

Contribution of the frontal lobe to externally and internally specified verbal responses: fMRI evidence

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It has been suggested that within the frontal cortex there is a lateral to medial shift in the control of action, with the lateral premotor area (PMA) involved in externally specified actions and the medial supplementary motor areas (SMA) involved in internally specified actions. Recent brain imaging studies demonstrate, however, that the control of externally and internally specified actions may involve more complex and overlapping networks involving not only the PMA and the SMA, but also the pre-SMA and the lateral prefrontal cortex (PFC). The aim of the present study was to determine whether these frontal regions are differentially involved in the production of verbal responses, when they are externally specified and when they are internally specified. Participants engaged in three overt speaking tasks in which the degree of response specification differed. The tasks involved reading aloud words (externally specified), or generating words aloud from narrow or broad semantic categories (internally specified). Using fMRI, the location and magnitude of the BOLD activity for these tasks was measured in a group of ten participants. Compared with rest, all tasks activated the primary motor area and the SMA-proper, reflecting their common role in speech production. The magnitude of the activity in the PFC (Brodmann area 45), the left PMA and the pre-SMA increased for word generation, suggesting that each of these three regions plays a role in internally specified action selection. This confirms previous reports concerning the participation of the pre-SMA in verbal response selection. The pattern of activity in PMAv suggests participation in both externally and internally specified verbal actions.

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Many of the functional behaviors that humans perform involve voluntary actions: from the actions necessary to live, such as eating, to highly skilled actions such as speaking, typing and playing music instruments. Voluntary actions can be broadly classified along a continuum from externally to internally specified. A purely externally specified action is directly contingent upon an external event that specifies the action to perform and when to perform it. The relationship between the stimulus and the response is straightforward, and the execution of the action is largely automatic. A purely internally specified action, in contrast, is contingent upon an internal event and necessitates a conscious decision of the action to perform (i.e., the selection of an action) and when to initiate it. Importantly, for an action to be internally specified the choice of an appropriate response must be made between two or more equally appropriate responses (Frith et al., 1991). If there is no choice, there is no selection, and the action is not internally driven. Within these two extreme types of behaviors—externally and internally specified—are a large number of possible manifestations of voluntary action.

It has been suggested that these two classes of response specification rely on two distinct cortical regions (e.g., Goldberg, 1985; Seitz et al., 2000; Siegert et al., 2002) involving the supplementary motor area (SMA) and the lateral premotor area (PMA), both regions being located in subfields of Brodmann area 6. Goldberg (1985) was among the firsts to propose a neurobiological framework distinguishing externally and internally specified actions suggesting that the SMA is concerned with internally specified actions whereas the PMA is concerned with externally specified actions (e.g., Goldberg, 1985; Godschalk et al., 1985; Mushiaké et al., 1991; Deiber et al., 1991). Behavioral support for the dissociation of internally and externally specified actions in the central nervous system comes from investigations of motor impairments associated with several neurological diseases, such as Parkinson's disease (PD) (e.g., Kritikos et al., 1995; Majsak et al., 1998; Praamstra et al., 1998; Siegert et al., 2002), SMA syndrome (e.g., Zentner et al., 1996; Pai, 1999; Russell and Kelly,

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2003; Mendez, 2004) and lesions to the premotor cortex (Halsband and Passingham, 1982; Sasaki and Gemba, 1986; Halsband and Freund, 1990). In patients with PD or SMA-syndrome, voluntary movements or speech can be initiated upon verbal command (externally driven) but are either absent or severely reduced when attempted spontaneously. Even when preserved, it has been shown that internally specified actions are produced with significantly slower reaction times than similar externally specified actions (e.g., Siegert et al., 2002). There is also scattered evidence that externally driven actions can be impaired in the absence of a concomitant impairment to internally driven actions. It has been shown that experimentally induced damage to the premotor cortex (by means of cooling) can cause a temporary reduction of externally specified movements in monkeys (Sasaki and Gemba, 1986). After the cooling, monkeys could perform spontaneous actions but could no longer perform learned externally specified actions. Similar symptoms have been reported when the premotor cortex is ablated in animals (Halsband and Passingham, 1982) and in humans (Halsband and Freund, 1990). These observations indicate that externally and internally specified actions can be differentially impaired, suggesting that these two distinct classes of motor behaviours have distinct neural networks involving both the SMA and PMA.

