Voxel-based lesion–symptom mapping

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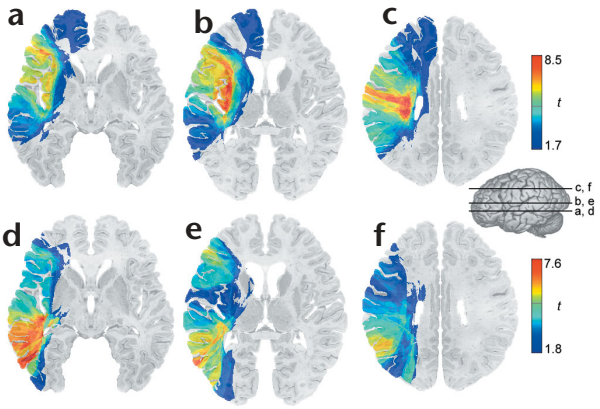

Fig. 1. Representative slices from VLSM maps computed for fluency and auditory comprehension performance of 101 aphasic stroke patients. These maps are colorized depictions of *t*-test results evaluating patient performance on a voxel-by-voxel basis. Patients with lesions in a given voxel were compared to those without lesions in that voxel on measures of fluency (**a**–**c**) or auditory comprehension (**d**–**f**). High *t*-scores (red) indicate that lesions to these voxels have a highly significant effect on behavior. Dark blue voxels indicate regions where the presence of a lesion had relatively little impact on the behavioral measure. Only voxels that were significant at $P = 0.05$ (controlling the expected proportion of false positives) are shown. The Bonferroni-corrected significance cutoffs are also indicated on the scales by means of gray bars. Lesions within the insula (**b**) and deep parietal white matter (**c**) had the most impact on fluency, whereas injury to the middle temporal gyrus (**d**) produced the largest effect on measures of auditory comprehension. The study was approved by the VA Northern California Health Care System and UCSD Human Research Protection Programs, and all participants gave informed consent.

For more than a century, lesion–symptom mapping studies have yielded valuable insights into the relationships between brain and behavior, but newer imaging techniques have surpassed lesion analysis in examining functional networks. Here we used a new method—voxel-based lesion–symptom mapping (VLSM)—to analyze the relationship between tissue damage and behavior on a voxel-by-voxel basis, as in functional neuroimaging. We applied VLSM to measures of speech fluency and language comprehension in 101 left-hemisphere-damaged aphasic patients: the VLSM maps for these measures confirm the anticipated contrast between anterior and posterior areas, and they also indicate that interacting regions facilitate fluency and auditory comprehension, in agreement with findings from modern brain imaging.

Localization of cognitive processes through lesion analysis continues to reveal new information about brain–behavior relationships in patient populations[1–6]. In lesion analysis, patients are typically grouped either by lesion or by behavior. In the 'lesion-defined' approach, the behavioral performance of a group of patients with a common area of injury (for example, dorsolateral prefrontal cortex) is compared to that of a control group or another patient group[4,5]. This method is valuable for assessing the functional roles of particular regions of interest (ROIs), but can lose information if an ROI contains multiple subregions that each contribute to behavior. In addition, regions outside the ROI that are part of a distributed functional network may be overlooked. In the 'behavior-defined' approach, patients are grouped according to whether or not they show a specific behavioral deficit[1,2,6], and their lesions are reconstructed in a common stereotactic space. Lesion reconstructions from patients with the deficit are overlaid to find common area(s) of infarction, and compared to lesion overlays from patients without the deficit. These contrasting overlays or subtracted images are effective in identifying brain regions that may contribute to a cognitive skill, but in situations where the behavioral data are continuous rather than binary, a cut-off must be applied, and information reflecting varying degrees of performance can be lost.

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies in normal adults have produced a host of new findings that have refined previous lesion-based models of neural organization[7,8]. The VLSM method described here uses the same voxel-based procedures that are used to analyze functional neuroimaging data, thus avoiding some of the limitations of traditional lesion analysis methods. Notably, VLSM does not require patients to be grouped by either lesion site or behavioral cutoff, but instead makes use of continuous behavioral and lesion information. By analyzing continuous behavioral data on a voxel-by-voxel basis, this method is also related to recent voxel-based morphometry studies that associate gray and white matter tissue density with continuous behavioral data[9]. Another important precursor is work correlating continuous metabolic data for a number of ROIs with continuous behavioral measures[10].

