Neuroimaging of Language Processes: fMRI of Silent and Overt Lexical Processing and the Promise of Multiple Process Imaging in Single Brain Studies

Ron Borowsky, PhD; William J Owen, PhD; Tammy L Wile, MA; Chris Kelland Friesen, PhD; Jennifer Lynn Martin, BA; Gordon E Sarty, PhD

Abstract

Objective: To implement and evaluate a multiple-process functional magnetic resonance imaging (fMRI) paradigm designed to effectively and efficiently activate several language-related regions for use with neurosurgical patients. Both overt and covert response conditions were examined.

Methods: The fMRI experiments compared the traditional silent word-generation condition versus an overt one as they engage frontal language regions (Experiment 1) and silent versus overt semantic association conditions as they engage multiple language processing regions (Experiment 2).

Results: In Experiment 1, the overt condition yielded greater magnitude of activation, but not volume of activation, in the left inferior frontal and insular cortices than did the silent condition for most, but not all, participants. Experiment 2 demonstrated that the activation of multiple established language processing regions (ie, orthographic, phonological, and semantic) can be achieved in a significant number of participants, particularly under overt semantic association conditions and that such activation varies in predictable ways.

Conclusion: The traditional silent response condition cannot be considered as equivalent to the overt response condition during word generation or semantic association. The multiple-process imaging method introduced here was sensitive to processing robust orthographic, phonological, and semantic regions, particularly under the overt response condition.

Abrégé

Objectif : Appliquer et évaluer un paradigme aux processus multiples de l'imagerie par résonance magnétique fonctionnelle (IRMF) destiné à activer de façon efficace et efficiente plusieurs régions liées au langage, pour les patients de la neurochirurgie. Des conditions de réponse ouvertes et fermées ont été examinées.

Méthodes : Les expériences d'IRMF comparaient la condition silencieuse classique de la production de mots avec une condition ouverte, toutes deux faisant appel aux régions du langage frontales (expérience 1), et une condition silencieuse avec une association sémantique ouverte mobilisant les multiples régions de traitement du langage (expérience 2).

Résultats : Dans l'expérience 1, comparativement à la condition silencieuse, la condition ouverte donnait une plus grande ampleur d'activation, mais pas de volume d'activation,dans le lobe frontal inférieur gauche et le lobe insulaire, pour la plupart des participants, mais pas tous. L'expérience 2 a démontré que l'activation de multiples régions établies du traitement du langage (c.-à-d., orthographique, phonologique et sémantique) peut se faire chez un nombre significatif de participants, surtout dans des conditions ouvertes d'association sémantique, et que cette activation varie de façon prévisible.

Borowsky, Sarty — Department of Psychology, University of Saskatchewan, Saskatoon, SK
Owen — Department of Psychology, University of Northern British Columbia, Prince George, BC
Wile—Nova Scotia Rehabilitation Centre, Halifax, NS
Friesen — Department of Psychology, North Dakota State University, Fargo, N.D.
Martin — Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, AB

Address for correspondence: Dr Gordon Sarty, Dept of Psychology, University of Saskatchewan, Saskatoon, SK S7N 5A5; fax 306 966-6630; gordon.sarty@usask.ca

Submitted Apr 1, 2005

Accepted June 1, 2005

Can Assoc Radiol J 2005;56(4):204–213.

Conclusion : La condition de réponse silencieuse classique ne peut être considérée comme étant équivalente à la condition de réponse ouverte, durant la production de mots ou l'association sémantique. La méthode d'imagerie aux processus multiples introduite ici était sensible au traitement dans les régions orthographique, phonologique et sémantique robustes, en particulier dans une condition de réponse ouverte

Of all the cognitive tasks that we engage in on a regular basis, one of the most frequent and important is generating words (or in other words, using language), be it overtly or silently. Indeed, when brain surgery is required (eg, to remove epileptogenic tissue), great care is taken to avoid removal of so-called eloquent cortex. In so doing, rather invasive methods have typically been used to ascertain where language-related cortex resides. For example, Wada's test involves the injection of sodium amobarbital to anesthetize one hemisphere of the brain at a time (thus paralyzing the contralateral side of the body), so as to evaluate errors in speech and memory and thus determine the dominant hemisphere for language processing. Prior to the removal of brain tissue, neurosurgeons typically use electrodes to directly stimulate cortex while the patient is conscious and responding to linguistic tasks, so as to determine a safe boundary for tissue removal. The functional magnetic resonance imaging (fMRI) method described in this paper provides a noninvasive alternative for localizing language function.

Over the past decade fMRI has developed into a method for measuring blood oxygenation level–dependent (BOLD) changes, thereby identifying regions of brain activation, specifically excitatory local field potentials reflecting input and intracortical processing.[1] The utility and safety of fMRI in the context of localizing language processes in the brain is less invasive relative to the other commonly used methods described above. However, access to magnetic resonance imaging (MRI) equipment is often limited, and fMRI experiments are often time-consuming (usually involving several separate tasks to permit task subtraction) and are conducted on a costly device at an expensive hourly rate. One major goal of the present research is to evaluate the effectiveness and efficiency of a new technique that attempts to activate many language-related processing regions simultaneously and in a very brief time (ie, less than 10 minutes). Such a technique may prove to be useful not only for theoretical research (particularly in its potential for effectively activating multiple language functions without the need for subtracting multiple, hierarchical tasks), but also for its potential application as an efficient pre- and postsurgical technique for language localization.

To experimentally study tasks like word generation with some confidence that the participant is properly engaged in the task, it is desirable to have a condition where they are able to respond aloud. Responding aloud is a challenge in the MRI environment, where any motion of the head and magnetic susceptibility changes in the sinus cavities due to air volume changes can result in artifactual activation. Therefore, silent responding has traditionally been preferred by fMRI researchers. Nonetheless, the development of tasks that allow the participant to generate words to completion is critical for veridical and comprehensive localization of language function in the brain.