Recent anatomical and physiological studies indicate that the rostral sector of the SMA, the pre-SMA, may be involved in higher-level aspects of movement specification, such as the internal selection of actions. In nonhuman primates, differences in brain cytoarchitecture (Matelli et al., 1991; Geyer et al., 1998), inter-regional connectivity (Matelli and Luppino, 1996; Inase et al., 1999), and excitability properties (Luppino et al., 1991) support the division of the SMA into a rostral area, the pre-SMA, and a caudal area, the SMA-proper. In humans, the pre-SMA can be differentiated from the SMA-proper based on cytoarchitecture (Vorobiev et al., 1998) and in terms of behavior (e.g., Picard and Strick, 1996, 2001). The border between these areas corresponds roughly to the VAC line, a vertical line passing through the anterior commissure (Picard and Strick, 1996; Vorobiev et al., 1998). The pre-SMA is densely interconnected with the prefrontal cortex, an important cognitive and executive center, but has no connection with M1 or the spinal cord (e.g., Luppino et al., 1993). The SMA-proper, in contrast, has projections with M1 and the spinal cord but not with the prefrontal cortex. These different connectivity patterns argue in favor of functional heterogeneity within the SMA, with the pre-SMA involved in higher order aspects of action such as action selection, and the SMA-proper involved primarily, in conjunction with M1, in action execution.

Support for a role of the PMA in externally specified actions is not as strong as the support for a role of the SMA in internally specified actions. As mentioned, there is some evidence that lesions to the PMA lead to a decrease in externally specified actions, suggesting that an intact PMA is necessary for their production. Anatomical and physiological studies, however, suggest that the PMA may be functionally heterogeneous, being involved in both externally and internally specified actions. Similar to SMA, multiple sub-regions within PMA have been identified based on cyto- and myeloarchitecture (Matelli et al., 1985; Barbas and Pandya, 1987; Matelli et al., 1991) and connectivity (Muakkassa and Strick, 1979; Matelli et al., 1989; Matelli and Luppino, 1996). The PMA can be divided into a ventral region—the PMAv, and a dorsal region—the PMA_d. Both parts can be further divided into rostral and a caudal area. The rostral portions of the

PMA_d (Lu et al., 1994) and the PMAv (e.g., Matelli et al., 1986; Barbas and Pandya, 1987; Lu et al., 1994) receive significant input from the prefrontal cortex. This connection with the prefrontal cortex suggests that the PMA, like the pre-SMA may participate in higher-level motor functions, such as the selection of action based on internal events. The caudal portions of the PMA, unlike the rostral PMA_d, receive strong parietal (sensory) input but few prefrontal inputs (Dum and Strick, 1991; for a review, see Rizzolatti and Luppino, 2001) and projects directly to the primary motor area contributing to the corticospinal and corticobulbar tracts. The strong parietal projections to the PMA, combined with the direct access that the PMA has to M1 and the spinal cord, suggest this region may be involved in sensorimotor integration or stimulus-response association; externally specified movements rely heavily on these two functions. Overall, the fact that the PMA receives both prefrontal (cognitive) and parietal (sensory) input, and connects to motoneurons suggests that the PMA is a functionally heterogeneous region, possibly involved in both externally and internally specified actions.

In addition to the clinical, anatomical and physiological data providing partial support for Goldberg's hypothesis, there are human neuroimaging data supporting a functional dissociation of the PMA and SMA for externally and internally specified actions, including speech (Ojemann et al., 1998; Schlösser et al., 1998; Rosen et al., 2000; Zubicaray et al., 2000; Palmer et al., 2001; Crosson et al., 2001; Alario et al., 2006). For example, using fMRI, Alario et al. (2006) examined the contribution of the pre-SMA and SMA-proper in word generation from a semantic category (internally specified) and word reading (externally specified). For word generation, pre-SMA activity was increased differentially compared to the word reading. In a similar study, Crosson et al. (2001), using a more complex set of experimental conditions, demonstrated that the pre-SMA is preferentially activated for internally specified compared to externally specified (covert) verbal responses. In this study, participants were asked to covertly generate as many words as possible related to a broad or narrow semantic category with or without cueing (internally specified) and to repeat heard words (externally specified). Results showed that activation in the SMA and PMA was related to the task, with the SMA-proper predominantly engaged in the externally driven task (repetition) with a progressive shift in activation toward the pre-SMA, as the degree of internal specification increased (word generation). The pattern of activity in the PMA was not as straightforward, with a tendency for the activity in the PMAv to show the opposite pattern as found in SMA for the internally specified conditions. The authors interpreted this finding as an indication that the PMA is involved in externally driven actions, as suggested by Goldberg (1985) and others (e.g., Mushiake et al., 1991). However, for the word repetition task, the most externally specified task, no activity was observed in the PMA, which argues against a role of this region in externally specified actions. Overall, it appears that the role of the pre-SMA in internally selected actions is better supported by the literature on language production than the role of the PMA in externally selected actions. In fact, there is some evidence that the PMA may be involved in the internal selection of action, that is, in the choice of an appropriate motor response when there are two or more equally appropriate responses, a finding at odds with Goldberg's hypothesis. Recent imaging studies have shown that the magnitude of the activity in the PMA is stronger for internally specified than for externally specified verbal responses (Abrahams et al., 2003; Fu et al., 2002)

and finger movements (Dimberger et al., 1998), which argues in favor of a role of the PMA in internally specified actions.