We analyzed data on speech fluency and language comprehension for 101 left-hemisphere-injured stroke patients who showed some degree of speech or language impairment. Dissociations between speech production and comprehension have had an important role in the history of aphasiology. For this reason, we focused on the fluency and auditory comprehension subtests of a standard assessment tool, the Western Aphasia Battery (WAB)[6]. Fluency scores reflect a combination of articulatory, word-finding and sentence-production skills, whereas the auditory comprehension measure represents the average score on yes/no questions, single-word recognition and enactment of 1-, 2- and 3-part commands. Patients' lesions were reconstructed onto templates by a board-certified neurologist (R.T.K.) who was blind to the clinical status of each patient[2,5]. The lesion reconstruction technique has been used by many laboratories using a variety of templates[1,3,6,11] and has been shown to be reliable in a number of studies[4,11]. Patients were tested at least one year after

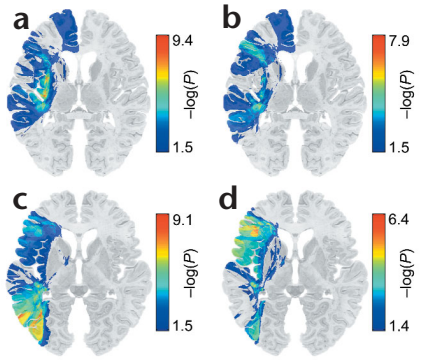

Fig. 2. Representative slices from maps of voxel-by-voxel ANCOVAs covarying out particular anatomically defined voxels of interest. One-tailed *P*-values are plotted. (**a**) Fluency, factoring out a voxel at the center of Broca's area. (**b**) Fluency, factoring out a voxel in the anterior insula. (**c**) Comprehension, factoring out a central voxel in Wernicke's area. (**d**) Comprehension, factoring out a voxel in the center of the MTG.

stroke. All were native English speakers with normal or corrected-to-normal vision and hearing.

For each voxel, patients were divided into two groups according to whether they did or did not have a lesion affecting that voxel. Behavioral scores were then compared for these two groups, yielding a *t*-statistic for each voxel (**Fig. 1**). Fluency was most affected by lesions in the insula (**Fig. 1b**) and in the arcuate/superior longitudinal fasciculus in parietal white matter (**Fig. 1c**). Auditory comprehension was most affected by lesions in the middle temporal gyrus (MTG; **Fig. 1d**), with significant contributions also seen in dorsolateral prefrontal cortex (**Fig. 1e**) and parietal association cortex (**Fig. 1f**). Alternatives to the *t*-statistic are also possible with VLSM, such as measures of effect size; in the present study, maps of effect size were very similar to the *t*-maps shown here.

This anterior–posterior contrast for fluency versus comprehension is consistent with historical findings in aphasia. However, the regions typically associated with these deficits (Brodmann areas (BA) 44 and 45 in the inferior frontal gyrus (Broca's area) for fluency; posterior BA 22 in the superior temporal gyrus (Wernicke's area) for comprehension), were not the areas most reliably associated with deficits. In fact, the regions with the highest *t*-scores were the middle temporal areas, previously implicated in lesion[12] and fMRI[8,13] studies of auditory comprehension, inferior parietal and dorsolateral prefrontal cortex, implicated recently in sentence comprehension[12], and the left anterior insula, identified as a region important for speech production through lesion analysis[2] and recent PET studies[14,15]. Finally, VLSM also indicated a role for white matter in fluency, further complementing results from functional imaging.