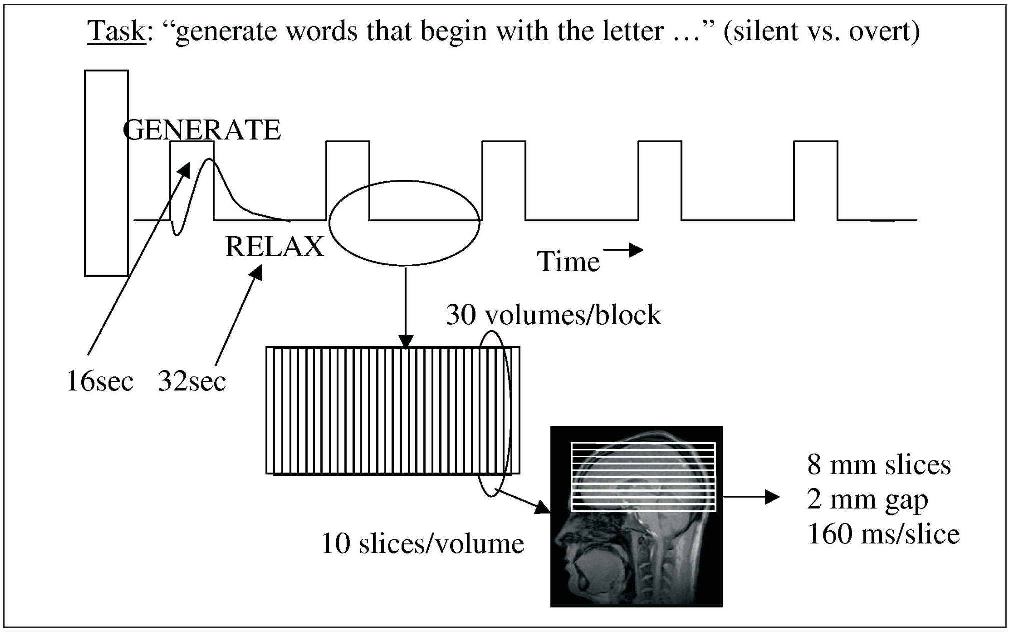
Although head motion has been a source of problematic artifacts in fMRI, there have been some laudable efforts to develop techniques that permit the participant to speak aloud.[2–6] Recently, Rosen et al conducted a small-sample fMRI experiment in which the participants ($n = 5$) engaged in both silent and aloud word generation to 3-letter visual cues (eg, generating "steak" for "STE").[7] The authors concluded that there were no average differences in activation magnitude between silent and aloud conditions in the language-related cortical regions that they examined, including a region that has long been implicated in verbal language processing, which includes the left frontal operculum and inferior frontal gyrus (IFG), often associated with Broca's area (see reviews by Binder and Price,[8] Demb et al,[9] and Grodzinsky[10]). Rosen et al's conclusion is at odds with some of the neuroimaging literature (eg, see review by Demb et al[9]), given that the anterior limb of the IFG appears to be more active during an overt response in semantic generation and semantic decision tasks compared with a covert response,[4,11] implicating articulation-related differences (or attentional differences) between silent and overt conditions in generation and decision tasks.

A region neighboring Broca's area that may also be involved in differences between silent and overt word generation is the insular cortex. Raichle et al have suggested that the insular cortex responds to familiarity with word naming tasks,[12] so we chose to explore activation in this region in case it was also sensitive to silent versus overt response conditions. In Experiment 1, we conducted a detailed comparison of activation in these left frontal language regions (ie, inferior frontal regions including the frontal operculum and IFG, plus the insular cortex) as a function of silent and overt word generation in order to determine whether these conditions differentially engage language processing systems. The results of this experiment had important implications for the design of Experiment 2, in that they were expected to reveal whether one condition (silent or overt) was better than the other at activating language-related regions, and whether there were any language processing differences for silent and overt conditions in individuals.

Material and Methods

These experiments were performed in compliance with the relevant laws and institutional guidelines and were approved by the University of Saskatchewan Behavioral Sciences Ethics Committee. All imaging was conducted using a 1.5T Magnetom Symphony (Siemens, Erlangen, Germany) imager. Both experiments used TR = 1600 ms, TE = 55 ms, a 64 × 64 acquisition matrix, and a 128 × 128 reconstruction matrix.

Figure 1 Design of Experiment 1



Echo planar imaging (EPI) slice thickness was 8 mm, with a 2 mm gap between slices. The first 10 volumes were used to achieve a steady state of image contrast and were discarded prior to analysis. To capture a full cortex volume of images for each participant, either the third or fourth inferior-most slice was centred on the posterior commissure, depending on distance between the posterior commisure and the top of the brain for each participant. T1-weighted high-resolution spin-echo anatomical images (TR = 525 ms, TE = 15ms, 192 × 256 acquisition matrix) were acquired in axial, sagittal, and coronal planes for the purpose of overlaying the activation maps. The position and thickness of the T1 axial images matched the echo planar images. A microcomputer running Micro Experimental Laboratory (MEL) software (Psychology Software Tools, Inc, Pittsburgh, PA) was used to trigger each image acquisition to keep the stimulus presentations synchronized with the images. Auditory instructions and stimuli were presented using the standard pneumatic headphones and intercom system supplied with the imager. Visual stimuli were presented using a Sharp Notevision [3] data projector controlled by a personal computer using MEL software, which also triggered each slice imaging sequence. All participants were right-handed, spoke English as a first language, and had university-level education.