There is also evidence indicating that the left prefrontal cortex, an area not included in Goldberg's original framework, contributes to higher-level movement specification. The comparison of internally and externally specified tasks has revealed strong activity in the left lateral prefrontal cortex, for finger movement (Frith et al., 1991; Deiber et al., 1996; Hyder et al., 1997; Rowe et al., 2000) and speech (Friston et al., 1991; Buckner et al., 1995; Phelps et al., 1997; Crosson et al., 2001). This activity has been associated with the volitional selection of an action (e.g., Frith et al., 1991). There is, however, no agreement as to the region of the prefrontal cortex that is involved in actions that are internally specified. For speech, activity in different areas of the prefrontal cortex has been reported when comparing word generation (internally specified) to word reading or word repetition (externally specified). Activity was found in the dorsolateral prefrontal cortex, corresponding to BA 46/10 (Friston et al., 1991; Rowe et al., 2000, Buckner et al., 1995) and in the ventrolateral prefrontal cortex, corresponding to BA 44/45 (Phelps et al., 1997; Crosson et al., 2001; Buckner et al., 1995) or BA 47 (Crosson et al., 2001). Thus, which part of the lateral prefrontal cortex is involved in the internally specified selection of verbal responses remains unclear.

It appears that the simple hypothesis originally proposed by Goldberg (1985) is in need of revision and expansion. The contribution of the SMA and the PMA to the generation of externally and internally specified verbal responses needs to be clarified, as these areas may have overlapping rather than exclusionary roles. Further, this hypothesis needs to be expanded to include the prefrontal cortex, a region that was not included in Goldberg's original framework but which appear to be involved in the internal generation of spoken language. The purpose of the present study was to examine the relative contributions the SMA, PMA and prefrontal cortex to the planning and execution of externally and internally specified verbal responses. We compared single word reading aloud to the overt generation of single words using a delayed response event-related design. The key difference between the word reading and word generation tasks is that the word generation tasks required a response to be selected from a number of possible choices (internally specified) whereas the word reading task was fully externally specified.

Material and method

Subject

Twelve healthy right-handed fluent English speakers (3 males) participated in the study (average age 26 years; SD 4.91 years). All the subjects were students at McGill University and had a minimum of 13 years of education. All subjects gave their informed consent.

Procedure

A set of experimental tasks were used in which subjects either read a word or generated a word from a semantic category in response to different instructions back-projected on a screen. Both tasks involved speaking aloud. Two levels of word generation were used in which an accurate response was more or less constrained by the instruction. For the more externally constrained task participants had to generate a word from a subcategory with a limited number of possible responses (e.g. Name a red flower). For

the less constrained tasks, participants had to generate a word from a category with a large number of possible responses (e.g., Name a flower). In the word reading task, the words were one or two syllables real words. Stimuli in the word reading task were selected from the set of possible responses to the two word generation tasks (e.g., Say "tulip"). From reading to word generation (subcategory), and again from word generation (subcategory) to word generation (category), the degree of internal control over the selection of an appropriate verbal response increased. In terms of the manner how the verbal responses were initiated, however, all were initiated upon presentation of an external cue.

The baseline task was visual fixation of a crosshair located in the centre of the projection screen. Three sets of thirty-three stimuli, one set for each experimental task, were randomized and presented twice. The presentation of the instructions was time-locked to the onset of volume acquisition and the instruction remained visible during the entire volume acquisition. The design used was a delayed response paradigm rather than a reaction time paradigm. Subjects were given a period to prepare their response (± 2 sec) and were instructed to wait until the end of this period to produce the response. The rationale for using a delayed response paradigm was twofold. First, we wanted to ensure that subjects avoided speaking during the acquisition of a volume, in order to circumvent the problem of speech-related motion artefact. Second, we wanted to ensure that all motor acts occurred at a fixed time in the trial in order to make the tasks comparable.

In order to eliminate movement artifacts associated with producing speech in the scanner, a clustered or sparse image acquisition technique was used (Eden et al., 1999; Edmister et al., 2000; Gracco et al., 2005) in which, at the end of each trial, a 1.5 s period of silence occurred during which the gradients were switched off. For the experimental trials, participants produced the verbal response during this period. For the baseline trials, participants fixated on a crosshair but did not produce any verbal response. Each experimental trial was preceded and followed by 9.04 s of baseline (2 TR's), in order to allow the hemodynamic response to return to baseline before the next experimental trial. The duration of the experiment was 44 min.

Participants were trained before the scanning session with a training set that was different from the test material to minimize the effect of repetition. The training session lasted for approximately twenty min. During the training session, participants were provided the opportunity to listen to an audio recording of the scanner noise.

