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PET activation studies comparing two speech tasks widely used in surgical mapping

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Abstract

"Automatic" speech, especially counting, is frequently preserved in aphasia, even when word production is severely impaired. Although brain sites and processes for automatic speech are not well understood, counting is frequently used to elicit fluent speech during preoperative and intraoperative cortical mapping for language. Obtaining both behavioral and functional brain imaging measures, this study compared counting with a word production task (generation of animal names), including non-verbal vocalizations and quiet rest as control states, in normal and aphasic subjects. Behavioral data indicated that normal and aphasic groups did not differ in counting or non-verbal vocalizations, but did differ significantly in word production ("naming" animals). Functional brain imaging results on normal subjects using partial least squares analysis of PET rCBF images revealed three significant latent variables (LVs): one for naming and vocalizing, identifying bilateral anterior areas, with left predominating over right; a second LV for naming, identifying left and right frontal and temporal areas. For the third, only marginally significant LV, which was associated with automatic speech alone (counting), right and subcortical sites predominated. For patients, two LVs emerged, identified with naming and vocalization, and corresponding to a variety of cerebral sites; the analysis failed to find a specific latent variable for counting. A comparison between group data for normal subjects and patients suggested that the naming, counting, and vocalization tasks were performed differently by the two groups. These results suggest that word generation as a verbal task is more likely to elicit activity in classical language areas than counting. Further studies are suggested to better understand differences between neurological substrates for non-propositional and automatic speech.

Keywords: Speech; Functional mapping; Language; Human; Cerebral blood flow; Automatic speech

1. Introduction

Within the adult human brain, the left cerebral hemisphere plays a crucial role in most aspects of oral and written language. From clinical–pathological studies in brain-injured patients, it is well known that damage to different regions of the left hemisphere causes aphasic syndromes with different patterns of language impairments. Extensive damage can cause global aphasia, in which most aspects of speech production and comprehension are severely impaired. Many such patients, however, retain striking areas of speech competency. Although unable to generate novel words or sentences, these patients produce serial speech such as counting, other lists (e.g., days of the week), and expletives (Van Lancker & Cummings, 1999), recite of pledges, nursery rhymes and other well-known texts, and sing familiar songs, with ease, fluency, and normal articulation (Van Lancker, 1988, 1993). Similarly, patients with Broca's aphasia, whose sparse, effortful speech output is usually limited to single, poorly articulated nouns and verbs, can, under limited circumstances, produce normal sounding "subsets" of speech often referred to as "automatic" speech (Albert & Helm-Estabrooks, 1988; Espir & Rose, 1970). As Benson

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(1979) states, "The [Broca] patient often performs considerably better in automatic activities such as counting, or naming the days of the week or the months; even the articulation often improves greatly with these automatic verbal tasks. It is striking to note how well a patient articulates when reciting a series but cannot articulate the same words correctly in a repetition task" (p. 67). The same discrepancy is observed in fluent and anomic aphasia, whereby semantic and word finding deficits contrast with normal production of counting and other overlearned speech.

Although this dissociated speech ability has been recognized for well over a century (Broca, 1865; Code, 1982, 1989; Critchley, 1962, 1970; Henderson, 1985, 1987; Jackson, 1878; Van Lancker, 1988, 1993), it remains uncertain whether residual, intact utterances depend on neural structures within undamaged regions of the left cerebral hemisphere, on cortical structures in the nominally non-dominant right hemisphere, or on subcortical nuclear areas such as the basal ganglia (or on some combination of these). Because the types of "automatic" speech are varied and they often appear to be used "voluntarily," this category is better referred to as "non-propositional" speech. It is not known whether these two apparently disparate speech functions—non-propositional and propositional speech—are subserved by common or different underlying structures in the normal brain.

Lum and Ellis (1994) studied "non-propositional" speech tasks such as counting 1–10, reciting the days of the week, months of the year, nursery rhymes, and repeating familiar phrases in patients with aphasia. Overall performance differences were found for counting, and six of 28 patients tested showed a clear non-propositional advantage. A similar investigation revealed superior sentence completion for familiar idiomatic expressions compared with propositional expressions (Van Lancker & Bella, 1996). In a survey of recurrent utterances preserved in severely aphasic persons, Code (1982) reported numbers, expletives, and familiar expressions, categories pertinent to this study. Similar results were reported for German-speaking aphasic patients by Blanken (1991) and colleagues (Blanken, Wallesch, & Papagno, 1990).

Although much has been written about preserved "automatic speech," we know of only one study of its impairment (Speedie, Wertman, Ta'ir, & Heilman, 1993). Following a stroke to the right basal ganglia, a 75-year-old, right-handed man was unable to recite well known prayers, count 1–20, or sing familiar songs. Another study observed physical features in aphasic speakers engaged in automatic and propositional tasks. Measurement of mouth opening sizes comparing production of automatic and propositional speech in patients with left hemisphere stroke revealed greater left-sided mouth openings for recitation and singing, again implicating the right hemisphere (Graves & Landis, 1985). These studies on preserved and impaired automatic speech in persons with brain damage implicate right hemisphere cortical and subcortical structures in production of non-propositional speech.

The question of the neurological structures underlying non-propositional versus propositional speech is of importance and interest for at least three reasons. It is important, first, for our understanding of basic brain structures underlying normal speech ability. Secondly, to develop viable theories of compensation and rehabilitation following language loss due to brain damage, this information is important, because intact neurological structures subserving overlearned speech may have different properties. For example, the brain structures subserving residual speech may have constraints and limitations that should be known by the rehabilitation specialist designing a treatment plan. Third, this information will help lead to better informed choices of presurgical and intrasurgical speech-mapping tasks to delineate specific brain regions in the treatment of conditions such as epilepsy (see Lebrun & Leleux, 1993, for review).

Regarding the third rationale for this study, selection of cortical speech-mapping tasks, two different tasks are commonly utilized during pre- and intraoperative cortical speech mapping when surgical excision may impinge on speech and language areas: (1) Counting (Ojemann, 1983, 1994, 1995; Penfield & Roberts, 1959) as a method for eliciting continuous, fluent motor speech and (2) word retrieval using confrontation naming (Berger & Ojemann, 1992; Mateer, 1983; Penfield & Roberts, 1959) as a vehicle for probing semantic processes of word retrieval.

Some attempts to replace cortical mapping with fMRI (Tomczak et al., 2000) and PET functional imaging studies (Hunter et al., 1999) have been undertaken. In the Tomczak et al. (2000) study, preoperative location of motor areas using fMRI was more successful than mapping of language areas, which is to be expected. However, reservations regarding the limitations of both PET and fMRI as clinical tools in neurosurgery for localization of cognitive function have been expressed (Fried, Nenov, Ojemann, & Woods, 1995, p. 860). The low statistical power of these methods raises the possibility for false negative results, a situation that is particularly problematic when the clinician is attempting to establish that a particular brain area does not support a particular function such as memory or language. Our goal in this paper is not to establish a clinical test with imaging. It is more modest: to contribute to a better understanding of the neuroanatomical substrates underlying these tasks in the normal, intact subject and in the aphasic patient. Convergent information leading to knowledge about whether disparate neurological structures subserve overlearned serial

speech versus propositional speech may aid in selecting the optimal intraoperative speech-mapping procedures for identifying speech/language cortex.