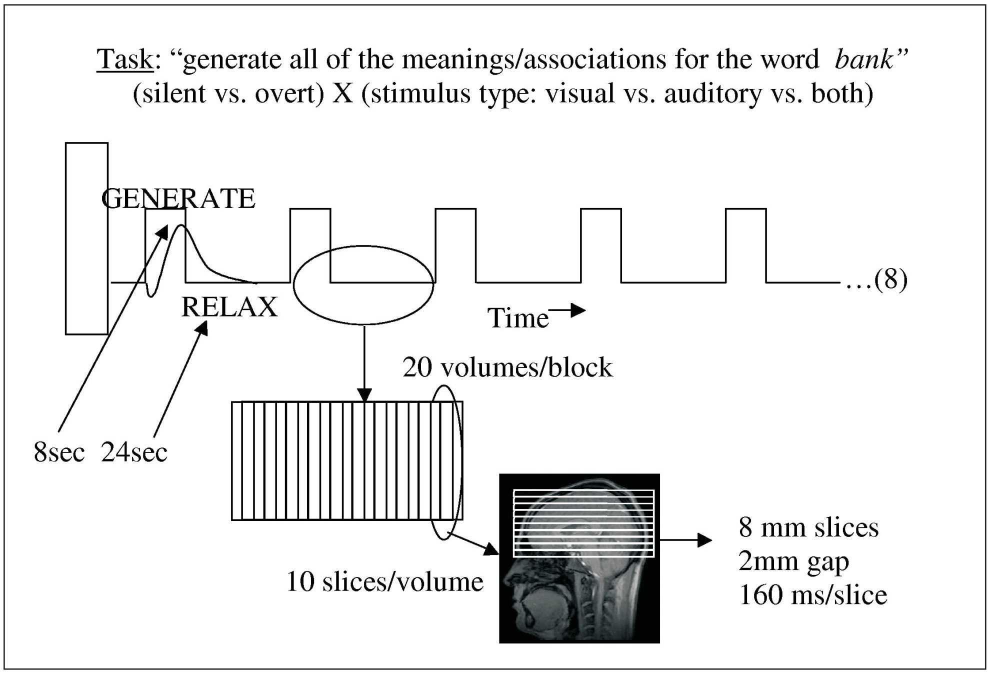
Experiment 1

Eight participants (6 men, 2 women) performed the word-generation tasks, one-half with the aloud condition prior to the silent condition and one-half with the silent condition prior to the aloud condition. This experiment was a periodically blocked, event-related design (Figure 1), a more sensitive design than randomly presented single events for detecting the effects of subtle BOLD functions[13] that are correlated with the task. For each condition (silent and aloud), 180 volumes of 10-slice axial single-shot echo planar images were obtained. Total imaging time per condition was 288 seconds. Volumes were organized into 5 blocks of 30 volumes (48 seconds per block) with 5 volumes (8 seconds) between blocks that were discarded in the subsequent analysis. The extra 5 volumes between blocks were inserted to allow the hemodynamic response to completely recover before the next block. The rationale for the duration of relax time (see also Wise et al[11]) was to ensure that the BOLD response had adequate time to fully return to baseline (as determined from a preliminary pilot study in which the relax time was varied). Each block consisted of 10 volumes (16 seconds) of response followed by 20 volumes (32 seconds) of relax. The critical trials consisted of 5 alternating blocks of word generation to an aurally presented cue (eg, "E as in echo," with the stimulus letters occuring equally often in silent and aloud conditions across participants), to which participants were instructed to generate as many words as they could for 16 seconds that begin with the stimulus letter and then to relax and concentrate on their breathing for 40 seconds (including the between-block time) after the experimenter said "stop." Responses were monitored over the MRI intercom during the overt condition.

Experiment 2

Seven participants performed a semantic association task with visual stimuli, 6 participants performed the same task but with auditory stimuli, and 7 participants performed the task with simultaneous visual and auditory stimuli. There were 9 male and 11 female participants, distributed similarly across the

Figure 2 Design of Experiment 2



3 stimulus conditions, one-half with the aloud condition prior to the silent condition and one-half with the silent condition prior to the aloud condition.

The experiment was similar in design to Experiment 1 (Figure 2). Specifically, for each condition (silent and aloud), 170 volumes of 10-slice axial single-shot echo planar images were obtained for a total imaging time per condition of 272 seconds. Volumes were organized into 8 blocks of 20 volumes (32 s per block) with no volumes between the blocks. Each block consisted of 5 volumes (8 s) of response followed by 15 volumes (24 s) of relax. It was determined during pilot testing that 8 seconds was more than sufficient time for participants to do this task and that 24 seconds was sufficient time for the BOLD functions to return to baseline levels. T1-weighted anatomical images were acquired, exactly as for Experiment 1, to underlie the activation maps. Thus the critical trials consisted of 8 alternating blocks of semantic association to a polysemous (ie, multiple meaning) word cue stimulus.

Our word stimuli were taken from Borowsky and Masson,[14] who presented empirical results and a computational neural network model of the effects of these polysemous stimuli and their controls across 3 different behavioural tasks. Their results suggest that the greater the semantic demands of the task, the more likely one is to find an effect of polysemy on behavioural measures like reaction time (RT). In the Borowsky and Masson study, there was no significant effect of polysemy on simple naming task RT (ie, time from word onset to vocalization onset), nor on shallow lexical decision task RT (ie, time from word onset until it is identified as being a real word, in the context of an equal number of nonwords that are simple strings of consonants). However, in more semantically demanding tasks like reading for comprehension and standard lexical decision (ie, words are presented in the context of pronouncable nonwords), there were significant effects. The reading-for-comprehension task (as measured by eyetracker time on target) is known to produce a polysemy disadvantage when polysemous words are read in a neutral context, reflecting the time to evaluate multiple meanings, whereas the standard lexical decision task yielded a polysemy advantage on RT, reflecting the benefit of multiple meanings to the time it takes for a network to reach a criterial level of familiarity. The present task was chosen it because it is similar in nature to the reading-for-comprehension task, as it requires the evaluation of multiple words.