Acoustical recordings

Participants' responses were recorded through an MR compatible microphone (Resonance technology, Northridge, CA, USA) and digitized directly to disk. Reaction time and response duration were calculated offline, using MATLAB 7.0.4 (The MathWorks, Natick, MA, USA), only for the correct trials. Incorrect trials were discarded. The percentage of correct responses per category and subject was obtained.

Image acquisition

The data were acquired on a 1.5 T Siemens Sonata MR scanner at the Montreal Neurological Institute. Thirty-five axial slices (whole brain coverage) oriented parallel to the AC-PC line (thickness=4 mm, no gap, FOV=256×256 mm², matrix=64×64) were acquired in 2.98 s using a multislice EPI sequence

(TE=50 ms, TR=4.52 s, delay in TR=1.54 s.). The delay in TR occurred following each volume acquisition. The slices had a spatial resolution of $4 \times 4 \times 4$ mm. Two experimental runs (22 min each) resulted in the acquisition of 297 T2*-weighted BOLD images acquired in descending order.

High-resolution T1-weighted volumes were acquired for anatomical localization (matrix 256×256 mm, 160 slices, $1 \times 1 \times 1$ mm, no gap, TE=9.2 ms, TR=22 ms). Subject's head was immobilized by means of a vacuum-bag filled with polystyrene balls and a forehead-restraining device (Hybex Innovations, St-Leonard, Qc, CAN).

Image analysis

The functional images were realigned across runs by performing a rigid-body transform with the 4th frame of the 1st functional run as a target image (AFNI, Cox and Jesmanowicz, 1999). The six movement parameters (x, y, z and roll, pitch and yaw) were inspected for each volume. Volumes in which the movement correction algorithm was unable to compensate for the motion were discarded from the analysis. Data were low pass filtered using a 6-mm FWHM Gaussian kernel. Statistical analysis of fMRI data was performed using a linear model with correlated errors (FMRISTAT, Worsley et al., 2002). The fMRI data were first converted to percentage of whole volume. The design matrix of the linear model was convolved with a hemodynamic response function modeled as a difference of two gamma functions timed to coincide with the acquisition of each slice. Temporal drift was removed by adding a cubic spline in the frame times to the design matrix (one covariate per 2 min of scan time), and spatial drift was then removed by adding a covariate in the whole volume average. The correlation structure was modeled as an autoregressive process of degree 1. At each voxel, the autocorrelation parameter was estimated from the least squares residuals using the Yule-Walker equations, after a bias correction for correlations induced by the linear model. The autocorrelation parameter was regularized by spatial smoothing, then used to 'whiten' the data and the design matrix. The linear model was then re-estimated using least squares on the whitened data to produce estimates of effects and their standard errors. In order to compute group data, subject data were transformed into stereotaxic space (Collins et al., 1994), and combined using a mixed effects linear model for the effects (as data) with fixed effects standard deviations taken from the previous analysis. This was fitted using restricted maximum likelihood (REML) implemented by the Expectation/Maximization (EM) algorithm. A random effects analysis was performed by first estimating the ratio of the random effects variance to the fixed effects variance, then regularizing this ratio by spatial smoothing with a Gaussian filter. The variance of the effect was then estimated as the smoothed ratio multiplied by the fixed effect variance. The amount of smoothing was chosen to achieve 100 effective degrees of freedom. The resulting T-statistic images were thresholded using the minimum given by a Bonferroni correction and random field theory, taking into account the non-isotropic spatial correlation of the errors. We computed t-statistical images for three contrasts, that is, for each experimental task compared against the baseline.

ROI analysis

Additional within subject statistical analyses were conducted on a set of five minimally overlapping regions of interest (ROI). These ROIs were the pre-SMA, the SMA-proper, the PMAv (left and

right), the inferior frontal gyrus (left and right), and the primary motor area (left and right). Each ROI was defined as a cubic region, whose size was set to 10 mm^3 and whose center was determined based on the statistical parametric maps for the group. For the pre-SMA and the SMA-proper, we selected regions located on the medial aspect of the superior frontal gyrus, close to the midline, but centered on the left hemisphere. However, because the volume of these areas was relatively large (10 mm^3), and because the center of the regions was so close to the midline, voxels located on both hemispheres were included in the region. The pre-SMA area was located anterior to the VAC line (from $y=0$, to $y=+10$) whereas the SMA-proper was located caudal to the VAC line (from $y=0$ to $y=-10$). There was no spatial overlap between these ROIs. For the PMA, we selected a region located on the anterior portion of the precentral gyrus, near the precentral sulcus (center coordinates: $\pm 45, 3, 31$), which did not spatially overlap with the region that we identified as M1. The latter was located on the posterior segment of the precentral gyrus, near the central sulcus (center coordinates: $\pm 47, -10, 40$). The last region for which we extracted a time-series is the inferior frontal gyrus (center coordinates: $\pm 48, 32, 10$).

