motion was a consistent feature that occurred in all experiments. This implies that OHCs deformed, as vectors from different points along the cell membrane had orientations incompatible with rigid rotation around the same center of rotation.

Standard confocal images were acquired before and after acquisition of each image pair obtained during sound stimulation. Structural changes were not seen in any preparation. In a separate series of experiments, Reissner's membrane was penetrated with microelectrodes to measure the cochlear microphonic potential evoked by stimulation with the identical level, duration and frequency that was used during actual experiments. The stimulation caused no change of the microphonics.

The motion pattern was sensitive to manipulations known to affect OHC function. After 15–20 minutes of continuous acoustic overstimulation at levels 12–20 dB above those used during image acquisition, reticular lamina displacements increased in 7 of 8 image pairs (mean increase 76%, range –22 to +240%). Basilar membrane displacements also increased (mean +18%, range –4 to +78%). OHCs were deformed also after the overstimulation, although minor changes of vector orientation occurred. In one preparation, 20 mM of 2,3-butanedione monoxime was perfused through the scala tympani. This compound blocks OHC electromotility *in vitro*[13]. Thirty minutes after adding the drug, OHC vectors had the same orientation as vectors at the reticular lamina, implying absence of deformation. Reticular lamina vibration amplitudes increased after application of the drug (+32%), whereas basilar membrane displacement decreased by 50%. Thus, OHCs controlled a part of the vibration despite the relatively high stimulus level.

In summary, we found that sound stimulation caused cyclic deformation of OHCs and that the basilar membrane and reticular lamina had different centers of rotation. OHC deformation may have important implications, given that these cells respond to mechanical stimuli directed at the cell membrane[14], and that they possess a chloride current activated by membrane stretch[15]. By showing that the basilar membrane and reticular lamina are capable of independent motion, an important feature of the dynamic model (**Fig. 1c**) is confirmed, although we did not observe compression of the organ. The classical rigid-body theory of organ motion is thereby refuted. This differential motion also explains how forces generated by prestin can so profoundly affect hearing sensitivity. Contrary to previous assumptions, the hearing organ has a highly dynamic structure that provides a flexible framework for coupling force generation to vibration.

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

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Voxel-based lesion–symptom mapping

Elizabeth Bates[1], Stephen M. Wilson[2], Ayse Pinar Saygin[1], Frederic Dick[1], Martin I. Sereno[1], Robert T. Knight[3,4] and Nina F. Dronkers[4,5]

[1] *Department of Cognitive Science, University of California, San Diego, California 92093, USA*

[2] *Neuroscience Interdepartmental Program, University of California, Los Angeles, California 90095, USA*

[3] *Department of Psychology and Helen Wills Neuroscience Institute, University of California, Berkeley, California 94720, USA*

[4] *Center for Aphasia and Related Disorders, VA Northern California Health Care System, 150 Muir Road, Martinez, California 94553, USA*

[5] *Departments of Neurology and Linguistics, University of California, Davis, California 95616, USA*

Correspondence should be addressed to N.F.D. (dronkers@ucdavis.edu)

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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

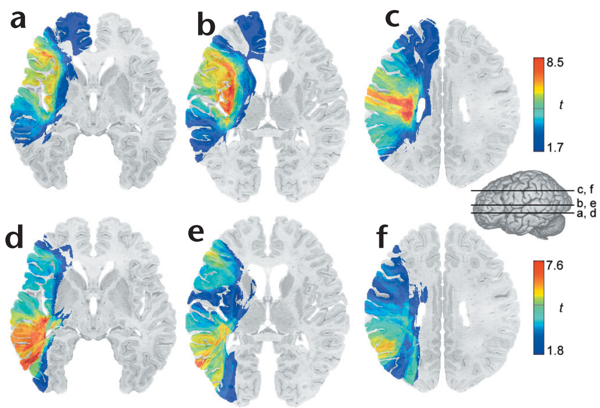

Fig. 1. Representative slices from VLSM maps computed for fluency and auditory comprehension performance of 101 aphasic stroke patients. These maps are colorized depictions of *t*-test results evaluating patient performance on a voxel-by-voxel basis. Patients with lesions in a given voxel were compared 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.