In the present task, the polysemous words were presented in 1 of 3 ways (visual, auditory, or both), with the silent and overt response conditions counterbalanced to occur first equally often across participants. Participants were instructed to begin generating as many meanings or associations for a target word as possible in an 8-second period (coinciding with the offset of the word in the visual stimulus condition, with the experimenter saying "stop" in the auditory stimulus condition, and with both in the visual + auditory condition).

Generating all of the meanings and associations for a polysemous word cue, such as bank, should serve to activate regions that represent semantic and phonological processing.

By manipulating whether the stimulus cue is visual or auditory, we can make further predictions. Participants should be more likely to show activation in orthographic processing regions—lateral temporal-occipital (LTO), lateral occipital (LO), and medial extrastriate (ME) cortex—when a visual orthographic cue is available, whereas phonological processing should be more evident when an auditory stimulus is present, such as during the overt response condition or when an auditory cue is given. Finally, a visual-plus-auditory cue condition was also included to evaluate whether the 2 modalities could be combined to assess lexical processing more efficiently.

We also examined some brain regions that have been included in other recent studies of word generation. Specifically, Raichle et al have suggested that the insular cortex represents familiarity with word naming,[12] and Rosen et al have suggested that the thalamus and putamen respond to increases in motor demands of word generation.[7] However, it would be premature to generate strong predictions about these regions.

Image analysis

The BOLDfold method of analysis requires that sufficient time elapse between active task conditions for the hemodynamic response (or the BOLD function) to fully return to its baseline level.[15] After correction for linear baseline drift, the mean BOLD function for each voxel, collapsing across the repetitions of task and baseline, was empirically determined as the average response of the repeated blocks and then repeated and correlated to the actual data as a measure of consistency across repetitions. Activation maps, which were displayed with AFNI software[16] were constructed using a criterial correlation (η) of 0.63 for Experiment 1 and 0.60 for Experiment 2.

Activation maps from Experiment 1 were masked to examine volume (number of voxels) and magnitude of activation (maximum minus minimum of the average BOLD function) in the left inferior frontal cortex, including the frontal operculum, and the anterior portion of the insular cortex. These regions were identified within 2 axial slices: the inferior slice was the first slice above the eye sockets (approximately $z = 0$, the plane running through the posterior commissure), and the superior slice was the next slice up (approximately $z = 10$). We adopted this approach to identifying the regions of interest as opposed to choosing a fixed z plane because the z plane is typically defined relative to the anterior commissure–posterior commissure line,[17] which varies in angle between individuals. Student t-tests were used to compare volumes and magnitudes between the silent and aloud conditions in data averaged across participants.

Nonparametric sign tests were used on Experiment 2 data to compare individual activations. The number of participants showing activation in a particular region was considered significant at $\alpha = 0.05$ by the sign test variant of chi-square if at least 4 out of 4 participants show an effect ($\chi^2(1) = 4.0$, $p = 0.0455$), whereas 6 of 7 participants showing an effect would be marginal ($\chi^2(1) = 3.571$, $p = 0.0588$).

To identify a robust set of language processing regions, we considered a recent review of the neuroimaging of language processing. Demb et al have suggested that there is some consensus in the literature with respect to regions that represent orthographic (ie, visual spelling), phonological (ie, speech sound), and semantic (ie, meaning) processing.[9] Specifically, phonological processing tends to activate superior temporal (ST) (including primary auditory cortex) and posterior temporal (PT) (including Wernicke's area) regions, semantic and phonological processing tend to overlap in activating lateral prefrontal (LPr) and inferior frontal (including Broca's area) regions, and orthographic processing tends to activate LTO, LO (including primary visual cortex), and ME cortex.

Results

Experiment 1

For this word-generation task, the aloud condition resulted in greater activation magnitude than did the silent condition in the left frontal language regions, with the exception that the difference was only marginally significant in the inferior perspective of the insular cortex (Table 1). Six of the 8 participants showed greater activation in the regions of interest in the overt condition, whereas 2 of the participants showed greater activation in the silent condition **(**Figure 3). The most similar slice to our superior slice perspective in the Rosen et al study is $z = 8$ mm, and they did not include any analyses of the next inferior slice.[7] There were no significant differences when activation volume (ie, number of active voxels) was used as the dependent variable, although the superior perspective of the insular cortex showed a trend toward greater activation volume for the aloud condition.

Experiment 2

Activation maps for semantic association were constructed for each participant using a criterial $\eta = 0.60$ ($r(158) = 0.60$, $p = 9.245 \times 10^{-17}$) (Figure 4, shown in red to yellow). For comparison purposes, and to ensure that our consistency criterion was appropriate, activation at the level of $\eta \geq 0.50$ was also mapped (shown in green). Activation in 11 regions of interest across the axial slices shown in Figure 4 was examined for each participant and recorded as present or absent at the level of $\eta \geq 0.60$. Following Barch et al,[18] we examined the number of participants showing activation in each of these regions of interest as a function of stimulus type, hemisphere, and task condition (silent versus overt) (Table 2).

