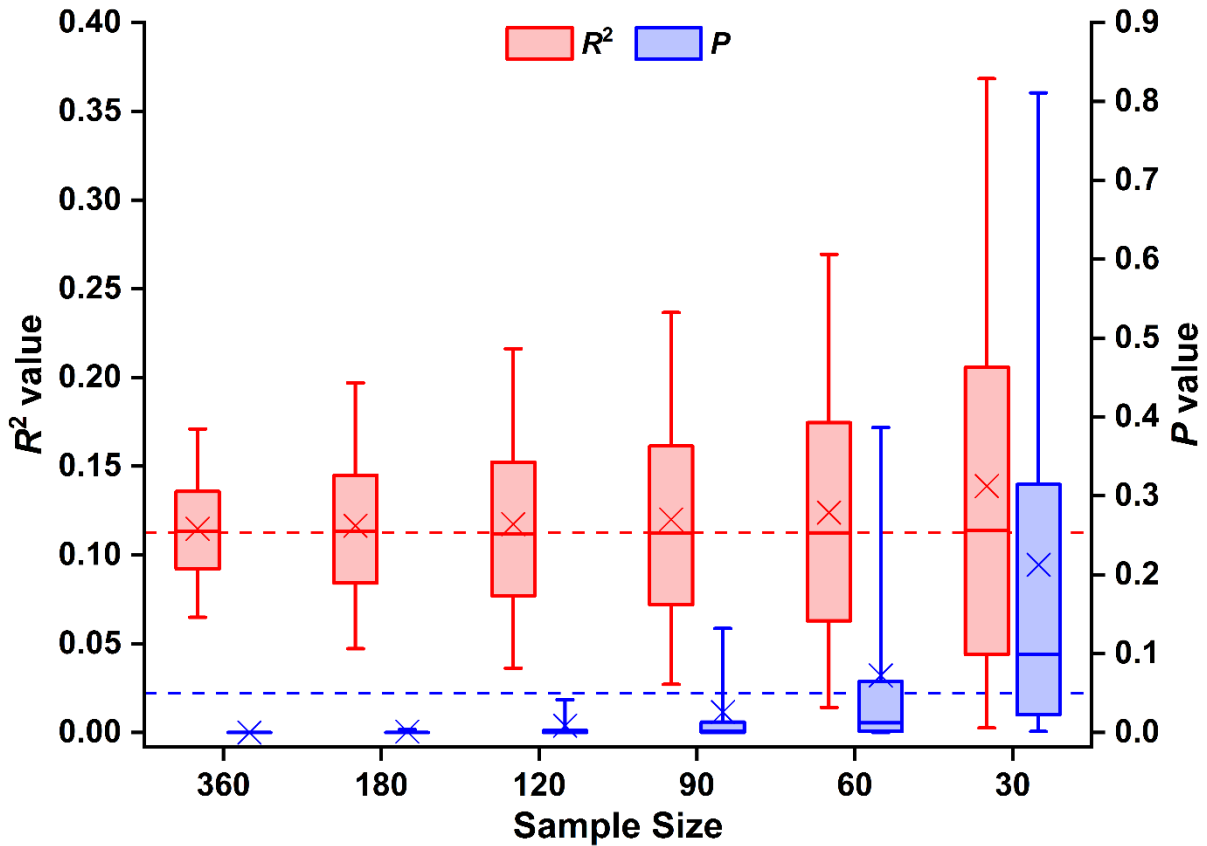


Fig. 4. Differential sensitivity of effect sizes and p values to sample size. The figure highlights that, while the mean and median of the effect size distributions remained relatively constant across the different sample sizes, the mean and median of the p value distributions exhibited substantial and systematic variability. Box plots depict medians with interquartile ranges and whiskers represent the 5th and 95th percentiles. The crosses indicate the mean for each sample size. The horizontal dashed line in red signals the R^2 value obtained in Analysis 1 (including data from all 360 patients), whereas the horizontal dashed line in blue shows the standard alpha level (i.e. 0.05).