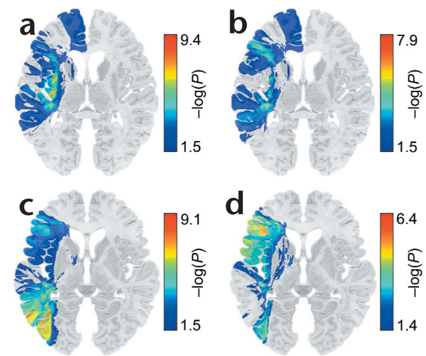

Fig. 2. Representative slices from maps of voxel-by-voxel ANCOVAs covarying out particular anatomically defined voxels of interest. One-tailed *P*-values are plotted. (**a**) Fluency, factoring out a voxel at the center of Broca's area. (**b**) Fluency, factoring out a voxel in the anterior insula. (**c**)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

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 deficit1[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 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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Conflict adaptation effects in the absence of executive control

Ulrich Mayr, Edward Awh and Paul Laurey

Department of Psychology, University of Oregon, Eugene, Oregon 97403, USA
Correspondence should be addressed to U.M. (mayr@darkwing.uoregon.edu)

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According to the 'conflict-monitoring' model, a leading theory of cognitive control[1–4], information-processing conflict registered in the anterior cingulate cortex (ACC) triggers the prefrontal cortex to reduce conflict susceptibility. Here we show that the existing empirical support for an online modulation of susceptibility to conflict through immediately preceding conflict, the 'conflict-adaptation effect'[1,5], needs to be reevaluated. In a human cognitive control task, we found that it was not the stimulus-independent level of conflict that was responsible for the conflict-adaptation effect but rather an episodic memory phenomenon: stimulus-specific priming[6].

The so-called flanker task[7,8] is frequently used to study cognitive control. Subjects respond with a left or right key press to a central target arrow while ignoring congruent (>>>) or incongruent (<><) flanker arrows. The presumed role of cognitive control in this situation is to enhance target processing and/or exclude flanker processing. Control efficiency is indexed by the congruency effect, the performance decline on incongruent compared to congruent trials. An open question is how control itself is controlled in such a situation[1]. That is, how does the cognitive system determine when regulation becomes necessary? The conflict-monitoring model suggests that control is modulated through a relatively 'dumb' system, situated in the ACC, which constantly extracts from ongoing information processing an abstract index of information-processing conflict[1]. A high value on this index triggers regulative control sites (such as prefrontal cortex) to boost control activity.

Voxel-based lesion–symptom mapping

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ボクセルに基づく病変・症状マッピング

1 世紀以上にわたり， 病変-症状写像研究は，脳と行動の関係について貴重な洞察をもたらしてきた。 しかし，新しい画像技術は， 機能的ネットワークを調べる上で病変分析を凌駕している。 我々は， 機能的脳画像のように， 組織の損傷と行動の関係をボクセル単位で解析する新しい手法 VLSM (Lesion-symptom mapping) を用いた。 左半球に損傷を受けた失語症患者 101 名の流暢性と言語理解の測定に VLSM を適用したところ， これらの測定項目に対するVLSM 地図は， 予想されていた前方領域と後方領域のコントラストを確認し， また， 相互作用する領域が流暢性と聴覚理解を促進することを示し， 最新の脳画像の知見と一致した。

病変解析による認知プロセスの局所化は， 患者集団における脳と行動の関係について新たな情報を提供し続けている(1-6)。 病変解析では，通常患者を病変ごと， あるいは行動ごとに分類する。 「病巣別」アプローチでは， 共通の損傷部位 (例えば背外側前頭前野) を持つ患者群の行動成績を，対照群または別の患者群と比較する (4,5)。 この方法は， 特定の関心領域 (ROI) の機能的役割を評価するのに有効だが，ROI にそれぞれ行動に寄与する複数の下位領域が含まれている場合， 情報が失われる可能性がある。 また， 分散した機能ネットワークの一部である ROI 外の領域が見落とされる可能性もある。 「行動定義型」アプローチでは， 特定の行動障害を示すかどうかで患者をグループ分けし(12,6)， 共通の定位空間で病変部を再構成する。 損傷を持つ患者の病巣再構成を重ね合わせて共通の梗塞部位を見つけ， 損傷のない患者の病巣再構成と比較する。 このような対照的な重ね合わせ画像や減算画像は， 認知能力に寄与する可能性のある脳領域を特定するのに有効であるが， 行動データが 2 値ではなく連続的なものである場合には， カットオフを適用する必要があり， 様々な程度の成績を反映する情報が失われる可能性がある。

