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Patterns of neural activity predict picture-naming performance of a patient with chronic aphasia

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ABSTRACT

Naming objects represents a substantial challenge for patients with chronic aphasia. This could be in part because the reorganized compensatory language networks of persons with aphasia may be less stable than the intact language systems of healthy individuals. Here, we hypothesized that the degree of stability would be instantiated by spatially differential neural *patterns* rather than either increased or diminished *amplitudes* of neural activity within a putative compensatory language system. We recruited a chronic aphasic patient (KL; 66 year-old male) who exhibited a semantic deficit (e.g., often said "milk" for "cow" and "pillow" for "blanket"). Over the course of four behavioral sessions involving a naming task performed in a mock scanner, we identified visual objects that yielded an approximately 50% success rate. We then conducted two fMRI sessions in which the patient performed a naming task for multiple exemplars of those objects. Multivoxel pattern analysis (MVPA) searchlight revealed differential activity patterns associated with correct and incorrect trials throughout intact brain regions. The most robust and largest cluster was found in the right occipito-temporal cortex encompassing fusiform cortex, lateral occipital cortex (LOC), and middle occipital cortex, which may account for the patient's propensity for semantic naming errors. None of these areas were found by a conventional univariate analysis. By using an alternative approach, we extend current evidence for compensatory naming processes that operate through spatially differential patterns within the reorganized language system.

1. Introduction

Although some degree of language recovery occurs over time in many patients with chronic aphasia, object naming remains a challenging task for these individuals. One interesting observation of the naming deficits in patients with aphasia is that performance on particular items often fluctuates in an unpredictable and sometimes seemingly random manner; this manifests itself during picture-naming tasks as inconsistent name retrieval when the same pictures are repeatedly presented (e.g., 'cat' is named either 'cat' or other similar animals such as 'dog').

Various neuroimaging techniques have offered helpful insights for understanding the neuroanatomical basis of naming deficits in aphasia (Saur and Hartwigsen, 2012; Thompson and Ouden, 2008). For instance, voxel lesion symptom mapping (VLSM) is useful for identifying the distribution of lesions associated with different subtypes of aphasia (Bates et al., 2003; Schwartz et al., 2011). By contrast, functional magnetic resonance imaging (fMRI) allows for online measurement of neural activity in spared brain regions while patients with aphasia perform a particular language task such as overt picture naming (Fridriksson et al., 2009; Léger et al., 2002; Meinzer et al., 2013; van Oers et al., 2010; Postman-Caucheteux et al., 2009; Szaflarski et al., 2011). This approach has proven useful in highlighting changes in compensatory networks over the course of spontaneous language recovery (Saur et al., 2006).

However, standard fMRI analysis methods, which explicitly assume 'greater' or 'less' brain activation across different tasks or populations, are limited and often produce puzzling results in aphasia research. For example, Fridriksson and colleagues (2009) measured neural activity during a naming task in both chronic aphasics and normal subjects. Despite normal subjects clearly outperforming patients in the language task, no significant areas were found to differentiate healthy controls from aphasics with respect to neural activity in the language network. One potential explanation for this discrepancy is that successful retrieval of names may not depend on the intensity of activation but rather on the pattern of activation within the newly engaged language network. The central aim of the present fMRI study is to explore the compensatory neural processes that sustain language performance in

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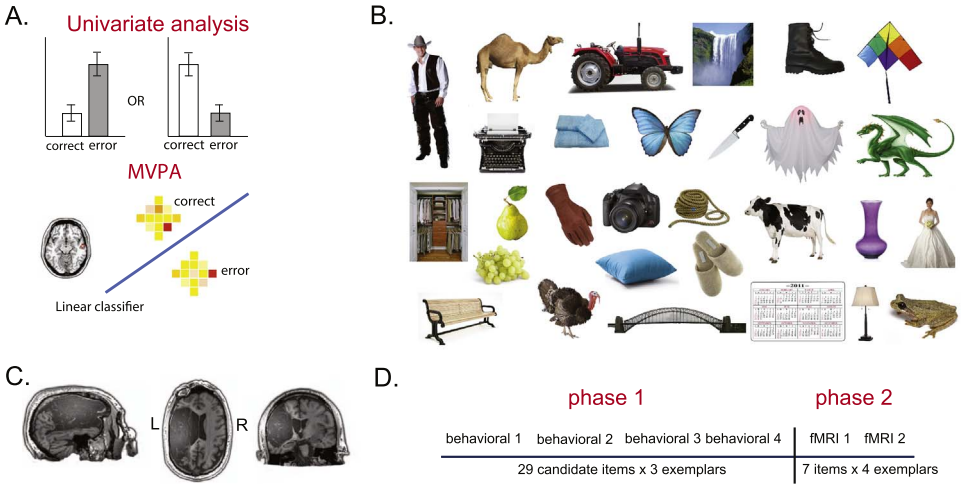

Fig. 1. A. Contrast of the rationale for conventional univariate analysis versus MVPA in linking neural activity to behavior. B. Some of the candidate pictures chosen from an existing PNT test-retest data set. These were presented during Phase 1 of behavioral sessions. C. Anatomical lesion profile of patient KL. An expansive lesion is shown in the left hemisphere encroaching the frontal, parietal, and temporal lobes.

aphasic patients by testing this hypothesis. To do this, we employed multivariate pattern-based analysis (MVPA), an alternative approach for relating neural activity to behavioral success or failure using machine-learning techniques (Mahmoudi et al., 2012). Fig. 1A depicts differences in the hypothesis between MVPA and the standard univariate analysis.