For each subject, the motion-corrected and low-pass filtered data were converted to stereotaxic space and multiple time-series of intensity (BOLD) values were extracted for each of the ROIs. For each ROI, the extracted voxels were averaged, with the mean values comprising the time-series. Each value of the resulting time-series was then converted to percent change relative to the baseline time-series. A series of two-way ANOVAs (task, hemisphere) with repeated measurements were conducted for each ROI in order to evaluate whether the magnitude of the activity in the ROIs varied significantly as a function of the experimental tasks and hemisphere. Note that for the pre-SMA and the SMA-proper, we conducted one-way ANOVAs (task) because only one (medial) region was extracted. When significant, the tasks were compared using paired sample t-tests.

Results

Behavioral results

Three behavioral measures were examined: response duration, reaction time, and accuracy. For each dependent measure, a one-way repeated measures ANOVA (task) was conducted. Results revealed no significant main effect of task on response duration, $F(2,20)=0.374$, $p=0.692$, and no significant main effect of task on reaction time, $F(2,20)=2.378$; $p=0.118$ (Table 1). There was, however, a significant main effect of task on accuracy, $F(2,20)=$

Table 1
Behavioral results

Task	Reaction time	Response duration	Accuracy
Word reading	0.981 (0.343)	0.547 (0.071)	98.181 (1.357)
Word generation (subcategory)	0.999 (0.358)	0.542 (0.072)	95.954 (3.498)
Word generation (category)	1.00 (0.358)	0.541 (0.073)	91.018 (6.949)

Behavioral results (mean and SD) by experimental task. Reaction times and response durations are measured in seconds; accuracy is measured as a percentage of the correct responses relative to the total responses.

Table 2
Location and associated t-values of the activated areas of interest

Region	BA	Side	Word reading				Word generation (subcategory)				Word generation (category)			
			x	y	z	t value	x	y	z	t value	x	y	z	t value
Central sulcus (M1)	4	left	-52	-8	25	5.8	-55	-7	24	5.39	-56	-7	23	4.92#
	4/3	left	-46	-17	39	5.74	-48	-16	41	6.36	-47	-17	40	6.43
	4	right	47	-10	35	8.83	46	-11	35	8.5	44	-13	35	8.75
Precentral sulcus/inferior frontal sulcus (PMAv)	6	left	-	-	-	-	-45	4	35	5.33	-42	3	27	6.2
	6	right	-	-	-	-	-	-	-	-	-	-	-	-
SMA-proper	6	left	-1	-2	58	7.27	-2	-1	58	7.5	-2	-1	58	7.2
Pre-SMA	6	left	-	-	-	-	-2	4	57	8.73	-2	4	57	8.61
Inferior frontal gyrus	45/46	left	-	-	-	-	-46	33	10	5.2#	-51	32	9	6.14

Location (in MNI space) and associated t-values of the activated areas of interest, for each task compared to rest. A # identifies contrasts that were not statistically significant.

8.78, $p=0.002$), with a significantly higher percentage of correct responses for word reading (98.2%) compared to subcategory (95.9%) and category generation (91%). Post hoc testing revealed that the difference between the reading and the category generation was significant ($p=0.03$) as was the difference between subcategory and category generation ($p=0.004$). The errors consisted of missing (4.296%) or incorrect responses (0.65%).

Neuroimaging results

Table 2 lists the coordinates and magnitude of activation in the regions of interest for the word reading and word generation tasks when contrasted with the baseline. Only the results for these ROIs will be discussed although other regions were significantly activated.

Fig. 1 illustrates significant activations along the precentral and central sulcus for the group. For all tasks, the bilateral activation in primary motor area (BA 4) was significant. The rANOVAs revealed no significant main effect of task or hemisphere and no interaction. Activation was also found anterior to the left M1, along the inferior portion of the left precentral sulcus, at the junction of the precentral sulcus and the inferior frontal sulcus, corresponding to the left ventral premotor area (PMAv, BA 6). In this region, the magnitude of the activation increased from word reading to word generation. In the word reading task, activation in the left PMAv was only seen when the threshold was lowered. A two-way rANOVA (task x hemisphere) revealed a significant main effect of task ($F(2,20)=14.605$, $p=0.000$), a significant main effect of side ($F(1,10)=5.617$, $p=0.039$), and a significant task by side interaction ($F(2,20)=9.570$, $p=0.001$). Overall, the magnitude of the activity in the left