In lesion studies, an area may emerge as relevant either because it has a direct causal role or because of a diaschitic effect involving highly correlated lesions some distance away. Indeed, the apparent role of the insula in fluency could be an indirect consequence of lesions to Broca's area, and the role of the middle temporal gyrus in comprehension could be a consequence of lesions to Wernicke's area. VLSM can be used to test hypotheses such as these. Based on anatomical criteria, we identified central voxels in four *a priori* ROIs: Broca's area, the anterior insula, Wernicke's area and the middle temporal gyrus. We constructed four maps factoring out the effects of these voxels by carrying out analyses of covariance (ANCOVAs) at all other voxels using the state (intact or lesioned) of each voxel of interest as the covariates (**Fig. 2**). These maps showed that the anterior insula is critical for fluency, independent of Broca's area (**Fig. 2a**), whereas Broca's area is not especially important for fluency once lesions to the insula have been accounted for (**Fig. 2b**). The MTG remained a significant factor in auditory comprehension after Wernicke's area was factored out (**Fig. 2c**), but after the MTG was factored out, the contribution of Wernicke's area was no longer apparent (**Fig. 2d**).

With VLSM, similarity between statistical maps can be assessed by calculating the correlation between *t*-scores on two tasks, treating voxels as subjects. When fluency and auditory comprehension were compared in this manner, a correlation of 0.59 was obtained (see **Supplementary Fig. 1** online). This correlation reflects approximately 35% overlap in the variance and suggests that areas associated with performance on one measure can, to some extent, predict areas associated with the other. Indeed, many patients with lesions in the peri-Sylvian areas had moderate-to-low scores in both fluency and comprehension, suggesting that these areas might support core language functions common to both measures. Future work will use similar correlative techniques to quantitatively compare VLSM maps with activation maps from functional imaging studies of normal subjects performing the same or similar tasks.

Here we used a new technique to analyze lesion–symptom relationships in a large group of left-hemisphere-lesioned patients, using behavioral data from two well-studied tasks: fluency and language comprehension. VLSM is an improvement on previous lesion–symptom mapping techniques because it uses all available information, eliminating reliance on cutoff scores, clinical diagnoses or specified regions of interest. Thus, it allows for additional areas to emerge in the exploration of networks that support a given behavior. As such, it also serves as a bridge between classic approaches to lesion–symptom mapping and modern functional imaging.

Note: Supplementary information is available on the Nature Neuroscience website.

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Competing interests statement

The authors declare that they have no competing financial interests.

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1. Adolphs, R., Damasio, H., Tranel, D., Cooper, G. & Damasio, A.R. *J. Neurosci.* **20**, 2683–2690 (2000).
2. Dronkers, N.F. *Nature* **384**, 159–161 (1996).
3. Naeser, M.A. & Hayward, R.W. *Neurology* **28**, 545–551 (1978).
4. Friedrich, F.J., Egly, R., Rafal, R.D. & Beck, D. *Neuropsychology* **12**, 193–207 (1998).
5. Chao, L.L. & Knight, R.T. *J. Cogn. Neurosci.* **10**, 167–177 (1998).
6. Kertesz, A. *Aphasia and Associated Disorders: Taxonomy, Localization and Recovery* (Grune & Stratton, New York, 1979).
7. Petersen, S.E., Fox, P.T., Posner, M.I., Mintun, M. & Raichle, M.E. *Nature* **331**, 585–589 (1988).
8. Price, C.J. *J. Anat.* **197**, 335–359 (2000).
9. Maguire, E.A. *et al. Proc. Natl. Acad. Sci. USA* **97**, 4398–4403 (2000).
10. Metter, E.J. *et al. Arch. Neurol.* **47**, 1235–1238 (1990).
11. Knight, R.T., Scabini, D., Woods, D.L. & Clayworth, C. *Electroencephalogr. Clin. Neurophysiol.* **70**, 499–509 (1988).
12. Dronkers, N.F., Wilkins, D.P., Van Valin, R.D. Jr., Redfern, B.B. & Jaeger, J. J. *Cognition* (in press).
13. Wise, R. *et al. Brain* **114**, 1803–1817 (1991).
14. Blank, S.C., Scott, S.K., Murphy, K., Warburton, E. & Wise, R.J.S. *Brain* **125**, 1829–1838 (2002).
15. Wise, R.J.S., Greene, J., Büchel, C. & Scott, S.K. *Lancet* **353**, 1057–1061 (1999).