In this proof-of-concept study, we carefully selected a set of pictures that our subject could correctly name with 50% accuracy. These pictures would allow us to directly compare patterns of neural activity for correct versus incorrect trials, while holding constant a number of potential confounds, including visual object features and the complexity of object names (e.g., number of syllables). By adopting this strategy, we ensure that any differences observed in the MVPA are attributable to performance accuracy across trials. The participant underwent multiple behavioral sessions involving object naming in order to identify the candidate items for the main fMRI sessions. Consistent with our hypothesis, we found that MVPA could be used to link patterns of neural activity to behavioral outcomes but that standard fMRI analysis was insensitive to differences in performance.

2. Methods

2.1. Participants and stimuli

We identified candidate participants and stimuli for this study from an existing data set (Walker and Schwartz, 2012), in which 25 chronic aphasic patients performed the Philadelphia Naming Test (PNT) twice on different days. Seven candidate participants demonstrated naming scores that fell within the mid-range [39–70%, mean=53%] among the 25 potential subjects, and 29 picture items that were neither too difficult nor easy (Fig. 1B); these items yielded errors once in either of the two PNT sessions in 35–70% of the patient cohort.

Among the seven candidate participants, one patient (KL) volunteered for the present study. The patient's lesion profile is shown in the Fig. 1C. He was a 66-year-old right-handed man with chronic nonfluent aphasia who had a stroke encompassing the left hemisphere 11 years prior to the study and had previously participated in a transcranial magnetic stimulation (TMS) study in our laboratory (Hamilton et al., 2010). Written consent was obtained from the patient's spouse as approved by the Institutional Review Boards of the University of Pennsylvania and the Moss Rehabilitation Research Institute.

2.2. Experimental procedure

2.2.1. Phase 1: behavioral sessions

Prior to the main fMRI study, the participant completed four behavioral sessions comprised of overt picture-naming tests performed in a mock MRI scanner (Fig. 1D). Sessions were separated by a gap of two to four weeks. We employed 3 exemplars (e.g. 3 different pictures of a camel) for each of the 29 candidate items that were selected based on the PNT test-retest data. All images were in color and were matched for their size and luminance using Photoshop CS5 (Adobe Inc.). The typicality of the images was ensured by testing several colleagues at Penn's Center for Cognitive Neuroscience. A random sequence of the 87 (29 items x 3 exemplars) picture stimuli was determined by the De Bruijn sequence (Aguirre et al., 2011). The first half of the sequence (1st–44th trials) was presented in the first block, and the second half of the sequence (45th–87th trials) was presented in the second block. To match the number of trials across the block and not to break the random sequence, the last trial of the first block (44th) was repeated as the first trial of the 2nd block. This repetition was removed from the time-series prior to data analysis. Another random De Bruijn sequence was created and presented in the same manner, totaling 176 trials (44 trials×4 blocks) split across different blocks. During each block of the test, KL's verbal responses were recorded using a digital voice recorder attached to the inside of the mock MRI scanner; these recordings were later transcribed by the experimenter. Additionally, KL's head motion was recorded while he performed the picture-naming task.

2.2.2. Phase 2: fMRI sessions

Over the course of the 4 behavioral sessions, we identified seven candidate items that were suitable for the second phase of the study involving fMRI scanning: “butterfly,” “boot,” “camel,” “closet,” “cow,” “pillow,” and “turkey” The average accuracy for each of these pictures was approximately 50%. “Closet” was later replaced with “blanket” because the “closet” images contained multiple other namable objects (e.g., clothes). We chose “blanket” because this item was semantically related to “pillow.” Furthermore, for each of the picture items, we included one additional exemplar (i.e., 4 exemplars per item) to decrease the repetition of images and to increase the visual variability of exemplars for each object. This resulted in a total of 28 stimuli for each run of the fMRI sessions, which were randomly presented using a slow event-related design (interstimulus interval=12 s). As was the case with the behavioral session, randomization was achieved based on a de Brujin cycle (Aguirre et al., 2011). There were a total of six functional EPI runs. KL's verbal response was monitored via a MRI-compatible

microphone and recorded using OptiMRI (v 3.1). A week later, we conducted a 2nd fMRI session in which we replaced "butterfly" and "boot" with "cactus" and "milk." This was done because KL had exhibited ceiling accuracy on "butterfly" and "boot" (Fig. 3B). We selected "cactus" and "milk" because they were semantically related to the items "camel" and "cow," respectively. The procedure for the 2nd fMRI session was identical to that of the 1st fMRI session.

MRI data were collected using a 3T Siemens Trio scanner (Siemens Medical System, Erlangen, Germany) equipped with an 8-channel head coil. Scanning began with acquisition of a T1-weighted structural volume using a magnetization prepared rapid acquisition gradient echo (MPRAGE) protocol [axial orientation, repetition time (TR) =1620 ms, echo time (TE) =3.09 ms, flip angle =15°, field of view (FOV) =187.5×250 mm, slices=160, voxel resolution =0.98×0.98×1 mm]. Subsequently, 6 runs of blood oxygenation level-dependent (BOLD) functional MRI scanning were performed (TR =2500 ms, TE =25 ms, flip angle =90°, FOV =234×234 mm, 44 slices, voxel resolution =3×3×3 mm). Finally, a B0 mapping sequence was acquired at the end of the scanning (TR =1010 ms, TE1=2.67 ms, TE2=5.28 ms, flip angle =60°, FOV =234×234 mm, 44 slices, voxel resolution =3×3×3 mm).