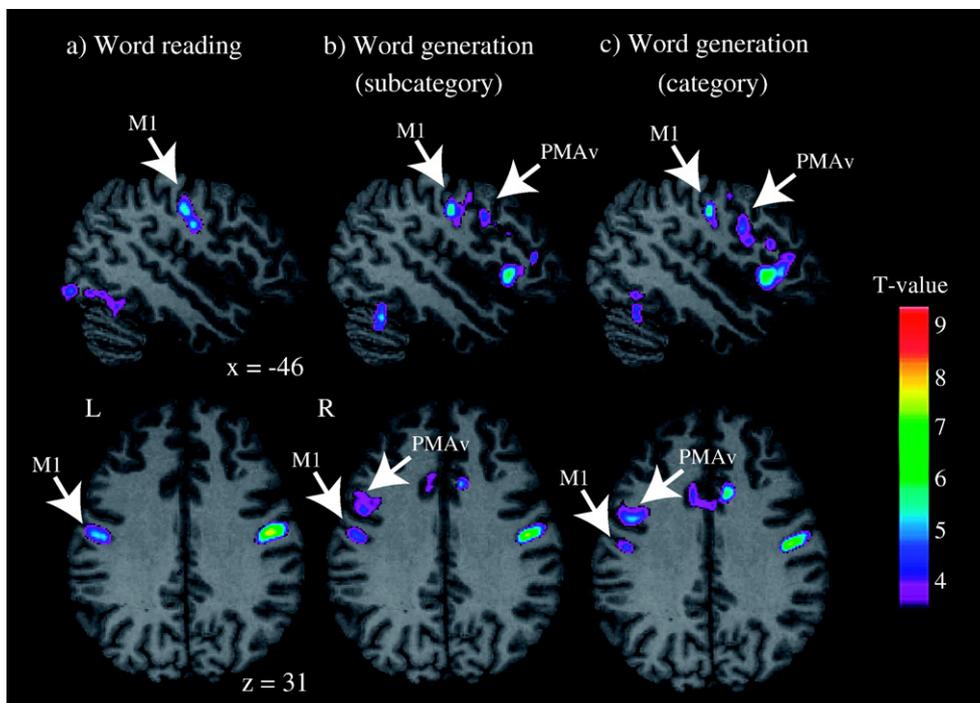


Fig. 1. Saggittal (top panel) and axial (bottom panel) views of the significant activation ($p<0.05$) in the ventral premotor area (PMAv) and primary motor area (M1) for each experimental task compared to the baseline, for the group. From left to right, word reading (externally specified), subcategory generation (internally specified), and category generation (internally specified). The areas of significant activation, for the group, are overlaid onto a standardized T1-weighted MRI. The MR images are displayed according to the MNI convention (left=left).

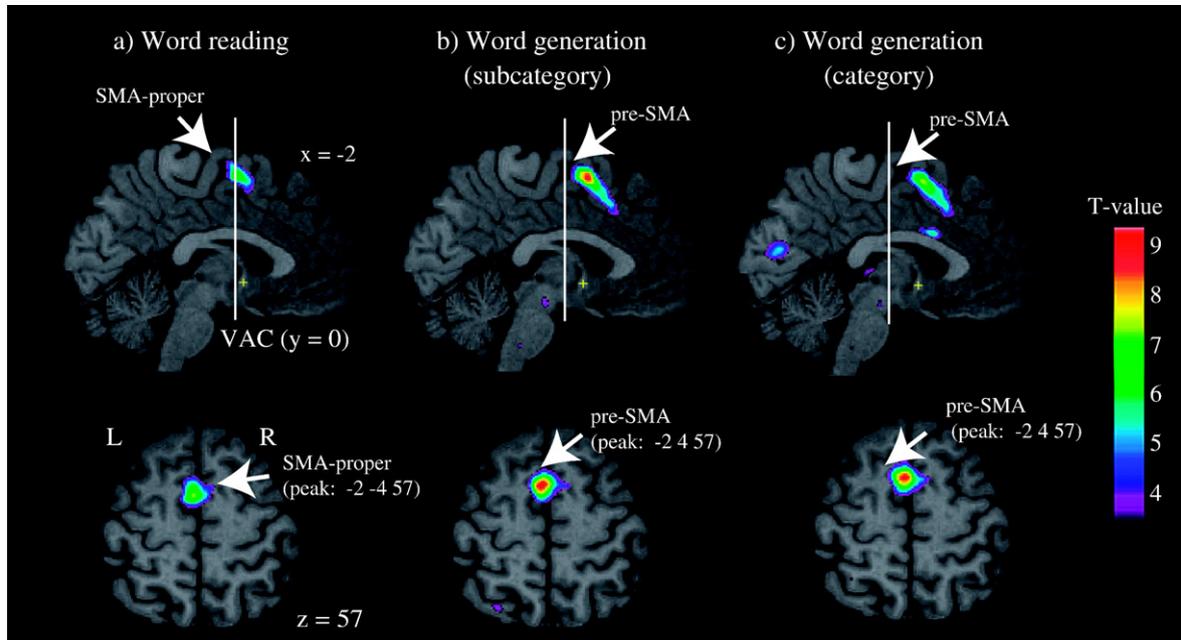


Fig. 2. Saggittal (top panels) and axial (bottom panels) views of the significant activation ($p < 0.05$) in the pre-SMA for each experimental task compared to baseline, for the group. From left to right, word reading (externally specified), subcategory generation (internally specified), and category generation (internally specified). The areas of significant activation, for the group, are overlaid onto a standardized T1-weighted MRI. The VAC line, identifying the SMA/pre-SMA division, is shown by the vertical line on the right panel.