Studies using PET imaging in normal and neurologically impaired subjects have begun to explore speech/language processing and verbal memory. Considerable variability in findings has resulted from studies of language functions in normal subjects, with criticism of method and technique appearing in the literature (Demonet, Wise, & Frackowiak, 1993; Haxby, Grady, Ungerleider, & Horwitz, 1991; Klein et al., 1997; Steinmetz & Seitz, 1991). Study design and method of data acquisition are likely to influence findings in language studies (Lange et al., 1999; Price et al., 1996). Complexity in this paradigm arises from individual variability in subjects, significant variation in levels and structure of language tasks, and questionable appropriateness of analysis methods involving subtraction and other algorithms with loss of information through extensive averaging of data (Friston, Frith, Liddle, & Frackowiak, 1991). Questions arise about the lack of coherence of PET findings with classic lesion models, in particular the frequently reported involvement of the right hemisphere in language functions traditionally believed to be strongly lateralized to the left hemisphere (Sidtis, 2000; Sidtis, Anderson, Strother, & Rottenberg, 1998). However, a number of consistent and reliable findings regarding brain mapping of speech functions have been reported (e.g., Howard et al., 1992; Paus, Petrides, Evans, & Meyer, 1993; Petersen & Fiez, 1993; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Raichle, 1991; Votaw et al., 1999) contributing to a foundation for developing a viable model of language function in the normal and diseased brain. A number of studies have identified left temporal (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996) and/or left inferior frontal lobe areas during semantic and phonological behavioral tasks. Studies of continuous speech production using PET have shown a significant relationship between speaking rate and activity in the left inferior frontal area and right basal ganglia (Sidtis et al., 2001), while fMRI studies reported activation of inferior parietal as well as temporal cortex (Kircher, Brammer, Williams, & McGuire, 2000; see Wise, Hadar, Howard, & Patterson, 1991 and Poldrack et al., 1999 for overviews of language studies; also Fiez et al., 1995; Vandenberge, Price, Wise, Josephs, & Frackowiak, 1996; see Cabeza & Nyberg, 2000, for review of imaging studies of cognition).

Fewer studies have assessed language function in brain damaged patients. Celesia et al. (1984) reported larger areas of depressed rCBF than appeared anatomically on the CT scan; remote effects were also seen. Metter et al. (1990) found hypometabolism in the left superior temporal areas in nearly all aphasic subjects, regardless of their diagnosis. Reading aloud and speaking of words was used successfully to map language areas in a single patient with an arteriovenous malformation (AVM), whereby the baseline PET scan first identified the location of the AVM (Leblanc, Meyer, Bub, Zatorre, & Evans, 1992). A study of recovery of language function post-stroke indicated increased activation of newly recruited areas when language areas remain non-functional (Karbe et al., 1998).

Keeping in mind the limitations of the PET activation paradigm, our protocol was designed to add to this growing foundation of knowledge by mapping "elementary" vocal production tasks in normal subjects in comparison with the same tasks elicited in aphasic patients with known left hemisphere lesions. The purpose of this study was to utilize functional neuroimaging with activation paradigms to (1) map brain structures in normal persons for performance of well articulated, preserved "automatic" speech production, as compared with more spontaneous speech; and (2) map brain structures in the chronic, non-fluent aphasic speaker while they are performing these apparently different kinds of speech tasks.

2. Materials and methods

2.1. Subjects

Fifteen subjects participated in this study after informed consent in accordance with the USC Institutional Review Board. Five patients (4 males, 1 female) had suffered a single, unilateral stroke in perisylvian region, resulting in non-fluent aphasia, without other neurological or psychiatric illness. They were compared to 10 normal-control subjects (6 males, 4 females). MRI scans were obtained for all subjects. All subjects were right-handed speakers of American English raised and educated in the United States. One male normal-control subject was eliminated due to inconsistencies in task performance, leaving 9 subjects in the normal-control group (see Table 1). Ages of patients ranged from 48 to 68, mean of 51.0; age range of the control subjects was

Table 1
Patient and normal-control data

Patient	Age	Ed	TPO	Diagnosis	AQ
RW	48	14	2.7	Broca	89.7
RG	51	16	9	Broca	49.9
KM	68	12	4.6	Anomic	92.6
LR	57	16	1.3	Anomic	77.2
AC	66	18	3	TSA	54.3
Pt means	51.0	15.2	4.1	—	—
NC means	51.7	16.9	—	—	—

TPO, time post-onset of injury, in years. AQ is Aphasia Quotient, a measure of severity, from the Western Aphasia Battery. TSA, transcortical sensory aphasia. Patient and normal-control means for age and education are given.

31–68, mean = 51.7; patients' education ranged from 16 to 23 years with a mean education of 15.2 years. For normal subjects, education ranged from 16 to 23 years, with a mean of 16.9 years. The study groups did not differ significantly in age or education. Normal subjects had no psychiatric, neurological, or medical disease factors that might interfere with their status as normal-control subjects. None were using recreational drugs or were on prescribed psychotropic medications. All patients had chronic (stabilized) aphasia: the time post-onset of injury was between 1.3 and 9 years (mean = 4.1 years). All patients were evaluated by a neurologist and a speech pathologist. All had a diagnosis of aphasia, distributed as follows: Broca (2), anomia (2), and transcortical sensory aphasia (TSA) (1); all five presented clinically with superior counting over spontaneous speech, confrontation naming, or word production ability. All were extensively evaluated by a speech-language pathologist using the Western Aphasia Battery (Kertesz, 1982). Their scores, including the Aphasia Quotient (AQ), a measure of aphasia severity, are shown in Table 1.

2.2. Neurobehavioral tasks

There were three speech tasks and one silent control task. The three types of speech elicited from all subjects were: (1) semantically meaningful speech (words generated by recitation of animal names), (2) serial speech (counting), and (3) non-linguistic vocalizations that engage phonation and buccal–facial movements. The latter task required the patient to make velar sounds similar to a "gargle," lip movements involving repetitive closure (as the "brrrr" sound), and palatal–nasal sounds similar to snoring. Animal name generation was induced by saying to the patient, "Name as many animals as you can: think of the ocean, the zoo, the jungle, pets, the farm, field; one example is 'dog.'" This task was selected because it is frequently used as a measure of speech fluency, it requires no visual input, it is an easy task to explain to subjects, and it engages semantic categorization and word retrieval, both classic language functions. Counting from 1 to 10 was chosen because it is the most universally observed manifestation of preserved "automatic" or "non-propositional" speech; the majority of aphasic patients are able to do this task; and it is simply explained to the subject. Non-verbal vocalizations were selected to provide a motor task similar to that used in speech but without linguistic phonological or semantic content. A rationale for use of this task comes from results described in the study by McAdam and Whitaker (1971a, 1971b), who compared verbal production (the syllables /ka, pa/) with non-verbal vocalizations (coughing, spitting gestures) using the auditory evoked response paradigm, and found that only the verbal vocalizations engaged the left hemisphere uniquely. All three activation tasks were audiotape recorded for later transcription and analysis.

The timing of tasks administered to each subject, patient and normal-control, were as follows:

90 s counting 1–10 repeatedly
10-min interval
90 s naming animals
10-min interval
90 s alternating, random non-linguistic vocalizations

Eyes were open and ambient sounds were permitted to occur throughout the activated state. In addition, a "generic" control condition was presented as follows:

90 s control (eyes open, ambient sounds, and no stimulation)
10-min interval

Each set (three activated scans, one resting scan) was presented three times, resulting in a total of 12 scans. Conditions were pseudorandomized (a different order was given) to eliminate potential problems associated with fixed order effects.

Verbal responses for all tasks produced by each of the subjects were recorded on audio tape for later transcription and analysis by taping a microphone approximately 5 in. from the patient's mouth.

2.3. Pet brain imaging studies

Positron emission tomography (PET) using radiolabeled (^{15}O) water provides a measure of local cerebral blood flow, in turn reflecting local functional activation within the human brain. ^{15}O PET scans were acquired using a modified autoradiographic method (Herscovitch, Markham, & Raichle, 1983; Raichle, Martin, & Herscovitch, 1983). For each scan, a bolus of 35 mCi of H^2O^{15} was injected intravenously at the start of scanning and the speech or control task. A 90-s scan was acquired and reconstructed using calculated attenuation correction, with boundaries derived from the emission scan sinogram. Arterial blood samples were not obtained. Images of radioactive counts were used to estimate relative cerebral blood flow as described previously (Fox, Mintun, Raichle, & Herscovitch, 1984; Mazziotta et al., 1985). PET images of rCBF were acquired with the Siemens 953/A tomograph, which collects 31 contiguous planes covering a 105 mm field of view. The axial resolution after reconstruction with a Hann .5 filter was 4.3 mm at full width half maximum (FWHM) and the trans-axial resolution was 5.5 mm FWHM as measured with a line source. The tomograph was oriented 10° steeper than the canthomeatal line to include all of the frontal lobe, parietal lobe, and most of the cerebellum. MRI anatomic images were obtained with a GE Signa 1.5 T device. A 3-D volumetric gradient echo (SPGR) image of 124 contiguous slices (voxel size =

.82 × .82 × 1.4 mm) was obtained using the sequence: TE = 5, TR = 21, (flip angle = 45 °). This sequence yields excellent anatomic detail and clearly differentiates gray and white matter.