2.3. fMRI data analysis

2.3.1. Preprocessing

All functional images acquired from the two fMRI sessions were combined for preprocessing (i.e., a total of 12 runs). We first unwarped data using the *prelude* and *FLIRT* routines from FSL version 5.0.5 (FMRIB Software Library, University of Oxford). These unwarped images were corrected in slice-timing and realigned using SPM8 (Wellcome Trust Centre for Neuroimaging). We then normalized the lesion images to the MNI space using ANTS (Avants et al., 2011): First, we acquired the transformation matrix by normalizing AAL_MNI_V4 atlas to the subjects' anatomical image (with an additional binary mask image defining lesioned areas) in the native space. Next, the matrix was inversely applied to normalization of both anatomical and functional images to the MNI space (Fig. 2A). For complementary univariate analysis, these normalized images were brought into SPM8 for smoothing with 8 mm FWHM Gaussian kernel.

2.3.2. Multivariate pattern classification (Searchlights)

Prior to the main analysis, unsmoothed images were further processed by applying a high-pass filter (128 s cut-off) and by mean-centering time-courses across the entire runs. For the purpose of binary classification using a GNB (Gaussian Naïve Bayses) algorithm (Raizada and Lee, 2013), we extracted time points from a subset of data consisting of "cow" and "blanket." (We note that data from the other five items were not included in order to maintain a balanced data set for the binary classification. See the behavioral and fMRI results for more details.) These two items were then labeled as correct and error depending on naming performance and were collapsed across the objects. The classification was performed only within the intact tissue of brain areas by creating local searchlight sphere comprised of a center voxel and neighboring voxels in a 2-voxel radius. For cross-validation, we employed a leave-two-out procedure in which the classifier was trained with (n-1) number of observations for each condition and tested on the remaining two observations (one for correct and one for error). The mean accuracy was stored at the center voxel of the searchlight sphere after cross-validation. Finally, a MonteCarlo simulation was performed to validate the classification accuracy. The simulation procedure was identical except that the classifier was trained on randomly shuffled labels between correct and error trials. This was performed 1000 times and the distribution of accuracies across the 1000 iterations was obtained for every center voxel of the searchlight sphere. Lastly, significant voxels were determined by comparing the classification accuracy to the random distribution at a threshold of significance of $P < 0.01$ (i.e., higher accuracy than the top 1% of the accuracy distribution).

2.3.3. Multivariate pattern classification (pattern similarity)

Our main searchlight analyses revealed two findings (discussed further in the Results below): 1) the right occipito-temporal cortex was the site with the largest and more robust cluster, and 2) the subject's naming performance was notable for the high prevalence of semantic

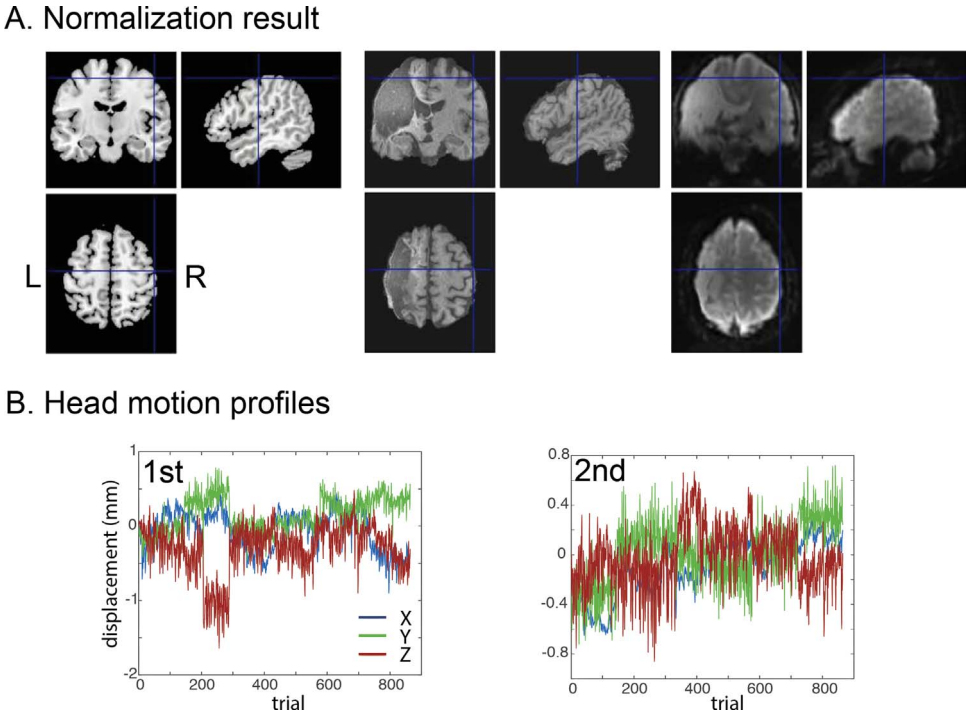

Fig. 2. A. Normalization output of KL's anatomical and functional images to the standard MNI space. B. Head motion profiles of the patient KL during the two fMRI sessions. The trial numbers across six runs are shown in the x-axis, and the degree of displacement is shown in the y-axis.

errors. Therefore, in an exploratory analysis, we contrasted the pattern of neural activity in the occipito-temporal cortex associated with a specific frequently-observed semantic error—misnaming "cow" as "milk"—compared to the patterns of activity associated with correct naming of "cow" and "milk." To do this, the time-courses of fMRI data were extracted within an ROI of the occipito-temporal cluster (a total of 127 voxels) corresponding to the following instances: 1) "cow" correctly named as "cow"; 2) "cow" incorrectly named as "milk"; and 3) "milk" correctly named as "milk." The Pearson-product moment coefficient was first obtained then converted to a Z′ score for every pair-wise comparison among the three instances: Z′(milk for cow vs. milk for milk), Z′(cow for cow vs. milk for milk), and Z′(cow for cow vs. other animals for cow).