PMAv was stronger than that in the right PMAv (0.95% vs. 0.56%, respectively). Activation on the right PMAv, however, did not differ with task ($p > 0.05$). Post hoc testing revealed that activation on the left PMAv was stronger for subcategory generation than for reading ($p = 0.003$) and stronger for category generation than for reading ($p = 0.002$). The mean percent change was 0.58% for word reading, 1.09% for subcategory generation and 1.18% for category generation. Overall, results show that the left, but not the right PMAv increases with the task.

Fig. 2 illustrates the activation loci in the medial motor areas (SMA-proper and pre-SMA). Activation in the medial areas was bilateral with left hemisphere predominance for all experimental tasks. From word reading to word generation, there was a caudal to rostral shift in the peak location. This shift was accompanied, in the pre-SMA, by an increase in activation magnitude. For SMA-

proper, the one-way rANOVAs revealed no statistically significant main effect of task or hemisphere and no interaction. For the pre-SMA, in contrast, the one-way rANOVA (task) revealed a significant main effect of task, $F(2,20) = 45.435$; $p = 0.000$. Post hoc testing showed that all the contrasts (reading vs. subcategory generation, reading vs. category generation and subcategory vs. category generation) were statistically significant ($p \leq 0.01$). The mean percent change was 0.51% for word reading, 1.17% for subcategory generation and 1.30% for category generation. Overall, results show that the pre-SMA activity increases with the tasks.

Fig. 3 illustrates the activation pattern on the left ventrolateral prefrontal cortex. Activation in this region was restricted to the left inferior frontal gyrus (BA 45/46) and was found only for word generation. The two-way rANOVA (task x hemisphere) revealed a

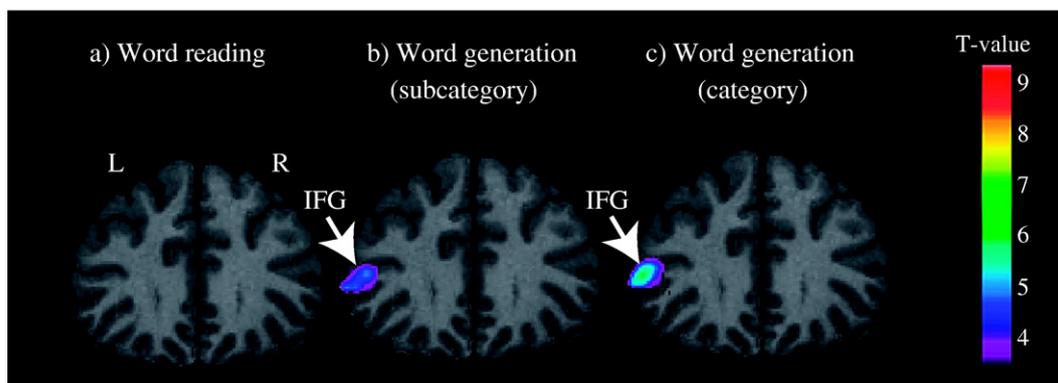


Fig. 3. Coronal views of the significant activations ($p < 0.05$) in the left prefrontal cortex for each experimental task compared to baseline, for the group. From left to right, word reading (externally specified), subcategory generation (internally specified), and category generation (internally specified). The areas of significant activation, for the group, are overlaid onto a standardized T1-weighted MRI.