2.4. Image analysis

All PET rCBF images were aligned to a common stereotaxic reference frame. This stereotaxic transformation is accomplished in three steps. First, a within subject alignment of PET scans is performed using an automated registration algorithm (Woods, Grafton, Holmes, Cherry, & Mazziotta, 1998a). A mean image of the registered and resliced images is then calculated for each subject. In the second step, the mean PET image from each individual is co-registered to the same subject's 3-D volumetric MRI scan (when available) using another automated algorithm (Woods et al., 1998a). In the third step, MRI scans from the different individuals in each group (i.e., patient or control) are coregistered to one of the subjects in that group who is centered in the Talairach coordinate reference space by using a stepwise transformation beginning with an affine transformation and followed by a higher order polynomial fit with progressively increasing degrees of freedom (Talairach & Tournoux, 1988; Woods, Grafton, Watson, Sicotte, & Mazziotta, 1998b). Once the MRI scans were coregistered, the same transformation matrix was applied to the appropriate PET images. To reduce the errors secondary to repeatedly reslicing and interpolating each of the PET images, all of the sequential reslice matrices for each scan were combined and a single transformation from each of the raw PET scans to the final image format in stereotaxic space was calculated.

2.5. Image analysis—statistical tests

To enhance signal detection after stereotaxic coregistration, PET rCBF images were smoothed to a final isotropic resolution of 15 mm full width half maximum, as verified with a line source. Because we were not interested in practice or time effects, the three repetitions for each task were averaged prior to subsequent analysis.

The tasks used in this experiment do not necessarily form a nested set in terms of cognitive subtraction. Therefore, we used a multivariate data analysis method that characterizes the variation across all four tasks and corresponding brain activity. The method of partial least squares (PLS) analysis was used to analyze the PET with respect to task effects. A detailed mathematical description of this method has been described previously (McIntosh, Bookstein, Haxby, & Grady, 1996). PLS was chosen as the primary analysis method as it is optimized to detect relations between experimental design factors and activity throughout the entire brain. The design-brain PLS analysis was conducted to determine how the differences in the speech tasks and control conditions were expressed in the brain. To do this, the cross-block correlation between orthonormal design contrasts and each voxel of the image data set was calculated. Singular value decomposition (SVD) was used to decompose the cross-block correlation matrix into orthogonal pairs of singular vectors or latent variables (LVs), which account for the covariance in the matrix in decreasing order of importance. The vector pairs reflect a symmetric relationship between those components of the experimental design most related to brain activity on one hand, and the optimal pattern of image-wide activity related to the identified design components on the other. This second vector, termed a singular image, can be displayed in image space. The numerical weights within this image, called *saliences*, identify the collection of voxels that as a group are most related to the design effects expressed in the LV. The PLS analysis, in another key result, yields brain scores for each latent variable, which are analogous to factor scores in classic factor analysis. Brain scores indicate how strongly individual subjects express the patterns on the latent variable. The scores are the minor product of the subject's within scan rCBF and the singular image on a particular LV. The brain scores are plotted by scan to show the subject variation in the singular images across scans. Design scores are similarly computed by the minor product of salience for contrasts and the contrasts themselves. This yields a new set of contrasts that optimally code for the effects represented in the singular image.

In this study, separate design-brain PLS analyses were run for the normal and patient populations. Then, a group-design-brain PLS was performed to identify brain areas with different profiles of activation between the two populations.

Statistical assessment of PLS was performed in two ways. First, we tested whether the pattern of effects represented in each of the LVs is sufficiently strong in a statistical sense. To do this we computed the squared multiple correlation (R^2) from the regression of brain scores on the design contrasts. Significance of the R^2 was assessed by means of a permutation test, using 500 permutations. Since the brain scores are derived in a single analytic step, it is not necessary to correct for multiple comparisons as is done for univariate image analysis. Secondly, to determine the stability of the saliences identified on the LVs, the standard errors of the salience were estimated through 100 bootstrap samples. A salience whose value depends greatly on which subjects are in the sample is less precise than one that remains stable regardless of the sample chosen (Cabeza et al., 1997). The figures and tables identify all maxima where the salience was greater than twice the standard error. (MATLAB and C-code for PLS is available through anonymous FTP at ftp.rotman-baycrest.on.ca/pub/randy/pls.)

To further substantiate the interpretation of the singular images, univariate analysis were performed using the general linear model and analysis of variance. Differences in activity across scans were assessed using a pixel by pixel ANOVA with weighted linear contrasts. Contrast weights were defined by the design scores generated with PLS. A significance threshold of $p < .005$, uncorrected for multiple comparisons was used. The statistical significance of the ANOVA should be considered as descriptive only. The significance of the LV structure comes from the permutation tests and bootstrap (McIntosh, Lobaugh, Cabeza, Bookstein, & Houle, 1998). Note that PLS and the univariate approaches are complementary: PLS provides an assessment of the contribution of distributed activity patterns to the distinction between tasks and/or groups, while the univariate analyses acts as an assessment of the importance of a given region within this larger pattern.

3. Results

3.1. Behavioral results

Performance on the three activation tasks (naming, vocalizations, and counting) was analyzed for all study subjects. Quantification of vocalizations and counting was straightforward for both study groups. For spontaneously produced animal names, repeated items, neologisms, unintelligible utterances, and non-animal words were noted but not included in this final tabulation. Fig. 1 shows performance for naming, non-verbal vocalizations, and counting in normal-control and patient groups; the behavioral data were compared using a student's t test. Normal-control subjects produced an average (over three sets) of 37.8 animal names in 90 s, compared to 11.6 animal names produced by aphasic patients, a statistically significant difference ($p < .0001$). Performance by normal subjects in this study is higher than that reported in a recent normative study (Kempler, Teng, Dick, Taussig, & Davis, 1998), likely due to the difference in mean education of the groups (10.3 in the Kempler et al. study; 16.9 in the current study). In that study, education was found to significantly influence animal name production (see also Lezak, 1995).

The normal and patient study groups reported here did not differ in education. The groups did not differ in production of non-verbal vocalizations (255.7 vocalizations for normal subjects vs. 220.0 for patients) ($p = .042$) or counting (78.7 vs. 75.3 numbers) ($p = .40$).

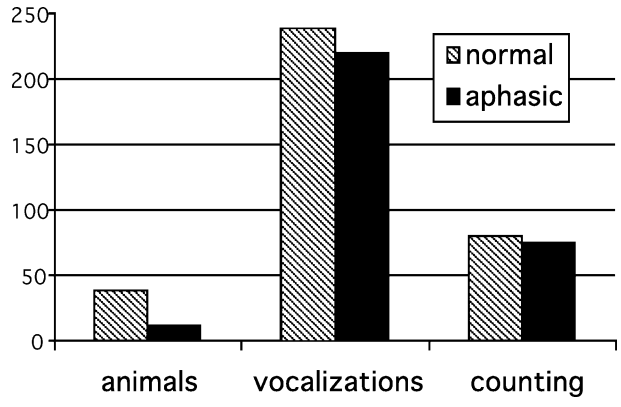


Fig. 1. Behavioral data for normal subjects and patients.