2.3.4. Univariate analyses

In addition to the searchlights, we performed a mass univariate analysis. The fMRI time-courses of each condition were convolved with a canonical hemodynamic response function (HRF) in order to obtain estimated responses under the general linear model (GLM) framework in SPM12. Six motion parameters were also included as regressors. For small volume correction, we constructed a region-of-interest (ROI) image covering the occipital and parietal cortex using the Anatomy tool box (Eickhoff et al., 2005). We then excluded voxels residing on the lesion site from the ROI. Resulting maps were obtained at the voxel-wise threshold of $P < 0.001$ (uncorrected) and the cluster size correction of $P < 0.05$ (family-wise error). The cluster size correction was removed in exploratory analyses.

3. Results

3.1. Behavioral data in the MRI mock scanner

The subject's performance was consistent across 4 visits (48.3%, 49.4%, 51.7%, 48.3% naming accuracy from visit 1–4 respectively), indicating no training effect over the course of the behavioral sessions. While overall performance was stable, accuracy on particular items varied from one experiment to another. For example, the accuracy of boot was 50%, 83%, 42%, and 38% from the visit 1 through 4. As noted above, by averaging accuracies across the 4 behavioral sessions, we identified the following 7 items that had an approximately 50% mean accuracy rate: "boot," "butterfly," "closet," "camel," "turkey," "pillow," and "cow" (Fig. 3A). Error type analysis revealed that majority of errors during the behavioral sessions were nonresponses (60.7%), followed by semantic (32.1%), and phonemic errors (7.1%) (Fig. 3D). Error types were distributed homogeneously across all exemplars and across the 4 visits.

3.2. Behavioral data during the fMRI experiments

KL's naming performance improved when naming a more limited number of pictures during the fMRI sessions (first session: 80%, second session: 81%; see Figs. 3B & C for accuracies on individual pictures). For both fMRI sessions, the majority of errors were semantic paraphasias (88% and 97%, for the first and second sessions, respectively), followed by a few phonetic errors (6% and 0%) and non-responses (6% and 3%). Fig. 3D shows the percentages of different errors types combined across the 2 fMRI sessions. Notably, the rate of nonresponses was substantially reduced during phase 2, compared to phase 1. KL's naming performance on two items—"boot" and "butterfly"—was at ceiling (100% and 96%, respectively) during the first fMRI session. Therefore, as described above, these items were replaced with the items "milk" and "cactus" in the second fMRI session. By averaging the accuracy across the two fMRI sessions, we identified two items ("cow" and "blanket") that yielded balanced data sets and thus used these items for a pattern-classification test. For both fMRI sessions, KL made minimal movements during the naming task (Fig. 2B).

3.3. fMRI data (multivariate searchlights)

Prior to performing a searchlight on data that combined sessions 1 and 2, we ran a searchlight in each of the two sessions separately to see if the overall resulting maps were consistent with each other. As can be seen in Fig. 4A, the searchlight yielded similar results, although higher sensitivity was seen in the second map. Based upon the resulting maps and comparable behavioral performance, we were reassured that these two data sets could be combined for purpose of the MVPA searchlight.

The main searchlight analysis on this merged data sets revealed separable patterns of neural activity between correct and error trials in multiple sites within intact cortical areas bilaterally (Fig. 4B; Table 1). Among the significant regions, the largest cluster with the highest accuracy was found within the right occipito-temporal cortex, encompassing the lateral occipital complex (LOC), middle occipital cortex, fusiform gyrus, and inferior temporal cortex. Additionally, the right superior temporal gyrus (STG), precuneus, insula, and precentral gyrus exhibited pattern separability in the right hemisphere. In the left hemisphere, significant clusters were found in the cingulate gyrus, postcentral gyrus, precuneus, LOC, and frontal pole. We repeated the searchlight after excluding no-response trials to see if this result could potentially be confounded by absence of motoric activity in that trials. Although the data were slightly unbalanced, the results were roughly the same as main analysis (Fig. 4C), militating against the possibility of motoric influence.

Then, we examined if the pattern of neural activity was more similar between "cow" and "milk" when KL erroneously named "cow" as "milk" than when he correctly named the object. We specifically examined the occipito-temporal region due to its robustness in differentiating correct from incorrect trials, as discussed above. Pair-wise comparisons of Z′ scores among the three naming responses in question yielded the following similarity results: Z′(milk for cow vs. milk for milk) =0.36; Z′(cow for cow vs. milk for milk)=0.09; Z′(cow for cow vs. other animals for cow)=0.28.

3.4. fMRI data (univariate analysis)

We first examined what areas were generally active during the naming task. This revealed a large expanse of clusters throughout the remaining tissues in cortical, subcortical, and cerebellar regions (Fig. 5A; Table 2). Next, we compared correct and error trials, which revealed no significant clusters for either [correct > error] or [error > correct] contrasts. However, when we removed the secondary cluster-size correction, a sizable cluster emerged within right STS in the [error > correct] contrast (Fig. 5B). To avoid stringent multiple comparison correction, we repeated this analysis via the small volume correction (SVC) using a mask image covering only occipital and parietal regions. This analysis revealed a single cluster located in the upper portion of right supramarginal gyrus, which was not found by the MVPA searchlight analysis (Fig. 5C, Table 2).