Table 1 Tests of volume of activation and mean activation magnitude as a function of region of interest and task condition in Experiment 1

	Volume of activation (voxel count)				Mean activation magnitude (% max)			
Location	Silent	Overt	*t*	*p*	Silent	Overt	t	*p*
z = 0								
IF	21.88	41.69	0.892	0.402	0.177	0.261	2.970	0.021
In	11.31	24.44	1.339	0.222	0.111	0.219	2.090	0.075
z = 10								
IF	27.19	46.50	1.158	0.285	0.125	0.247	2.762	0.028
In	13.00	27.44	1.905	0.098	0.116	0.197	4.320	0.003

z = Talairach inferior-superior coordinate, IF = inferior frontal cortex, In = insular cortex

Discussion

Experiment 1

Using a motion-robust method of image analysis that is particularly well suited for studying overt word generation,[19] the fMRI word-generation task presented here allowed us to quantify activation volume and magnitude in left frontal language regions for both silent and aloud conditions. The results of Experiment 1 demonstrated that we can examine overt speech in the MRI environment and that overt word generation results in greater activation in frontal language regions than does the more traditional silent condition. Specifically, fMRI activation magnitude in silent versus overt word generation showed that the left inferior frontal and insular cortical regions are more active during the overt condition. This finding is inconsistent with Rosen et al's recent study.[7] Given the smaller sample size used by Rosen et al (*n* = 5), it is likely that their study lacked sufficient power to reject the null hypothesis in these regions of interest (they were able to demonstrate greater activation for the aloud condition only in the motor cortex, auditory cortex, thalamus, and putamen). A related possibility is that even a single participant showing a strong reverse pattern compared with the remainder of participants could be sufficient to eliminate any effect. This latter possibility underscores the importance of including an analysis at the level of the individual participant (see Burton et al[3]). In the present study, most participants (ie, 6 of 8) support the pattern of differences obtained with the parametric analyses. Finally, there are differences in the exact nature of the word-generation tasks used in the 2 studies. Rosen et al's word-generation task involved stem completion, whereas our task involved generating words to a first letter cue. It is possible that our word-generation task required greater cognitive effort, and thus it may have recruited a higher degree of phonological lexical processing, particularly in the aloud condition where phonological lexical output is required. However, other tasks have elicited activation in inferior frontal language regions during overt conditions, including Stroop color naming and verb generation (eg, Barch et al[18]), which suggests that activation in these regions is not particular to the variant of word-generation task that we used.

The present findings are congruent, however, with Demb et al's review[9] of the literature regarding greater activation in the anterior limb of the left inferior frontal cortex for overt word-generation and decision tasks than for silent versions of these tasks.[4,11] Perhaps more importantly, our findings are supported by the results of a study by Palmer et al[20] that includes the data from Rosen et al study[7] with an additional 5 participants. Further, if we are to conceptualize the left inferior frontal cortex as a region that serves to translate lexical entities into their articulatory routines (ie, a phonological lexical output system; see Binder et al's review[8]), it seems quite sensible that greater activation should occur here in the overt condition for most of the participants.

The results of Experiment 1 support the notion that overt word generation is different from the more common silent version of the task, and the presence of individual differences in silent and overt word generation suggest that both conditions should be included when frontal regions are evaluated for language function. Thus in exploring a new technique for engaging multiple language processing regions in Experiment 2, we chose to use both silent and overt conditions.

Experiment 2

One critical region of interest is the speech tract region of motor cortex, which provides a means to evaluate data quality. We manipulated silent and overt response conditions in Experiment 2, with the prediction that motor cortex should be activated to a greater extent in the overt condition across the participants. Given the results of Experiment 1, we predicted that the overt response condition should also evoke greater

Figure 3 Activation magnitude maps from representative individuals for silent and overt word generation (Experiment 1) exemplifying (a) a pattern where frontal language regions (inferior frontal [IF] and insular [In] cortex) are more active for silent than overt conditions, which occurred in 2 of the 8 participants and (b) a pattern where these regions are more active for overt than silent conditions, which occurred in 6 of the 8 participants. Intensity values reflect activation intensity, thresholded at $\eta = 0.63$, in greyscale units divided by 100.