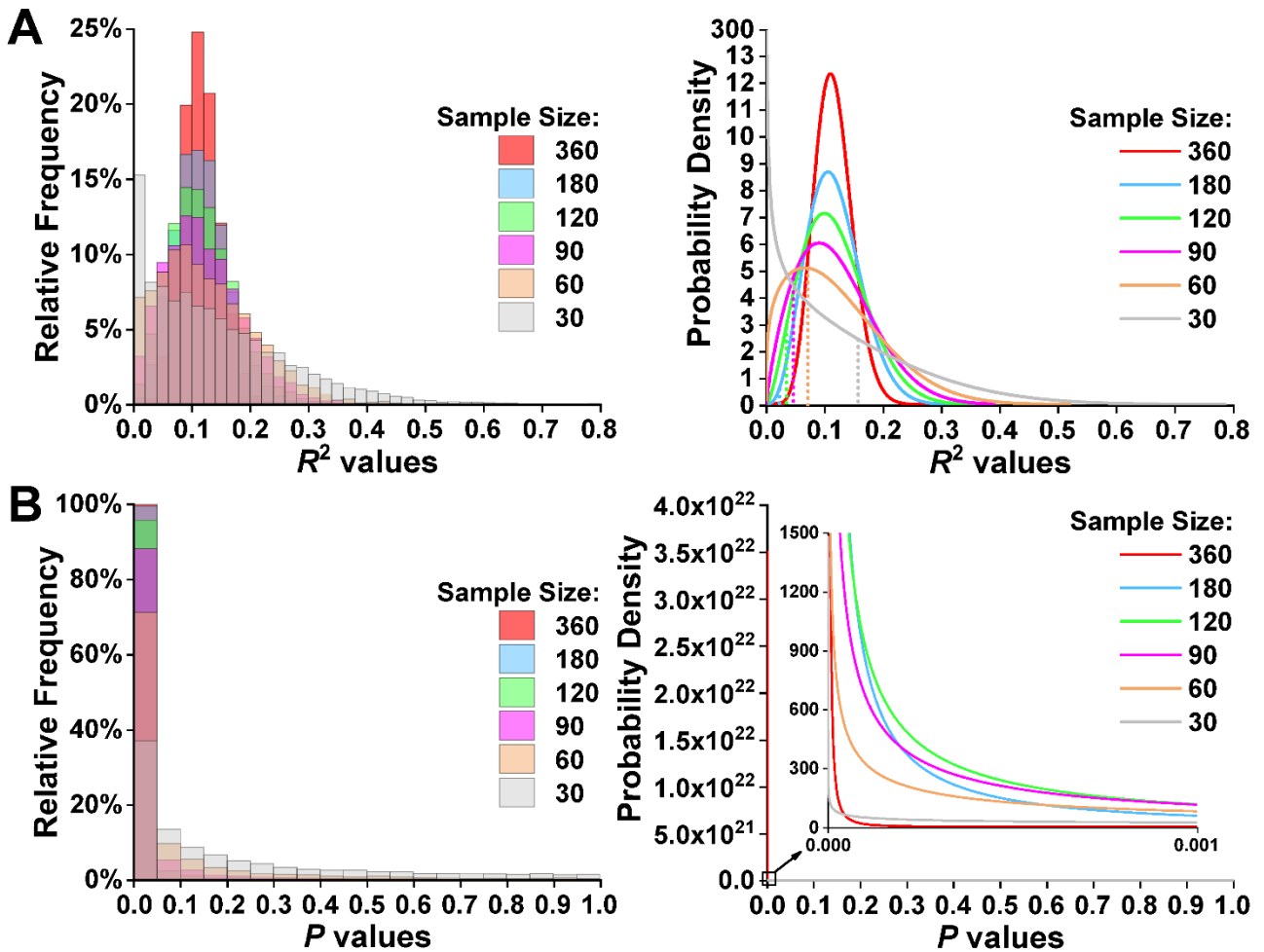


Fig. 5. Distribution of R^2 and p values. **(A)** From left to right, the frequency (in intervals of 0.02) and probability distributions of effect sizes for each sample size. The vertical dotted lines indicate the boundary between non-significant ($p \geq 0.05$; to the left) and significant ($p < 0.05$; to the right) R^2 values. **(B)** From left to right, the frequency (in intervals of 0.05) and probability distributions of p values for each sample size.

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Highlights

- The same lesion-deficit analysis was repeated on thousands of bootstrap samples.
- Replicability of the original effect was contingent upon the size of the sample.
- With smaller samples, only inflated effect size estimates reached significance.
- With larger samples, even trivial effect sizes yielded significant p values.