4. Discussion

In the present fMRI study, we tested the hypothesis that, in persons with aphasia, spontaneous naming errors are due to poor coordination among neural populations that are engaged in compensatory language processes. That is, good coordination (i.e., a stable, reliable, efficient representation) may allow for consistent and accurate access to the object identity, while poor coordination (i.e., an unstable, unreliable, and inefficient representation) may lead to compromised access. Crucially, we hypothesized that this neural coordination manifested itself as spatially differential patterns of brain activity evoked during compensatory language processing. Our MVPA searchlight revealed significant clusters exhibiting such a propensity throughout residual intact cortical tissues that are known to participate in different stages of naming processes, from visual recognition to articulation. Notably,

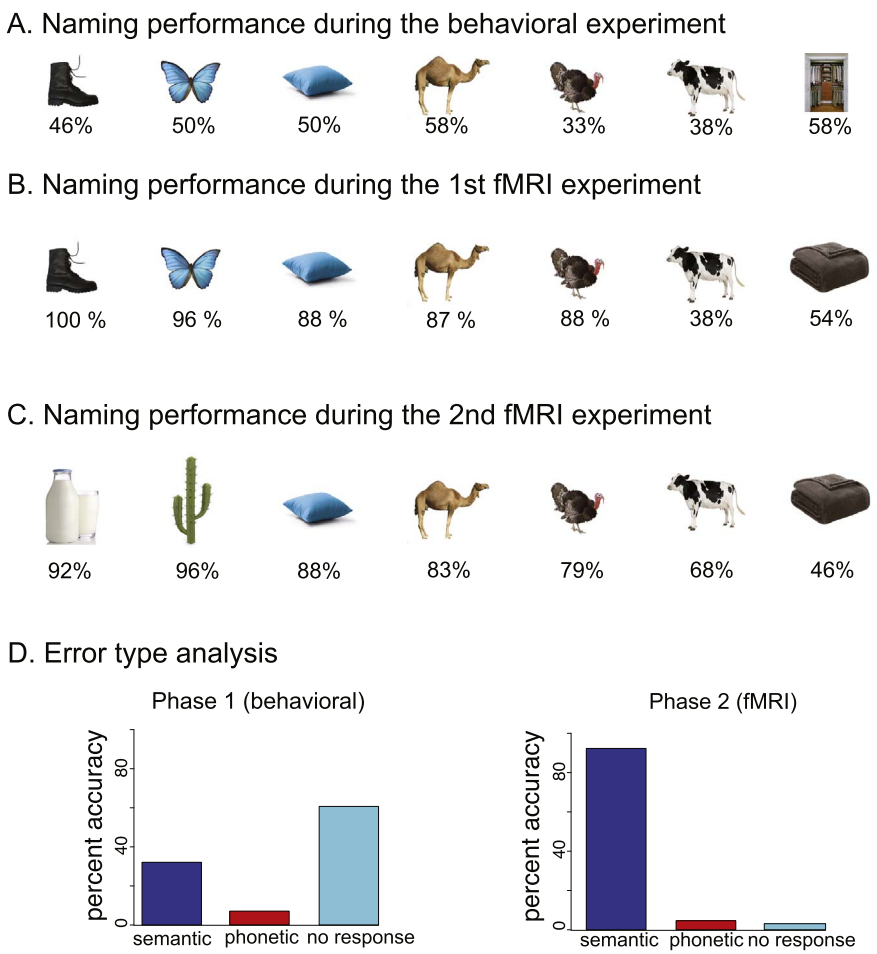

Fig. 3. A. Seven objects that were chosen during the Phase 1 of behavioral naming sessions in the mock scanner. Average accuracy is shown under each picture. B. The Naming performance on the seven items during the 1st fMRI session. C. The Naming performance on the seven items during the 2nd fMRI sessions. D. Error types and percentages are shown in the bar graph for both Phase 1 (behavioral) and Phase 2 (fMRI), indicating KL's semantic deficit.

none of these regions were found using standard univariate analysis, which instead yielded small non-significant clusters in either the right STG or right SMG. Among the MVPA clusters, the right occipito-temporal cortex—including the fusiform area and LOC—exhibited the most distinct and robust patterns of activity pertaining to naming outcomes. Our interpretation of these findings is that that the difference in pattern activation could relate to our patient's semantic impairments in naming.

4.1. Neural correlates of naming processes

The fact that naming performance is variable in chronic aphasia indicates that newly reorganized compensatory systems are still unstable while operating language processes. A number of past neuroimaging studies have delineated the compensatory language network in patients with aphasia and have demonstrated the neural correlates of naming retrieval (Turkeltaub et al., 2011). However, these reports are mixed with respect to lateralization. For example, some studies have reported naming-related cortical activity in residual perilesional areas of the left hemisphere (Fridriksson, 2010; Léger et al., 2002; van Oers et al., 2010; Szaflarski et al., 2011), while others have identified similar activity in the right hemisphere (Meinzer et al., 2006; Postman-Caucheteux et al., 2009). Some evidence suggests that the compensatory network can shift dynamically between left and right hemispheres over the course of aphasia recovery from the acute stage to the chronic stage (Saur et al., 2006). Together, these seemingly conflicting reports are due to a variety of differences between the studies (e.g., sample sizes, experimental paradigms, lesion configurations and the severity of patient's symptom) and thus may complement each other to reveal a bihemispheric network of both left and right hemisphere reorganization underlying language recovery (Turkeltaub et al., 2011).

In addition to differences in lateralization, previous reports are mixed with respect to the relevance of increased or decreased levels of neural activity (Hamilton et al., 2011). In this investigation, we have also compared the neural activity associated with correct and error trials using conventional univariate analysis. Although we did not find any significant regions at our initial statistical threshold, we found that a right superior temporal cluster evoked increased activity during the error trials compared to the correct trials under more lenient statistical threshold. We also found a smaller cluster within the right supramarginal gyrus yielding greater activity during error trials than during correct trials when SVC was employed using occipito-parietal mask. This result is consistent with a previous fMRI study reporting that error trials yielded stronger activity than correct trials within the right hemisphere in patients with chronic aphasia (Fridriksson et al., 2009; Postman-Caucheteux et al., 2009).