3.2. Imaging

Originally, data from normal and aphasic subjects were analyzed using subtraction methodology (Van Lancker & Grafton, 1999a, 1999b). These preliminary

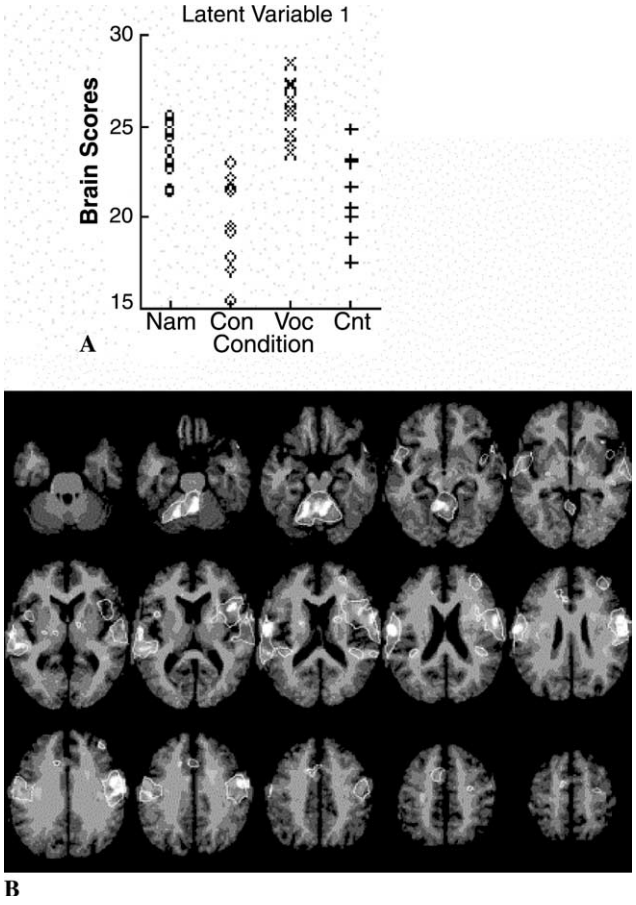


Fig. 2. Normal vocalization. (A) Design-brain scores from PLS in normal subjects. Weighting factors for the first latent variable after permutation testing reveal differences of naming and vocalizing versus counting and silence. (B) Brain saliences associated with the first significant latent variable with a ratio of salience to standard error greater than 2 after bootstrap testing by PLS analysis are shown in color, superimposed on the group mean MRI atlas. The results show where naming and vocalizing > counting and control. The contours show areas that are significant by univariate analysis using an uncorrected threshold of $p < .005$.

analyses indicated that naming engaged language areas in the left cerebral hemisphere, while counting did not. However, these tasks, being linguistic (naming), "quasilinguistic" (counting), and non-linguistic (vocalization), cannot be conceptualized as enfolded subcomponents of each other, and therefore subtraction methodology is especially inappropriate for analysis in this case (Friston et al., 1996; Jennings, McIntosh, Kapur, Tulving, & Houle, 1997; Sidtis, Strother, Anderson, & Rottenberg, 1999). Instead, partial least squares (PLS) analysis was selected for use as an analytic tool (McIntosh et al., 1998). This technique not only allows activity across the entire brain to be examined, but also avoids direct subtraction of brain states corresponding to task conditions. The starting point of the PLS analysis is the construction of four arbitrary orthonormal (uncorrelated) contrasts, representing critical distinctions among the four "tasks."

3.3. Functional localization—normal subjects

The design-brain PLS identified three significant latent variables. The first of these identified design scores shown in Fig. 2A. The brain scores associated with this latent variable identify areas where naming and vocalizing are different from counting or silent control. This LV was strongly significant ([put R2 values here if you have them, if not put% of covariance i.e., 55% of design-brain variance] $p < .0001$) after permutation testing and accounted for 55% of the design-brain variance. Areas were positive brain salience scores contributed to this effect (where naming and vocalizing > counting or control) are shown in Fig. 2B. Stability of the salience was determined by boot-strap testing. Only sites where the ratio of to standard error was >2 are shown and summarized in Table 2. The most prominent cortical areas are located in bilateral precentral gyrus (mouth motor areas), adjacent precentral sulcus (premotor cortex) and in bilateral superior temporal gyrus including contiguous auditory cortex. Left cortical areas predominate over right. In essence, these areas encompass known cortical areas involved in speech production and phonological processes. The anterior cerebellum was also identified, and subcortical activation was limited to the left caudate. All of these sites were also significant by standard univariate analysis, identified by the white contour lines in Fig. 2B. The results, with the Talairach coordinates, are presented in Table 2.

The second latent variable identified design effects where the naming task was different from the other tasks, as shown in Fig. 3A. This latent variable was also strongly significant on permutation testing ($p < .0001$) and accounted for 31% of the design-brain variance. Brain salience contributing positively and with stability by boot-strap analysis are shown in Fig. 3B. The most prominent cortical area is the left inferior and middle frontal gyrus and inferior frontal sulcus, involving Brodmann's areas 44, 45, and 6. As can be seen from

Table 2
Speech-associated regions in normal subjects ($p = .005$)

Anatomic location (Brodmann area)	Talairach coordinates (mm)			PLS	Univariate
	x	*y*	*z*	*SE*-max	*T*-max
First latent variable (naming and vocalization > control and naming)					
Cerebellum					
Bilateral anterior cerebellum	−2	−54	−16	8.61	5.57
L neocortical					
Bilateral dorsal frontal gyrus (6)—*SMA*	8	7	51	4.52	4.41
L central sulcus (4)	−56	−3	39	9.13	5.02
L frontal insula	−28	22	18	5.04	3.08
L inferior frontal gyrus (44)—"Broca's area"	−47	13	14	6.78	4.76
L middle frontal gyrus (9)	−40	40	33	4.39	3.63
L middle temporal gyrus (37)	−61	−64	2	4.13	2.82
L postcentral gyrus (40)	−53	−21	39	7.17	3.89
L superior temporal gyrus (42)	−57	−24	6	4.74	3.41
R neocortical					
R central sulcus (4)	51	−6	39	4.48	4.15
R postcentral gyrus (40)	48	−21	42	6.30	3.74
R superior temporal gyrus (42)	54	−32	9	7.35	4.39
Non-neocortical-subcortical					
L caudate	−26	−20	26	3.09	2.84

The table lists brain areas with a significant score associated with the first latent variable of the PLS analysis, with design scores corresponding to linear contrasts where naming and vocalization > counting and control. PLS *SE*-max is the maximum ratio of salience to standard error for the brain score at this location by book-strap testing. *T*-max and associated *p*-value are the results of univariate ANOVA at this location, using the design scores from PLS as the weighting factor.

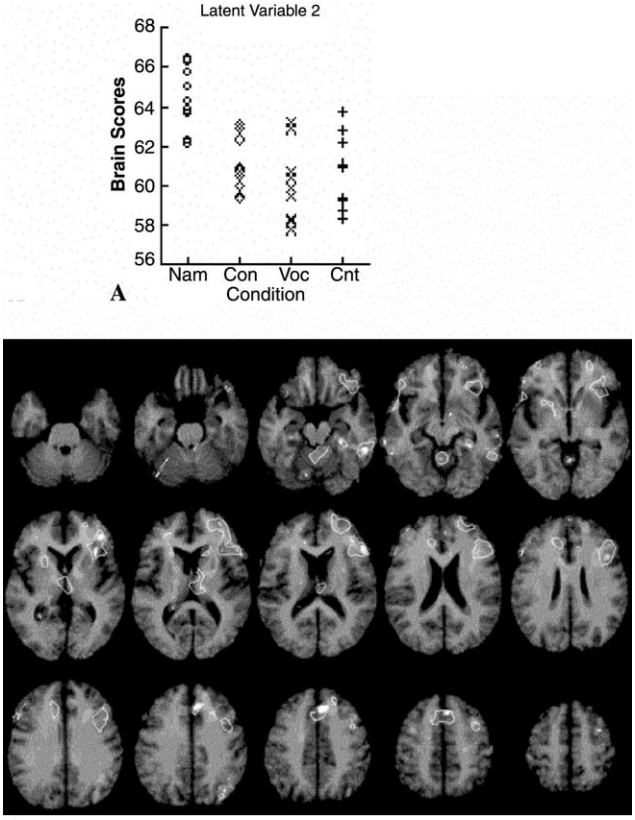


Fig. 3. Normal naming. (A) Design-brain scores from PLS in normal subjects. Weighting factors for the second latent variable after permutation testing reveal differences of naming versus vocalizing, counting, and silence. (B) Brain saliences associated with the second significant latent variable with a ratio of salience to standard error greater than 2 after bootstrap testing by PLS analysis are shown in color, superimposed on the group mean MRI atlas. The results show where naming > vocalizing, counting, and control. The contours show areas that are significant by univariate analysis using an uncorrected threshold of $p < .005$.