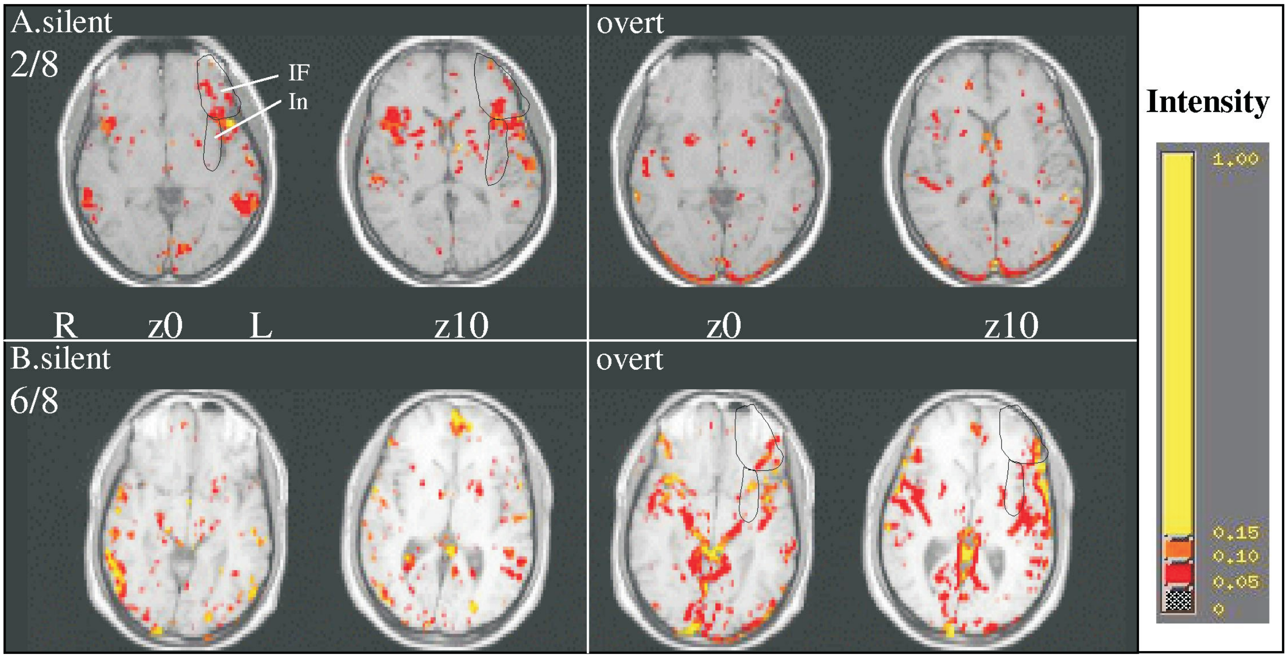


Figure 4 Activation consistency maps from representative individuals for the visual stimulus condition of the semantic association task (Experiment 2) under (a) overt and (b) silent conditions. Regions of interest (and the language processes that they have been argued to reflect) include motor (M) cortex (phonological output), lateral prefrontal (LPr) cortex (semantic), inferior frontal (IF) cortex (phonological), insular (In) cortex (phonological), superior temporal (ST) cortex (phonological input), putatmen (Pu, phonological output), thalamus (Th, phonological output), posterior temporal (PT) cortex (phonological and semantic), lateral temporal-occipital (LTO) cortex (orthographic), lateral occipital (LO) cortex (orthographic), and medial extrastriate (ME) cortex (orthographic). Eta values represent the correlation between each voxel's blood oxygenation level dependent (BOLD) function timecourse and that voxel's mean BOLD function, thus serving as a measure of activation consistency.

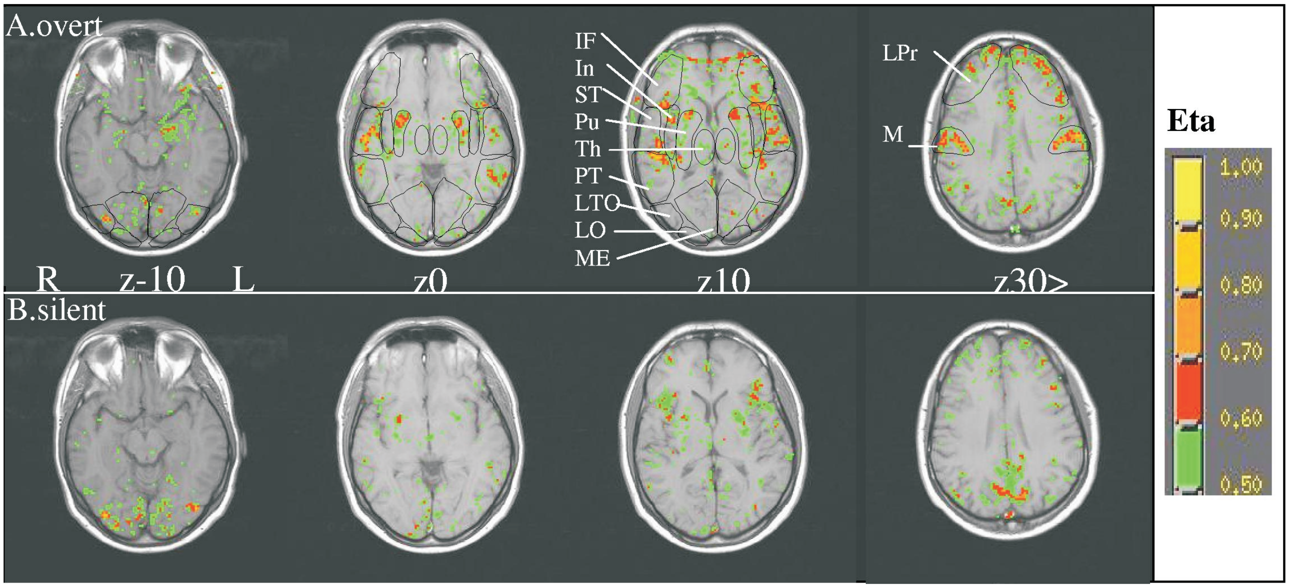


Table 2 Number of participants showing activation as a function of region of interest, stimulus type, hemisphere, and task condition, in Experiment 2

	Visual stimulus				Auditory stimulus				Visual and auditory			
	Left		Right		Left		Right		Left		Right	
	Silent	Overt	Silent	Overt	Silent	Overt	Silent	Overt	Silent	Overt	Silent	Overt
Valid *n* =	7	5^a	7	5^a	6	4^a	6	4^a	7	7	7	7
M	1	5**	1	5**	5	4**	5	4**	2	7**	1	7**
LPr (P,S)	6*	4	2	4	5	4**	4	4**	7**	7**	5	6*
IF (P,S)	6*	5**	3	5**	6**	4**	5	4**	6*	7**	5	7**
In	5	5**	5	4	4	4**	4	4**	4	6*	3	6*
ST (P)	4	5**	3	5**	6**	4**	6**	4**	5	7**	5	7**
Pu	5	4	5	4	4	4**	4	4**	3	7**	4	7**
Th	3	4	1	4	4	4**	3	4**	3	7**	3	7**
PT (P)	5	5**	4	5**	6**	4**	6**	4**	6*	7**	7**	6*
LTO (O)	7**	5**	7**	5**	3	4**	2	4**	6*	7**	7**	7**
LO (O)	7**	5**	7**	5**	3	4**	3	4**	7**	7**	7**	7**
ME (O)	7**	5**	7**	5**	4	4**	4	4**	6*	7**	6*	7**

M = motor cortex, LPr = lateral prefrontal cortex, IF = inferior frontal cortex, In = insular cortex, ST = superior temporal cortex, Pu = putamen, Th = thalamus, PT = posterior temporal cortex, LTO = lateral temporal-occipital cortex, LO = lateral occipital cortex, ME = medial extrastriate cortex (P) = phonological, (S) = semantic, (O) = orthographic, from Demb, Poldrack and Gabrieli's[9] review

[a] There were 2 participants in each of the visual stimulus and auditory stimulus conditions whose "aloud" data were not interpretable due to motion artifact and thus excluded.