Although it is possible that different loci within the compensatory language network may possess different neural properties that were detected by different analysis approaches, we stress that our MVPA searchlight revealed a number of significant behaviorally-relevant clusters that were not sensitive to univariate analyses (Lee et al., 2011, 2012). This confirms our hypothesis that naming errors could be due to less coordinated regional neural patterns, which are detected more readily using MVPA than a conventional univariate approach. To the best of our knowledge, this is the first fMRI study in which a

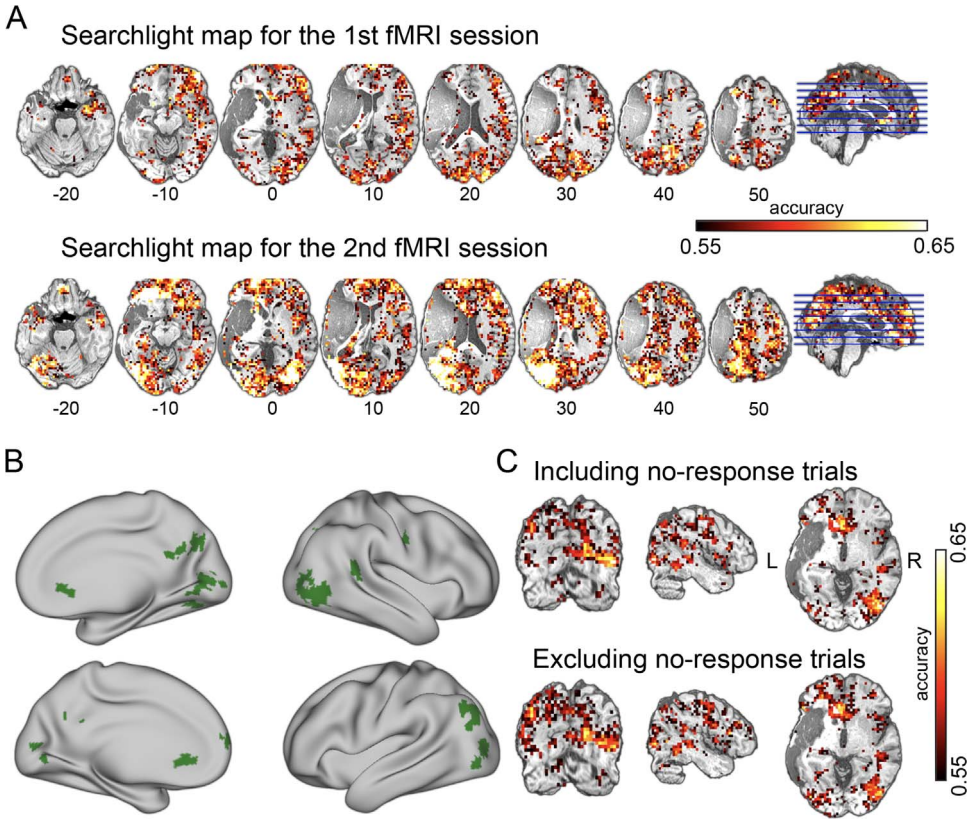

Fig. 4. A. Multi-slice view comparing searchlight map on 1st and 2nd fMRI data set. B. Significant clusters are overlaid in the surface rendering of a normal brain using workbench (Van Essen et al., 2012). C. Cross-section view depicting the searchlight result when no-response trials are included in the error condition vs. when they are excluded.

Table 1
Cortical regions exhibiting differential activity patterns between correct and incorrect trials.

	MNI coordinates				
Region name	x	y	z	Accuracy	# Voxels
Right lateral occipito-temporal cortex	44	−76	−1	0.65	205
Right occipital fusiform gyrus	31	−70	−2	0.64	
Right intracalcarine cortex	18	−83	8	0.64	
Right lingual gyrus	33	−59	1	0.63	
Right inferior temporal gyrus	41	−59	−3	0.63	
Right supracalcarine cortex	1	−82	5	0.63	
Right lateral occipital cortex	48	−74	8	0.58	
Left subcallosal cortex	−3	27	−1	0.63	12
Left cingulate gyrus	−3	37	−3	0.61	
Left postcentral gyrus	−18	−44	50	0.63	11
Left lateral occipital cortex	−27	−65	25	0.63	15
Left precuneous cortex	−24	−58	23	0.61	
Left frontal pole	−9	64	11	0.62	12
Left lateral occipital cortex	−39	−71	36	0.62	26
Precuneous cortex	0	−53	34	0.62	23
Right superior temporal gyrus	47	−28	−3	0.61	16
Right planum temporale	48	−35	15	0.61	
Right superior parietal lobule	27	−41	41	0.61	13
Right precuneous cortex	15	−62	31	0.61	21
Left lateral occipital cortex	−42	−80	−3	0.60	12
Right parietal operculum cortex	31	−30	22	0.60	15
Right insular cortex	33	−23	16	0.60	
Right precentral gyrus	40	−9	31	0.60	12

machine-learning classification scheme was employed for relating the on-line neural activity patterns to behavioral naming performance in aphasia (But see Saur et al., 2010 that applied a machine-learning classification to early fMRI data to predict prognosis of language performance 6 months after stroke).