Table 3, cortical sites, especially those on the left, predominated, including the bilateral superior temporal sulcus, bilateral anterior cingulate cortex and left intraparietal sulcus. The process of naming also recruited the left thalamus and identified extensive sites in the anterior cerebellum. The Talairach coordinates of these sites are described in Table 3.

The third latent variable identified design effects where the counting task was different from the other three tasks, as shown in Fig. 4A. This latent variable was weakly significant on permutation testing ($p < .1$) and accounted for 14% of the variance between design and brain activity. The cortical brain salience associated with this latent variable is shown in Fig. 4B. The results show a widely distributed set of small cortical areas that are recruited during counting compared to the other tasks. Sites include multiple right hemispheric areas such as inferior frontal gyrus, precentral gyrus, angular/supramarginal gyrus, middle temporal sulcus, superior temporal gyrus, and insula. Left hemisphere areas include the precentral gyrus and superior temporal gyrus. Subcortical sites were recruited in larger proportion than in either of the other LVs. No brain saliences were associated with thalamus or cerebellum. These sites are summarized in Table 4.

3.4. Functional localization—patients

MRI scans showing lesions for each of five individual patients are shown in Fig. 5. The design-brain PLS for the patient population identified two significant latent variables. The first of these identified design scores shown in Fig. 6A. The brain scores associated with this latent variable were similar to those in normal subjects and identified areas where naming and vocalizing are different from counting or silent control. This LV was significant ($p < .008$) after permutation testing and accounted for 54% of the design-brain variance. Areas were positive brain salience scores contributed to this effect (where naming and vocalizing > counting or control) are shown in Fig. 6B, superimposed on a composite image generated from all five patient MRI scans. Significant results by univariate testing are shown as contour lines. The most prominent cortical areas are located in bilateral precentral gyrus (mouth motor areas) and adjacent precentral sulcus (premotor cortex). There is also recruitment of bilateral cerebellum and dorsal frontal cortex, as in normal subjects. Unlike the results in normal subjects, the PLS analysis did not identify recruitment of left superior temporal gyrus. Locations of the brain saliences are summarized in Table 5.

As in the normal population the second latent variable in the patient group identified design effects where the naming task was different than the other tasks, as shown in Fig. 7A. This latent variable was also significant on permutation testing ($p < .0001$) and accounted for 35% of the design-brain variance. Areas where brain salience scores contributed positively to this effect are shown in Fig. 7B. The saliences are very weak and identify only a small subset of areas seen in the normal population. The patients recruit the left middle and dorsal frontal gyri, as do normal subjects. Unlike normal subjects they also recruit the right hippocampus, right parieto-occipital fissure and left posterior parietal cortex (Table 6).

3.5. Functional localization—normal-patient interactions

A group-design-brain PLS analysis was performed to identify potentially significant interactions between task and population. The analysis identified one significant latent variable after permutation testing ($p < .0001$). As shown in Fig. 8A, the design scores associated with this latent variable identified an effect such that the difference of naming and counting versus vocalizing and silent

Table 3
Naming-associated regions in normal subjects ($p = .005$)

Anatomic location (Brodmann area)	Talairach coordinates (mm)			PLS	Univariate
	x	*y*	*z*	*SE*-max	*T*-max
Second latent variable (naming > control, vocalization, and counting)					
Cerebellum					
L anterior cerebellum	−11	−45	−13	4.46	3.06
Bilateral anterior cerebellum	1	−56	−6	4.46	4.78
L neocortical					
L inferior frontal gyrus (47)	−39	31	−12	3.87	3.06
L inferior temporal gyrus (37)	−55	−47	−11	6.66	4.06
L inferior frontal gyrus (44, 45)	−53	23	17	6.20	5.57
L inferior frontal gyrus and frontal operculum (44, 45)	−36	21	8	6.46	4.04
L precentral sulcus (6) "premotor cortex"	−40	2	54	4.92	3.58
L rostral dorsal frontal gyrus (10)	−8	66	−4	3.21	3.19
L superior frontal gyrus (9)	−19	51	27	4.33	3.04
R neocortical					
R dorsal frontal gyrus (32)	11	29	35	4.66	3.50
R dorsal frontal gyrus (6, 8)	−7	24	46	8.36	4.57
R middle frontal gyrus (9)	54	20	32	5.80	3.93
R middle temporal gyrus (21)	67	−36	−6	3.87	3.15
R superior temporal (22) and inferior frontal (47) gyri	55	5	−5	3.90	3.10
Non-neocortical-subcortical					
L hippocampus	−29	−38	−9	7.64	3.89
L thalamus	−11	−22	14	5.31	3.58
R rostral putamen	25	7	3	4.13	4.43

The table lists brain areas with a significant score associated with the second latent variable of the PLS analysis, with design scores corresponding to linear contrasts where naming > vocalization, counting, and control. PLS *SE*-max is the maximum ratio of salience to standard error for the brain score at this location by book-strap testing. *T*-max and associated *p*-value are the results of univariate ANOVA at this location, using the design scores from PLS as the weighting factor.

control was different for normal subjects and patients. Fig. 8B shows areas of positive saliences where the contrast (naming, counting > vocalizing, and control) is greater in normals than patients. It demonstrates that normal subjects are able to recruit a widely distributed set of cortical areas throughout the left frontal parietal and temporal cortex during naming and vocalizing, and that they perform the tasks differently than the patients.

4. Discussion

In normal subjects, different patterns of cerebral activation were associated with three speech production tasks: word generation ("naming"), (non-linguistic) vocalization, and counting (1–10). Using a partial least squares analysis to detect how differences in the speech tasks were expressed in the brain, distinct profiles of activation were identified. Non-verbal vocalization and naming were associated with activation in areas previously associated with speech production. Bilateral sites include motor cortex in the mouth area, the supplementary motor area and the anterior cerebellum. All of these areas are associated with articulatory motor control. The result is consistent with the notion that naming and vocalizing are more engaging of articulatory processes than counting or silence. The latent variable also identified activation in bilateral superior temporal gyri. This area is known to be involved in auditory processing, with increasing activity for more complex auditory stimuli. There was more activity in this area for naming or vocalizing compared to the counting and silence tasks. In this profile, subcortical saliences were minimal, and right sites appeared as only 25% of the total identified sites.

The second latent variable identified areas where naming was different than the other three tasks. The strongest contribution for this effect was located in the left middle and inferior frontal gyri, also known as Broca's area. It is emphasized that the right middle frontal lobe, and bilateral anterior cingulate and superior temporal sulci as well as left hippocampus and left parietal lobule were also involved. Categorical noun generation requires a multitude of cortical systems for recall, attention and word production.