健常成人を対象としたポジトロン・エミッション・トモグラフィー (PET) や機能的磁気共鳴画像 (fMRI) の研究では， これまでの病変ベースの神経組織モデルに磨きをかける多くの新知見が得られている (7,8)。 ここで紹介する VLSM 法は， 機能的脳画像データを解析するのと同じボクセルベースの手順を用いているため， 従来の病変解析法の限界を回避することができる。
特に VLSMでは， 病変部位や行動のカットオフで患者を分類する必要はなく， 行動と病変の連続情報を利用する。 この方法は， 連続的な行動データをボクセル単位で解析することで， 灰白質や白質の組織密度を連続的な行動データと関連付ける最近のボクセルベースモルフォメトリーの研究にも関連している(9)。 また、いくつかの ROI の連続的な代謝データと連続的な行動測定値を関連付けた研究も重要な先駆けとなっている(10)。

本研究では，ある程度の言語障害を示した左半球損傷の脳卒中患者 101 名の流暢性と言語理解に関するデータを分析した。 発話と理解の解離は，失語症の歴史において重要な役割を果たしてきた。 そこで， 我々は， 標準的な評価ツールである Western Aphasia Battery (WAB) (6) の流暢性と聴覚的理解の下位検査に注目した。 流暢性は， 調音能力， 単語検索能力， 文章作成能力の組み合わせであり， 聴解力は，yes/no 形式の質問， 単一単語の認識，1 部，2部，3部形式の命令の実行の平均点である。 患者の病変は， 各患者の臨床状態を把握していない神経内科認定医 (R.T.K.) によってテンプレートに再構成された (2,5)。 この病変再構築技術は， 多くの研究室で様々なテンプレートを用いて行われており (1,3,6,11)，多くの研究で信頼性が高いことが示されている (4,11)。 患者は， 脳卒中から少なくとも 1 年後に検査を受けた。
全員が英語を母国語とし， 視力と聴力が正常または正常に矯正されていた。

各ボクセルについて，そのボクセルに病変があるかないかで，患者を 2 群に分けた。 この 2 群の行動得点を比較し， 各ボクセルの t-統計量を算出した (図1)。 流暢性は， 島皮質の病変 (図1b) と頭頂白質の弧状/上縦筋の病変 (図1c) によって最も影響を受けた。 聴覚理解は， 中側頭回 (MTG) の病変によって最も影響を受けたが， 背外側前頭前野 (図1e) と頭頂連合野 (図1f) でも大きな影響が見られた。 VLSM では t-統計量の代わりに，効果量の測定も可能であり， 今回の研究では，効果量地図は， ここで示した t-地図と非常によく似ていた。