* $p < .06$.

** $p < .05$.

activation in language processing regions (particularly frontal regions) in more participants than would the silent response condition.

As we predicted, motor cortex was activated to a greater extent in the overt condition across participants. Perhaps more interesting was our finding that many of the participants in the auditory stimulus group showed significant activation in motor cortex in the silent response condition as well, which supports one aspect of motor theory models of speech perception—that speech perception is thought to occur by way of accessing speech production representations (eg, Liberman and Mattingly[21]). Whenever an orthographic visual stimulus was available, however, only 1 or 2 participants showed any significant activation in motor cortex in the silent response condition.

Also examined in Experiment 2 were the cortical regions of interest described by Demb et al[9]: LPr (involving semantic and phonological processing), inferior frontal (including Broca's area, involving semantic and phonological processing), ST (including primary auditory cortex, involving phonological input processing), PT (including Wernicke's area, involving phonological processing), LTO (involving orthographic processing), LO (including primary visual cortex, involving orthographic processing), and ME (involved in orthographic processing). Our method was sensitive to processing in all of these regions, particularly under the overt response condition, as was predicted. A significant proportion of participants in the overt conditions showed significant activation in all of these regions and in both hemispheres, with the exception of the LPr region in the visual stimulus condition. Under silent response conditions, the pattern of results was also consistent with our predictions, in that participants were more likely to show activation in orthographic processing regions (LTO, LO, and ME cortex) when a visual orthographic cue is available and more likely to show activation in phonological processing regions (ST and PT cortex) in the presence of an auditory stimulus.

Although we did not manipulate semantic variables (ie, all stimuli were polysemous), our results are congruent with past research. Specifically, regions that are purported to process both semantic and phonological information (inferior frontal and LPr) were more likely to be activated in the left hemisphere (under silent response conditions); previous research has suggested a left hemisphere bias for processing within these regions (see Demb et al[9] and Binder et al[8]).

The insular cortex was found to be active in the left hemisphere under overt response conditions in a significant proportion of participants when presented with visual stimuli and in both hemispheres when presented with auditory stimuli. The putamen and thalamus have been implicated in overt response conditions[7,20] but were active in a significant proportion of participants in the present study only when the task involved an auditory stimulus and required an overt response.

The main reason for including a visual-plus-auditory cue condition was to evaluate whether these modalities could be combined to assess lexical processing more efficiently. If one is willing to settle for marginal effects in some cases (eg, in insular, PT, LTO, and ME regions, relative to single modality conditions), then this may be a reasonable condition to use. However, it is clear that the visual-plus-auditory cue condition does not represent a perfect combination of the single modality conditions, as this was the only condition that resulted in a significant number of participants showing activation in LPr cortex (in the left hemisphere only). It also appears that participants may rely more on the visual cue in this combined condition, given that there were not a significant number of participants showing activation in ST cortex despite the same degree of auditory stimulation as in the auditory stimulus condition. The best condition for producing activation in all participants was the overt, auditory stimulus condition, but given that 4 participants were excluded from the analyses of overt data for extreme motion artifacts, it would be inappropriate to recommend this as a “sufficient” condition. The best approach would include separate visual and auditory conditions, so as to manipulate (and thus dissociate) the activation of orthographic and phonological processing regions, and include both silent and overt conditions, so as to not miss individual differences on this factor. Notably, this experiment took less than 5 minutes, exclusive of anatomical scanning time, as its potential use for functional localization of language in pre- and postsurgical assessment depends on how efficiently it can be included within an existing clinical scanning schedule.

There are still many improvements to be made in our design for overt response conditions in the MRI, given that 4 of the 20 participants’ overt data in Experiment 2 were excluded because of excessive motion artifacts in the functional images (ie, a clearly visible ring of false activation along sinus cavities or cortical or ventricle boundaries). Motion artifact was not an issue in the silent condition data for these participants, thus supporting the inclusion of both a silent and an overt version of the task in patient studies. Nevertheless, we are striving to improve the overt response task design to better deal with motion artifacts. One improvement that we have subsequently explored is a “gap” image acquisition paradigm where, for example, participants are given a 1650–2000 ms gap segment (where there is no image acquisition) coinciding with the onset of a stimulus, followed by a 1650 ms image acquisition segment, in a regular alternating period throughout the experiment. During the gap, there is no noise from the imager (allowing the responses to be clearly heard), and given the delayed nature of the BOLD response, the BOLD time course function can still easily be resolved. We have begun to explore single word naming using this paradigm, and it could easily be applied to multiple-response paradigms with the constraint that participants respond during a gap in image acquisition.