The third latent variable identified areas contributing to the production of automatic speech (counting) to a greater degree than the other tasks. What is striking about the result in normals is the multitude of both cortical and subcortical sites within both hemispheres that contribute to this automatic task (Fig. 9). For this variable, increased subcortical sites was seen, and right

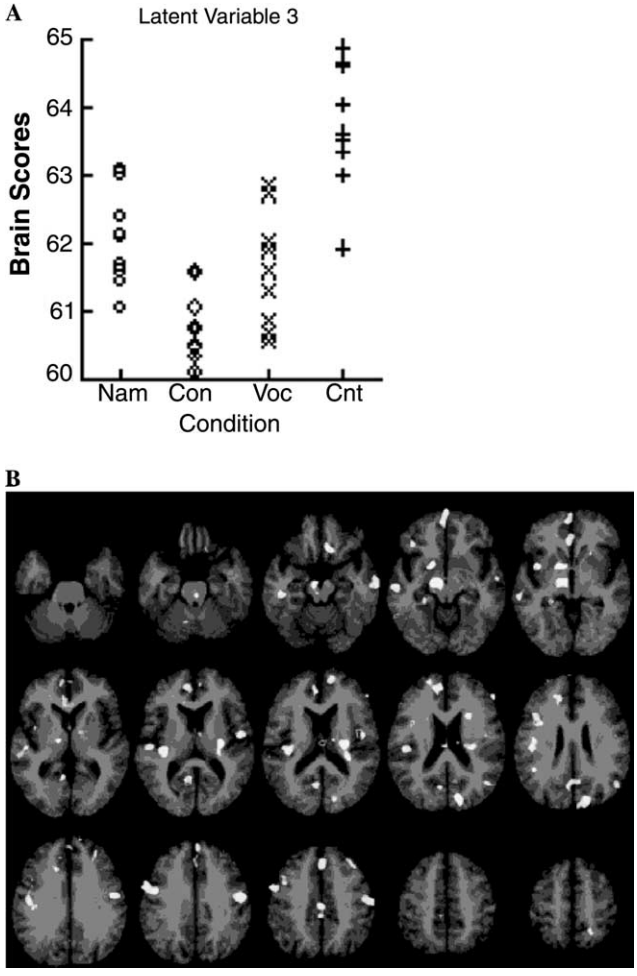


Fig. 4. Normal counting. (A) Design-brain scores from PLS in normal subjects. Weighting factors for the third latent variable after permutation testing reveal differences of counting versus naming, vocalizing, and silence. (B) Brain saliences associated with the third significant latent variable with a ratio of salience to standard error greater than 2 after bootstrap testing by PLS analysis are shown in color, superimposed on the group mean MRI atlas. The results show where counting versus naming, vocalizing and silence. The contours show areas that are significant by univariate analysis using an uncorrected threshold of $p < .005$.

cortical involvement predominated over left. Presuming that there is functional redundancy within this distributed set of areas, it is not surprising that patients with unilateral cortical lesions causing aphasia may have preservation of automatic speech. However, whether specific sites selectively and uniquely subserve counting cannot yet be determined.

The first latent variable derived from the aphasic patient results indicated that intact naming and nonverbal vocalization were associated with diminished activation throughout right hemisphere structures normally involved in articulation as well as reduced activity in left sided structures outside of the stroke lesion. There were no novel areas of recruitment to suggest functional reorganization of articulatory areas. The inter-group PLS also identified differences of areas involved in articulation (Fig. 8). In the direct comparison, the main finding was greater activation throughout preserved left frontal temporal and parietal cortex in the normal subjects compared to patients.

The results of the second latent variable, which was associated with naming alone, showed a preservation of activation in left middle frontal gyrus and left mesial frontal cortex. These areas, outside of the lesion, are normally recruited during naming. The patients also recruited several novel sites not active in the normal subjects, including the right hippocampus and mesial parieto-occipital cortex. We can not exclude the possibility that recruitment of these areas is due to task difficulty or effort. Nevertheless it is noteworthy that the mesial parieto-occipital cortex is known to be involved in visualization. It is possible that the patients use a different cognitive strategy than normals—one that involves more visual recollection than categorical noun generation.

The third latent variable in the patients was not significant. More importantly, there was no evidence that patients used a different set of brain areas for counting compared to the other tasks. In contrast, normal subjects do. It might be inferred that a residual set of undamaged regions in patients are used for both automatic and non-automatic speech. From the normal group it appears these areas are widely distributed throughout both cerebral hemispheres and subcortical sites.

It is useful to consider these functional imaging studies in light of previous models of language localization derived from lesion lesions, and later from a broader array of paradigms. The case for the left hemisphere subserving residual utterances comes from the older view of the left hemisphere as primary and as the only source of linguistic output. This view is supported by the frequency of speech deficits following left hemisphere damage and the paucity of speech deficits following right hemisphere damage. However, a role of the right hemisphere in linguistic competency has been postulated on the basis of symptomatic worsening in left-brain-injured aphasic patients after temporary right hemisphere inactivation by intracarotid amobarbital injection (Czopf, 1981; Kinsbourne, 1971) or permanent damage brought about by a new stroke to the previously intact right hemisphere (Cummings, Benson, Walsh, & Levine, 1979; Mohr & Levine, 1979). Earlier studies of cerebral blood flow associated right hemisphere activation with "automatic speech" (Ingvar, 1983; Larsen, Skinhoj, & Lassen, 1978; Ryding, Bradvik, & Ingvar, 1987). An adult left-hemispherectomized subject, who became profoundly aphasic following surgery, was able to use speech formulas and swear (Smith, 1966; Smith & Burklund, 1966; Van Lancker & Cummings, 1999). During right-sided/LH injection in a clinical Wada procedure (Wada & Rasmussen, 1960) observed by an

Table 4
Counting-associated regions in normal subjects ($p = .005$)

Anatomic location (Brodmann area)	Talairach coordinates (mm)			PLS	Univariate
	x	*y*	*z*	*SE*-max	*T*-max
Third latent variable (counting > naming, vocalization, and control)					
L neocortical					
L cuneate cortex (19)	−16	−83	25	4.76	3.52
L dorsal frontal gyrus (11)	−10	22	−13	3.27	3.30
L precentral gyrus (6), superior temporal gyrus (42)	−51	−9	14	3.55	2.97
R neocortical					
R angular/supramarginal gyrus (39)	42	−49	32	2.97	2.93
R inferior frontal gyrus (44)	40	9	31	2.97	2.97
R insula	38	1	2	2.85	2.99
R middle temporal sulcus (20)	45	−31	−11	3.30	3.60
R superior temporal gyrus (42, 22)	35	−26	14	4.73	3.67
Non-neocortical-subcortical					
L cingulate gyrus (23/31)	7	−59	9	3.00	3.67
L putamen	−28	−19	15	4.88	3.12
R globus pallidus	14	2	−2	3.55	3.39
R hippocampus	24	−38	−4	2.73	2.80
R subthalamic nucleus/red nucleus	11	−17	−5	7.73	3.93

The table lists brain areas with a significant score associated with the third latent variable of the PLS analysis, with design scores corresponding to linear contrasts where counting > vocalization, naming, and control. PLS *SE*-max is the maximum ratio of salience to standard error for the brain score at this location by book-strap testing. *T*-max and associated *p*-value are the results of univariate ANOVA at this location, using the design scores from PLS as the weighting factor.

author of this study (DVS), the patient, who was unable to respond to any aspect of the language testing, counted from 1 to 10 repeatedly. These observations, as well as the experimental study by Graves and Landis (1985) mentioned above, lead to the notion of the RH as substrate for some automatic speech behaviors. This assumption is supported by countless clinical observations of preserved speech in a large array of cases of extensive left hemisphere damage, leading to the inference that across these many cases, the right hemisphere is likely to subserve residual aphasic speech.