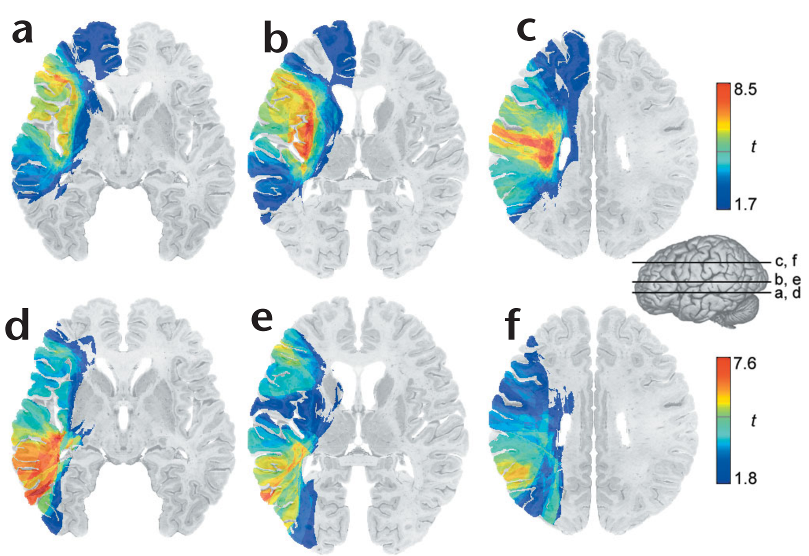


図 1. 脳卒中患者 101 名の流暢性と聴解力の成績を計算した VLSM 地図の代表的なスライス。 これらの地図は， 患者の成績をボクセルごとに評価した t 検定の結果をカラーで表したものである。 あるボクセルに病変がある患者は， そのボクセルに病変がない患者と比較して， 流暢性 (a-c) または聴覚的理解力 (d-f) の測定を行った。 高い t スコア (赤) は， そのボクセルに病変があると，行動に非常に大きな影響があることを示している。 濃い青のボクセルは， 病変の存在が行動測定に比較的少ない影響を与えた領域を示す。 P=0.05 で有意であったボクセルのみを示している （予想される偽陽性の割合をコントロールしている)。 ボンフェローニ補正した有意差のカットオフ値もグレーのバーで示した。 島皮質 (b) および頭頂葉深部白質 (c) の損傷は， 流暢性に最も影響を及ぼし， 中側頭回 (d) の損傷は， 聴解力の測定に最も影響を及ぼした。 本研究は， VA Northern California Health Care System および UCSD Human Research Protection Program の承認を受け，参加者全員がインフォームド・コンセントを得た。

この流暢性と理解力の前後関係は、失語症の歴史的知見と一致している。 しかし， これらの障害と一般的に関連する領域 (流暢性では下前頭回のブロドマン領域 (BA44 および BA45， 理解性では上側頭回の BA22 後方) は， 障害と最も確実に関連する領域ではなかった。 実際， 最も高い t 得点を示した領域は， 聴覚理解の病変研究 (12) や fMRI 研究 (8,13) で関与が指摘されている中側頭領域， 文の理解に関与していると最近指摘されている下頭頂部および背外側前頭前野 (12)， そして， 病変解析 (2) や最近の PET 研究 (14,15) で音声生成に重要な領域として同定された左前島であった。 最後に VLSM は白質が流暢性に関与していることも示しており， 機能的画像の結果をさらに補完している。

病変部の研究では， ある領域が関連していることが明らかになるのは， その領域が直接的な因果関係を持っているからか， あるいは， 遠く離れた場所にある相関性の高い病変部を含むディアスキット効果のためである。 実際， 流暢性における島皮質の役割は， ブローカ野の病変による間接的な結果かもしれないし， 理解力における中側頭回の役割は， ウェルニッケ野の病変による結果かもしれない。 このような仮説を検証するために VLSM を使用することができる。 解剖学的な基準に基づいて 4 つの先験的な ROI で中心的なボクセルを特定した。 ブローカ野， 前島皮質，ウェルニッケ野， 中側頭回の 4 つの領域で中心ボクセルを同定した。 そして， 各ボクセルの状態 (無傷か病変か) を共変量として， 他のすべてのボクセルで共分散分析 (ANCOVA) を行うことで， これらのボクセルの影響を相殺した 4 つの地図を作成した (図2)。 その結果，前島皮質はブローカ野とは無関係に流暢性に重要な役割を果たしており (図2a)， 一方， ブローカ野は島皮質の病変を考慮すると流暢性に特に重要ではないことがわかった (図2b)。 MTG はウェルニッケ領域を除外しても聴覚理解の有意な要因であり続けたが (図2c)， MTG を除外した後はウェルニッケ領域の寄与は明らかではなくなった (図2d)。