Conclusions

The experiments reported here clearly show that the silent response condition cannot be considered equivalent to the overt response condition during word generation or semantic association, contrary to results reported by Rosen et al[7] (see Barch et al[18] and Palmer et al[20] for additional support for our position). We argue that both conditions should be examined during the neuroimaging of lexical processes. The multiple-process imaging method introduced here was sensitive to processing in all of the robust orthographic, phonological, and semantic regions reviewed by Demb et al,[9] particularly under the overt response condition. We recommend that multiple-process imaging of language processes include both a visual and an auditory stimulus condition so as to help dissociate the activation of orthographic and phonological processing regions. Similarly, a semantic manipulation could be added (eg, polysemous versus nonpolysemous words) so as to help distinguish the activation attributable to semantics from the other processes. This initial attempt at multiple-process imaging suggests that it is a promising method for activating multiple language regions in a single brief experiment, which is an important characteristic in applications such as pre- and postsurgical functional language assessment. Given that there are individual differences in exact location of language functions across participants, this method could also prove to be valuable in experimental fMRI studies for determining an individual’s language processing regions before introducing specific manipulations. We note that there are other researchers who have also shown an interest in developing methods for constructing individual brain maps of language processing. Although some are quite cautious in recommending fMRI as a replacement for the invasive direct cortical stimulation procedure,[22] there is a growing body of evidence that supports the notion that robust individual functional brain maps are not only a possibility,[23] but an important and timely new direction in localization of language function for neurosurgical patients.[24] The challenge is to develop efficient paradigms that can be applied to the clinical situation (including such constraints as limited MRI time) without compromising the identification of eloquent cortex.

Acknowledgements

This research was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada in the form of grants (Borowsky and Sarty), a post-graduate scholarship (Owen), a post-doctoral fellowship (Friesen), and an undergraduate student research award (Martin) and by the Canadian Institutes for Health Research (CIHR) and the Saskatchewan Health Services Utilization and Research Commission (HSURC) in the form of grants (Sarty). The authors thank Jennifer Hadley for her technical assistance.

References

1. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. *Nature* 2001;412:150–7.
2. Birn RM, Bandettini PA, Cox RW, Jesmanowicz A, Shaker R. Magnetic field changes in the human brain due to swallowing or speaking. *Magn Reson Med* 1998;40:55–60.
3. Burton MW, Noll DC, Small SL. The anatomy of auditory word processing: Individual variability. *Brain Lang* 2001;77:119–31.
4. McCarthy G, Blamire AM, Rothman DL, Gruetter R, Shulman RG. Echo-planar magnetic resonance imaging studies of frontal cortex activation during word generation in humans. *Proc Nat Acad Sci U S A* 1993;90:4952–6.
5. Small SL, Noll DC, Perfetti CA, Hlustik P, Wellington R, Schneider W. Localizing the lexicon for reading aloud: Replication of a PET study using fMRI. *Neuroreport* 1996;7:961–5.
6. Yetkin FZ, Hammeke TA, Swanson SJ, Morris GL, Mueller WM, McAuliffe TL, Haughton VM . A comparison of functional MR patterns during silent and audible language tasks. *AJNR* 1995;16:1087–92.
7. Rosen HJ, Ojemann JG, Ollinger JM, Petersen SE. Comparison of brain activation during word retrieval done silently and aloud using fMRI. *Brain Cogn* 2000;42:201–17.
8. Binder J, Price CJ. Functional neuroimaging of language. In: Cabeza R, Kingstone A, editors. Handbook of functional neuroimaging of cognition. Cambridge (MA): MIT Press; 2001. p 187–251.
9. Demb JB, Poldrack RA, Gabrieli JDE. Functional neuroimaging of word processing in normal and dyslexic readers. In: Klein RM, McMullen PA, editors. Converging methods for understanding reading and dyslexia. Cambridge (MA): MIT Press; 1999. p 243–304.
10. Grodzinsky Y. The neurology of syntax: Language use without Broca's area. *Behav Brain Sci* 2000;23:1–21; discussion 21–71.
11. Wise R, Chollet F, Hadar U, Friston K, Hoffner E, Frackowiak R. Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain* 1991;114:1803–17.
12. Raichle ME, Fiez JA, Videen TO, MacLeod AM, Pardo JV, Fox PT, Petersen SE. Practice-related changes in human brain functional anatomy during nonmotor learning. *Cereb Cortex* 1994;4:8–26.
13. Buxton RB. Introduction to functional magnetic resonance imaging: principles and techniques. Cambridge (UK): Cambridge University Press; 2002.
14. Borowsky R, Masson MEJ. Semantic ambiguity effects in word identification. *J Exp Psychol Learn Mem Cogn* 1996:22:63–85.
15. Sarty GE, Borowsky R. Functional MRI activation maps from empirically defined curve fitting. Concepts in Magnetic Resonance. Part *B. Magnetic Resonance Engineering* 2005;24B:46–55.
16. Cox RW. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 1996;29:162–73.
17. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. New York: Thieme; 1988.
18. Barch DM, Sabb FW, Carter CS, Braver TS, Noll DC, Cohen JD. Overt verbal responding during fMRI scanning: Empirical investigations of problems and potential solutions. *Neuroimage* 1999;10:642–57.
19. Borowsky R, Owen WJ, Sarty GE. The role of the left hemisphere in motor control of touch: A functional magnetic resonance imaging analysis. *Brain Cogn* 2002;49:96–101.
20. Palmer ED, Rosen HJ, Ojemann JG, Buckner RL, Kelley WM, Petersen SE. An event-related fMRI study of overt and covert word stem completion. *Neuroimage* 2001;14:182–93.
21. Liberman A, Mattingly I. The motor theory of speech perception revised. *Cognition* 1985;21:1–36.
22. Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I. Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. *Neurosurgery* 2003;52:1335–45.
23. Rutten GJ, Ramsey NF, van Rijen PC, van Veelen CW. Reproducibility of fMRI-determined language lateralization in individual subjects. *Brain Lang* 2002;80:421–37.
24. Fernandez G, de Greiff A, von Oertzen J, Reuber M, Lun S, Klaver P, et al. Language mapping in less than 15 minutes: real-time functional MRI during routine clinical investigation. *Neuroimage* 2001;14:585–94.