Our approach and findings differ from previous aphasia neuroimaging studies in important ways. First, in previous studies, it was often the case that incorrectly named pictures tended to contain more syllables and were less familiar than correctly named pictures. Thus, neural activity associated with naming errors could have been attributable to differences in low-level visual or auditory characteristics (Postman-Caucheteux et al., 2009). In the present study, we sought to avoid such confounds by comparing the identical set of stimuli. That is, these pictures were matched for the visual and phonological characteristics, but the only differences were naming outcomes (e.g., correct and error). Secondly, previous studies made comparisons between correct and error trials that were not balanced; typically, there were more trials for the correct condition than for the the error condition (Fridriksson et al., 2009; Postman-Caucheteux et al., 2009). Like previous studies, we had more correct trials than error trials overall during the two fMRI experiments, even though the same item used in the fMRI experiments yielded approximately 50% naming accuracy during the prior behavioral sessions. As such, we specifically made use of a subset of the data set ('cow' and 'blanket') because these were the only data in the fMRI experiments that were suitable for a balanced comparison. Thirdly, in the previous literature, data were mostly collected in a single fMRI session. For machine-learning classification, however, small data sets often yield unsatisfactory results due to over-fitting (Pereira et al., 2009). To overcome this, we ran two separate fMRI sessions and concatenated the two data sets. We note that this was an a priori plan devised during the stage of conceptualization of the current study, not a post-hoc decision made after acquiring the first set of fMRI data. Given that both behavioral and neural data were comparable between the two fMRI sessions (80% and 81% of accuracy respectively), we were convinced that no significant relevant neurological change had occurred over the week between fMRI sessions. After the behavioral portion of this study (i.e., Phase 1) was complete, we were initially concerned about KL's tendency toward

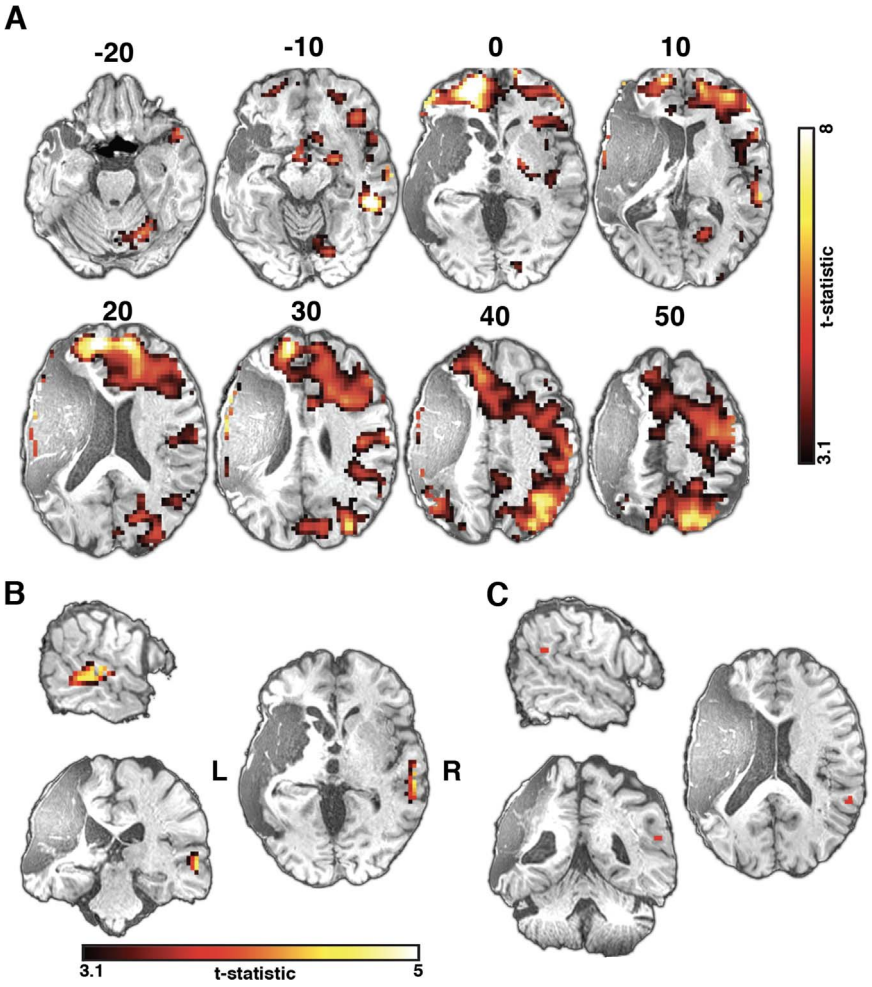

Fig. 5. A. Multi-slice view depicting cortical areas that are activated by picture stimuli. B. The right STS cluster exhibits stronger activity during error trials than correct trials when cluster-size correction is removed. C. A The right supramarginal gyrus is found when [error > correct] comparison is performed via small volume correction (SVC).

Table 2
Cortical regions identified by the conventional univariate analysis.

	MNI Coordinates					
Region name	x	y	z	t-stat.	z-stat.	# voxels
All > Base						
Left superior frontal gyrus	−15	55	−3	11.31	> 7.84	7967
Left inferior frontal gyrus	−57	19	18	10.84	> 7.84	
Left inferior frontal gyrus	−54	37	11	9.98	> 7.84	
Right inferior temporal gyrus	45	−38	−14	10.61	> 7.84	289
Right orbitofrontal gyrus	18	13	−17	8.55	> 7.84	
Right globus pallidus	21	−5	−3	7.55	7.48	
Right cerebellum	21	−59	−20	5.89	5.86	205
Right cerebellum	9	−65	−14	5.49	5.46	
Right lingual gyrus	18	−74	−10	5.46	5.43	
Error > Correct (no cluster corr)						
Right superior temporal gyrus	60	−26	0	4.64	4.62	75
Right superior temporal gyrus	60	−20	4	4.5	4.48	
Error > Correct (SVC)						
Right supramarginal gyrus	57	−44	18	3.4	3.4	2

nonresponses as this would have made it difficult to label those trials in our planned analysis during the fMRI sessions (i.e., Phase 2). As such, we encouraged the patient to name as best as he could before moving forward to the Phase 2. Impressively, KL did not exhibit a tendency for nonresponses during the Phase 2 and made naming attempts on nearly all trials.