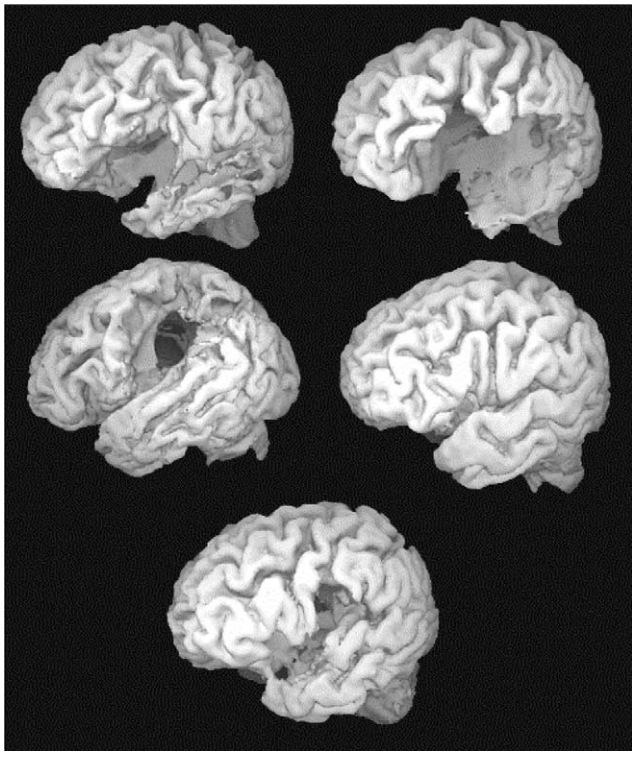
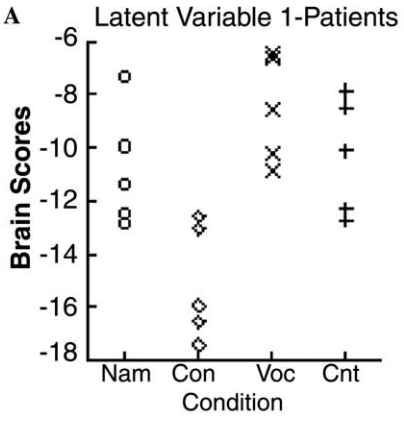


Fig. 5. Localization of lesions in five stroke patients. Three-dimensional reconstruction of structural MRI studies from the five patients demonstrating the location of left hemispheric infarcts. In subject 4 the lesion was entirely subcortical.

A key subcortical role in automatic speech has been inferred from informal observations of reduced output of such expressions in Parkinson's disease, hyperactivation of expletives in Tourette's syndrome (Van Lancker & Cummings, 1999), and the case report (Speedie et al., 1993) mentioned earlier describing a decrement in production of overlearned prayers and counting following an infarct in the right basal ganglia. Two neural systems for different kinds of cognitive processing, often referred to as procedural and declarative and correlating with habitual versus novel behaviors (Lounsbury, 1963; Sinclair, 1991) have been proposed, and may be associated with subcortical and cortical structures, respectively (Lieberman, 2001; Mishkin, Malamut, & Bachevalier, 1984; Mishkin & Petri, 1984; Robinson, 1976). Counting, as a subset of serial (automatic) speech, might well be classed as a behavior dependent on procedural memory, as contrasted to word production, which requires declarative (semantic) memory in normal subjects. In our study, more subcortical sites were identified in the third latent variable (LV), the one associated with counting, than in either of the other two LVs, which were associated with naming and vocalization (see Fig. 9).



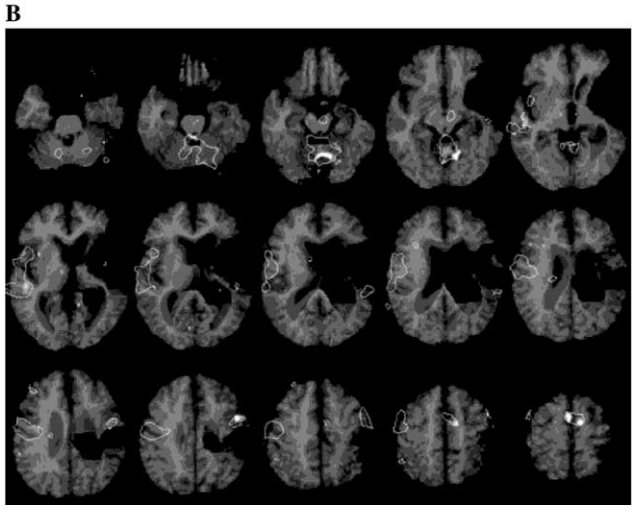
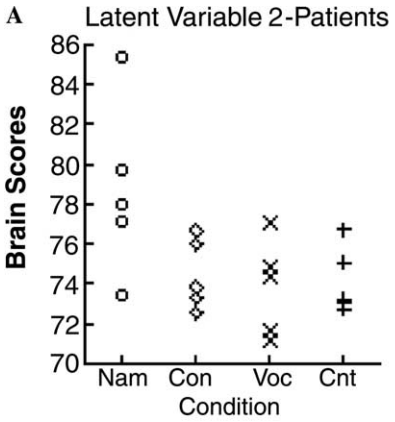


Fig. 6. Patient vocalization. (A) Design-brain scores from PLS in the five patients. Weighting factors for the first latent variable after permutation testing reveal differences of naming and vocalizing versus counting and silence. (B) Brain saliences associated with the first significant latent variable with a ratio of salience to standard error greater than 2 after bootstrap testing by PLS analysis are shown in color, superimposed on the group mean MRI atlas. The results show where naming and vocalizing > counting and control. The contours show areas that are significant by univariate analysis using an uncorrected threshold of $p < .005$.



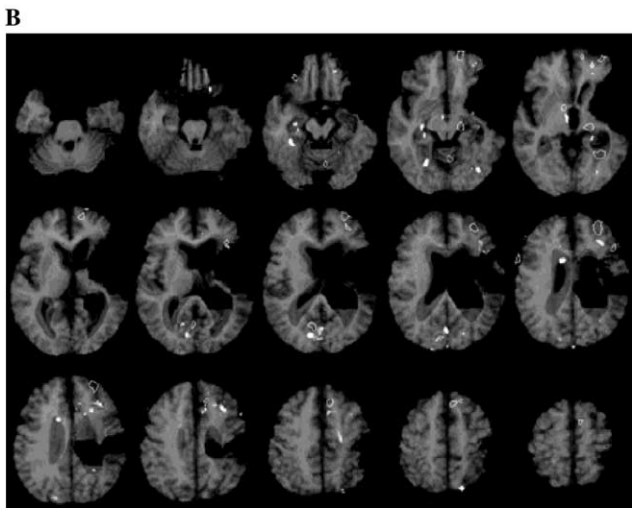


Fig. 7. Patient naming. (A) Design-brain scores from PLS in patient subjects. Weighting factors for the second latent variable after permutation testing reveal differences of naming versus vocalizing, counting, and silence. (B) Brain saliences associated with the second significant latent variable with a ratio of salience to standard error greater than 2 after bootstrap testing by PLS analysis are shown in color, superimposed on the group mean MRI atlas. The results show where naming > vocalizing, counting, and control. The contours show areas that are significant by univariate analysis using an uncorrected threshold of $p < .005$.

Several types of converging evidence suggest that counting as a speech behavior differs from other speech behaviors. In the cortical stimulation studies of Penfield and Roberts (1959), various kinds of naming errors as well as "confusion of numbers while counting" (p. 133) occurred in frontal, temporal, and parietal areas of the left hemisphere. The authors predict that misnaming and counting errors will also occur from the right hemisphere (pp. 126–127), but no actual incidences were reported. In these studies, number confusion was grouped with other "dysphasic or aphasic types of responses" (e.g., p. 130). In a study of the effects of cortical stimulation on speech production abilities, one patient was able to count forward from one by ones during stimulation of the basal temporal language area, but was unable to count by threes or say the days of the week (Lueders et al., 1991). He repeatedly reverted to counting by ones while attempting these other tasks. Confrontation naming was the most affected by stimulation of the language area with reading aloud and repetition of words also showing interruptions and paraphasias; counting alone remained fluent. Similarly, in a stimulation study using subdural electrodes, at one site speech arrest was observed during a naming task but counting was not disrupted (Fried et al., 1991). These stimulation studies support our findings that counting and naming involve different brain structures.