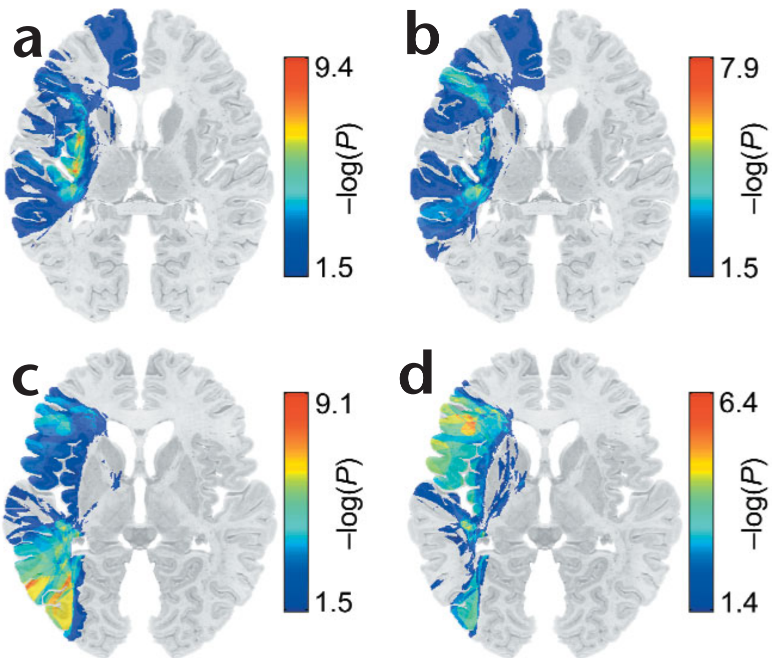
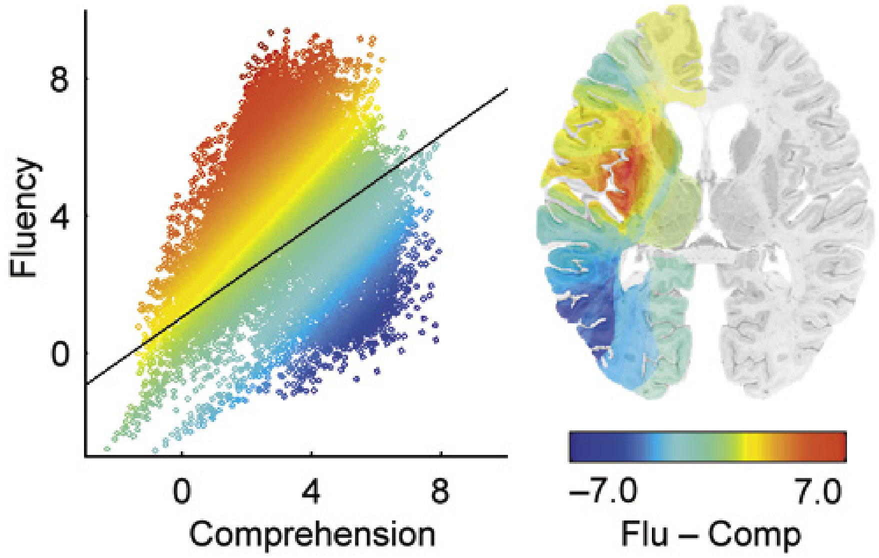


図 2. 解剖学的に定義された特定の注目すべきボクセルを共分散させたボクセルごとの ANCOVA 地図の代表的なスライス。 片側の P 値をプロットした。 (a) 流暢性，Broca 領域の中心ボクセルで因子分解したもの。 (b) 流暢性， 前島皮質のボクセルを因子分解したもの。 (c) 理解力， ウェルニッケ領域の中央ボクセルを因子分解したもの。 (d)理解力， MTG の中央ボクセルを因子分解したもの。

VLSM では， ボクセル を被験者に見立てて 2 つの課題 の t 値の相関を計算することで，統計地図の類似性を評価することができる。 この方法で，流暢性と聴解力を比較したところ， 0.59 の相関が得られた (補図 1)。 この相関は， 分散が約 35 %重複していることを示しており， 一方の課題の成績に関連する領域が， もう一方の課題に関連する領域をある程度予測できることを示唆している。 実際，シルビア裂周辺部に病変がある患者の多くは， 流暢性と理解力の両方で中程度から低い値を示しており， これらの領域が両測定法に共通する中核的な言語機能を支えている可能性が示唆された。 今後は，同様の相関手法を用いて VLSM 地図と， 同じ課題または類似の課題を行っている健常者の機能画像研究による活性化地図を定量的に比較する予定である。



本研究では，流暢性と言語理解という 2 つのよく研究された課題から得られた行動データを用いて，大規模な左半球病変患者グループにおける病変と症状の関係を新しい手法で分析した。VLSM は，従来の病変-症状地図作成技術を改良したもので，カットオフスコアや臨床診断，特定の関心領域に依存することなく，利用可能なすべての情報を使用している。そのため，ある行動を支えるネットワークを探索する際に，新たな領域が出現する可能性がある。このように，病変・症状写像の古典的なアプローチと，最新の機能的イメージングとの間の架け橋となっている。