4.2. Functional organization of naming processes implicated by pattern separability

Our MVPA searchlight found separable patterns of neural activity between correct and error trials in multiple cortical loci that have been implicated in the neuroimaging literature of overt picture naming (Fridriksson et al., 2009; Kemeny et al., 2006; Postman-Caucheteux et al., 2009). Significant clusters within the ventral part of the precentral and mid-portion of right STG/STS may reflect motoric and auditory differences between correct and error trials for the same pictures. The cluster in the anterior cingulate cortex is likely due to error monitoring during the naming task (Carter et al., 1998). Subject KL indeed reported that he was immediately aware of the errors that he was making but that he could not prevent himself from making them. Notably, the most significant and largest cluster was found in the right occipito-temporal cortex encompassing the lateral occipital complex, fusiform cortex, and mid-occipital gyrus. A similar result was reported by a previous fMRI study, in which incorrect trials yielded stronger activity within this region (Fridriksson et al., 2009). Nevertheless, in our data set, the standard univariate analysis did not yield any difference between correct and error trials. As mentioned above, this could be due to the fact that the same set of pictures were compared between correct and error trials.

Error-type analysis revealed that the subject KL mostly made semantic errors, with frequent confusion of "cow" as "milk" and "pillow" as "blanket." The "cow" picture was, at times, erroneously identified as other living objects such as "camel" or even "turkey." However, a systematic tendency toward perseveration errors was not observed. We took advantage of "milk" trials that were introduced in the second fMRI session in order to compare the neural similarity within the right occipito-temporal cluster between trials in which *KL* erroneously named "milk" instead of "cow," versus when he accurately named either "milk" or "cow." Among three pair-wise comparisons, the most similar neural patterns were elicited by instances in which the subject incorrectly named "milk" rather than "cow" and when he correctly named "milk." Together, current findings from our main searchlight and similarity analyses suggest that, for at least some persons with aphasia, semantic naming errors may be the consequence of eliciting incorrect representations of semantically-related targets in the right occipito-temporal cortex.

The occipito-temporal cortex is often implicated in neuroimaging studies of object recognition (Grill-Spector and Malach, 2004) and naming (DeLeon et al., 2007; Fridriksson et al., 2009; Kemeny et al., 2006). Evidence indicates that it is a site for an intermediate stage of object recognition beyond early visual processing. Although the LOC is frequently implicated in shape processing (Kim et al., 2009), this region also participates in semantic processing (Connolly et al., 2012; Fairhall and Caramazza, 2013; Kable et al., 2005) and object naming (Large et al., 2007). The right mid-fusiform gyrus has been implicated in the categorization of visual objects including faces (Kanwisher et al., 1997), and damage to this region results in errors in object recognition (James et al., 2003; Vandenbulcke et al., 2006).

Intriguingly, the right inferior frontal gyrus (IFG) did not emerge in the current study despite the fact that this region has been frequently implicated as playing a key role in compensatory language processing (Hamilton et al., 2011; Postman-Caucheteux et al., 2009). Of note, our subject had previously participated in studies in which he received multiple sessions of the TMS on the right IFG and had shown a substantive and persistent improvement in naming performance (Hamilton et al., 2010). One possibility is that the neural processes in this region might have been altered by the previous administration of therapeutic TMS. Further investigation is warranted in order to extend the current pilot results by employing a larger sample of subjects who are naïve to focused neuromodulation therapies.

4.3. Other considerations

There are some limitations that would need to be addressed and improved in future neuroimaging studies examining the neural correlates of naming processes in aphasia. First, we employed a slow-event related design for the purpose of spacing out successive naming trials with a 12 s ISI. For a healthy normal participant, the HRF typically peaks at 4–6 s and returns to baseline in around 12 s. However, the HRF time-course of a chronic aphasic patient may not correspond well with this assumption. Relatedly, a previous neuroimaging study reported a delayed temporal profile of HRF in the stroke patients (Bonakdarpour et al., 2007). In future investigations, the time-to-peak calculation should be performed prior to selecting time-points for MVPA classification. Secondly, we were unable to acquire reaction time data in the current experiment, as it was difficult to align the onset of stimulus presentation with the onset of recorded voice responses in a precise manner. If we had the opportunity to evaluate reaction time data, it could be possible to further characterize both behavioral and neural data pertaining to naming performance. Lastly, some of the picture items may not have been ideal exemplars and could potentially have caused confusion (e.g., some blanket images could have conceivably been mistaken for cushions). Although we tried to ensure typicality of all images by testing several colleagues in the institute, future studies should rely on a more systematic method of measuring the typicality of each image.

4.4. Conclusion

Variable naming performance in patients with chronic aphasia has inspired a body of neuroimaging research geared at characterizing the compensatory language mechanisms that are engaged during the process of overt naming. The present fMRI study suggests that retrieval of object naming depends on coordination among regional neural populations within the right occipito-temporal cortex, which is responsible for correct representation of the object. Our findings suggest that emerging imaging analysis approaches that employ novel pattern-recognition and machine-learning algorithms may ultimately prove superior to conventional neuroimaging analysis for characterizing certain brain-behavior relationships in aphasia. Thus, while preliminary, this proof-of-concept work has significant potential implications for future research linking subject-specific lesions to particular behavioral language deficits (e.g., semantic or phonetic impairments). This may, in turn, further facilitate the development and refinement of interventions that optimize successful performance in a patient-specific manner.

Conflicts of interest

The authors declare no competing financial interests.

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