A preliminary report using PET imaging indicated differences in brain activation patterns for counting compared with story telling (Blank, Scott, & Wise,

Table 5
Speech-associated regions in stroke patients ($p = .005$)

Anatomic location (Brodmann area)	Talairach coordinates (mm)			PLS	Univariate
	x	*y*	*z*	*SE*-max	*T*-max
First latent variable (naming and vocalizing > control and counting)					
Cerebellum					
Bilateral anterior cerebellum	−8	−63	−9	4.47	5.85
L neocortex					
Bilateral dorsal frontal gyrus (6)—*preSMA*	0	2	58	3.77	3.39
L precentral gyrus (4/6)	−51	1	43	3.05	4.37
L dorsal frontal gyrus (6)—*SMA*	−13	−4	56	3.35	3.51
R neocortex					
R precentral gyrus (4/6)	38	−9	34	2.68	4.39
R superior temporal sulcus (21, 22)	48	−30	4	2.86	5.15
Non-neocortex-subcortical					
R thalamus	6	−15	3	3.53	2.84

The table lists brain areas with a significant score associated with the first latent variable of the PLS analysis, with design scores corresponding to linear contrasts where naming and vocalization > counting and control. PLS *SE*-max is the maximum ratio of salience to standard error for the brain score at this location by book-strap testing. *T*-max and associated *p*-value are the results of univariate ANOVA at this location, using the design scores from PLS as the weighting factor.

Table 6
Naming-associated regions in stroke patients ($p = .005$)

Anatomic location (Brodmann area)	Talairach coordinates (mm)			PLS	Univariate	*p*-Value
	x	*y*	*z*	*SE*-max	*T*-max	
L neocortical						
L dorsal frontal gyrus (6/8)	−11	29	46	2.27	3.13	.005
L middle frontal gyrus (9)	−32	37	35	2.41	3.24	.005
L superor parietal lobule (7)	−20	−57	56	3.17	1.24	NS
R neocortical						
R parieto-occipital fissure	9	−65	17	2.46	5.11	.005
Non-neocortical-subcortical						
R hippocampus	26	−10	−9	2.69	3.17	.005

The table lists brain areas with a significant score associated with the second latent variable of the PLS analysis, with design scores corresponding to linear contrasts where naming > vocalization, counting, and control. PLS *SE*-max is the maximum ratio of salience to standard error for the brain score at this location by book-strap testing. *T*-max and associated *p*-value are the results of univariate ANOVA at this location, using the design scores from PLS as the weighting factor.

2001). Another study using PET imaging employed two speech tasks traditionally considered to be "automatic," a serial task (months of the year) and a well rehearsed, memorized text (the Pledge of Allegiance) (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 2000), compared to tongue movements and consonant–vowel syllable production. Continuous production of the Pledge of Allegiance showed activation in traditional language areas; reciting the months of the year selectively engaged, of language areas, Brodmann areas 44 and 22. These observations do not cast light on counting, which has been the most widely used task in cortical mapping, and is the most frequently observed preserved automatic speech behavior.

Clinical observations in chronic aphasia suggest that nearly all language-afflicted patients can count to ten; in contrast, a smaller number can recite other serial lists (e.g., the days of the week and the alphabet to G are performed more readily than months of the year). Ability to produce well established, longer discourse units, such as prayers and song lyrics, including the Pledge of Allegiance, is more variable and appears less frequently. It has earlier been proposed that speech competence is usefully viewed on a continuum from wholly novel (newly created) utterances to reflexive cries, with serial lists, memorized speech, interactional speech formulas, idioms, and other categories taking places along this continuum, according to the properties of each (Van Lancker, 1988). Brain function underlying these categories, as well as important phenomenological differences between them, remain to be studied and understood.

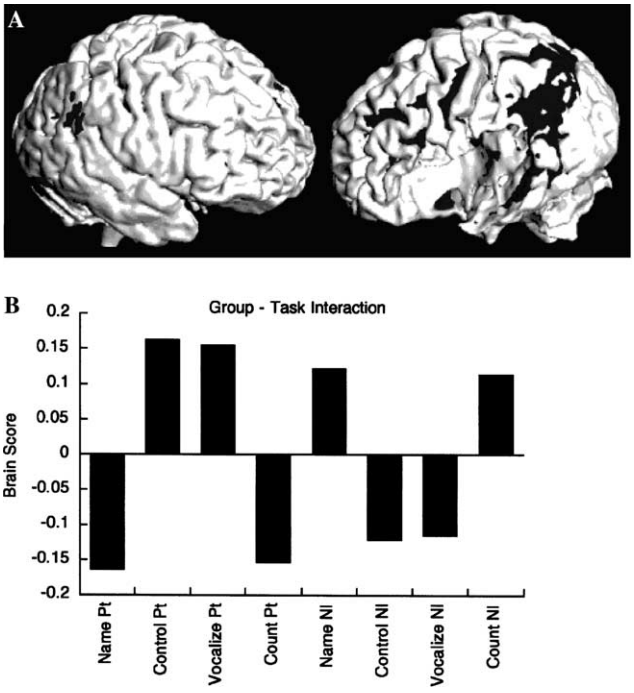


Fig. 8. Brain areas where there is a significant interaction between design-group-brain activity after PLS analysis. In panel A, areas in blue correspond to regions where normal subjects show greater activity during naming and counting compared to vocalizing or control relative to the patient group. These interactions are characterized in panel B.

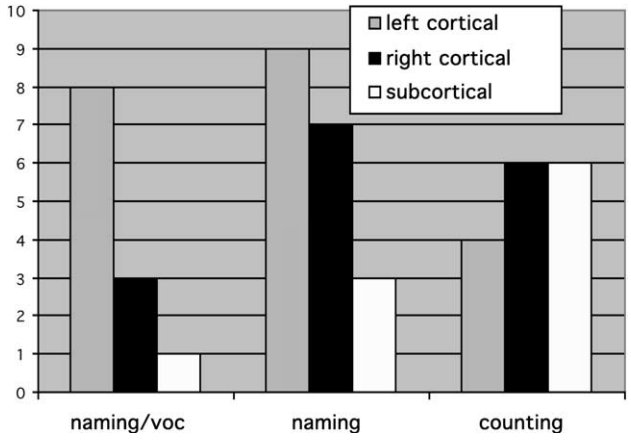


Fig. 9. Schematic chart of relative numbers of brain sites associated with three latent variables identified as naming-vocalization, naming, and counting in normal subjects.

In the study reported here, an unexpected result was that the task designated as "non-verbal vocalizations" and the word generation task (or "naming") patterned together in both study groups for the greatest proportion of variance (the first latent variable). These results are often difficult to compare with findings from other imaging studies, because of differences in design, subject population, and task demands, such as use of silent speech (e.g., Friedman et al., 1998). However, several studies have associated semantic and phonological processing with left inferior prefrontal cortex (Demonet et al., 1992; Desmond et al., 1995; Poldrack et al., 1999; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; but see Price, Moore, Humphreys, & Wise, 1997). In the present study, vocalization and naming patterned together, and the brain-group-profiles identified were primarily left prefrontal sites. Although the vocalization task was intended to be "non-linguistic," in actuality, subjects produced sequences of phonological sounds.

In summary, counting was not associated with coherently patterned brain areas in normal subjects; counting did not yield a significant set of brain sites in patients; and counting alone failed to distinguish between patient and normal groups. Counting patterned more consistently with the control (rest) task, suggesting that counting does not fall in the category with phonological or semantic processing. These results suggest that counting is not an optimal task for intraoperative cortical speech mapping. Counting may also not be optimal as a reference state or baseline in functional brain imaging studies (Hutchinson et al., 1999; Pihlajamäki et al., 2000). In agreement with the clinical observations on persons with aphasia, for whom counting is easier than word production, and who have various degrees of left hemisphere cortical damage, counting was identified with a greater array of subcortical and RH cerebral sites than word production in the present study. Functional mapping for surgical planning is likely to be more successful when the essential differences between propositional and non-propositional speech are recognized.

Uncited reference

(Graves, Landis, & Simpson, 1985).

Acknowledgments

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