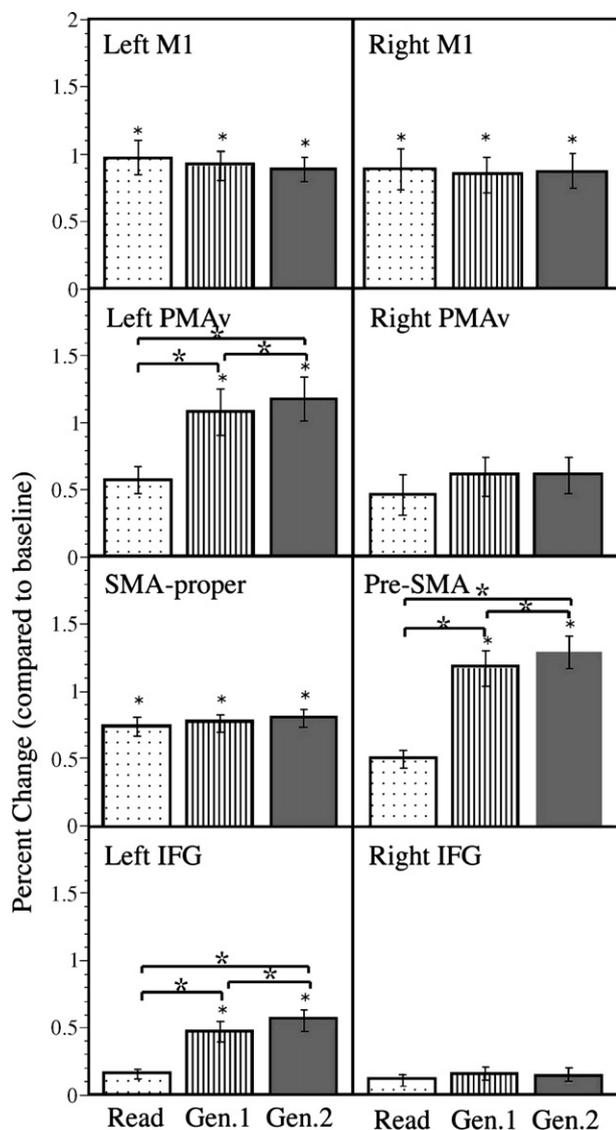


Fig. 4. Mean percent change in the BOLD signal (\pm one standard error of the mean) for each experimental task for left and right hemisphere sites (M1, PMAv and IFG, and SMA-proper and pre-SMA). The tasks are word reading (Read), word generation from a subcategory (Gen.1) and word generation from a category (Gen.2). For each region, an asterisk at the top of the column indicates that the change in activity (compared to rest) was significantly different from zero. A horizontal line connecting two columns indicates that the activity levels for two tasks are significantly different.

significant main effect of task ($F(2,20)=34.808$, $p=0.000$), a significant main effect of side ($F(1,10)=17.235$, $p=0.002$), and a significant task by side interaction ($F(2,20)=26.063$, $p=0.000$). Overall, the magnitude of the activity in the left IFG was stronger than that in the right IFG (0.4% vs. 0.14%, respectively). Post hoc testing revealed that the left side activation was stronger than right side activation for the two word generation tasks (subcategory: $p=0.002$; category: $p=0.000$) but not the word-reading task ($p=0.373$). All the contrasts (*i.e.* read vs. subcategory, read vs. category and subcategory vs. category, $p<0.01$) were significant on the left side ($p\geq 0.01$) whereas none reached significance on the right side. The mean percent change was 0.16% for word reading, 0.47% for subcategory generation and 0.56% for category

generation. Overall, results show that activation in the left ventrolateral prefrontal cortex increased from reading to subcategory generation and again from subcategory generation to category generation.

Fig. 4 is a graphic summary of the group results by task and region. As shown in this figure, all right sided activations (plus the SMA-proper activations), while significantly different from rest, did not differ by experimental task. Activity in left PMAv, pre-SMA and left IFG, in contrast, demonstrated significant effects of task ($p<0.01$). In all regions, the direction of this effect is similar, with activity increasing from word reading to subcategory generation, and again from subcategory to category generation.

Discussion

The objective of the present study was to examine the contribution of the frontal lobe, specifically, the SMA, the PMA and the lateral prefrontal cortex, to externally and internally specified verbal responses. We compared three overt speech production tasks, which differed in terms of the degree of external and internal response specification. The experimental tasks were designed such that the number of possible response choices increased from no choice (word reading), to a few choices (word generation from a semantic subcategory) to a large number of choices (word generation from a broad semantic category). Results indicated that both word reading and word generation produce significant changes in frontal lobe activity. However, only word generation was associated with task-related changes in frontal lobe activity.

Overall, the behavioral measures (reaction time and response duration) indicated that the actual movements were similar across the different tasks. Executing the movements resulted in similar levels of BOLD signal change in the primary motor area and SMA-proper. Whereas the participation of the primary motor area in motor execution is well known, the exact role of the SMA-proper is less certain. However, there is anatomical as well as neurophysiological evidence for the contribution of SMA-proper to motor execution, including speech production. Tracer studies have shown that the SMA-proper is interconnected with the speech and voice representation in M1 (e.g., Simonyan and Jurgens, 2002), with the spinal cord (e.g., Dum and Strick, 1991; Luppino et al., 1993) and with the cranial nerve nuclei (Morecraft et al., 2001). In addition, neurophysiological and neuroimaging studies have shown that SMA-proper is activated in relation to movement onset (e.g., Luppino and Rizzolatti, 2000; Lee et al., 1999). The presence of M1 and SMA-proper activation in the absence of task-related modulation of M1 and SMA-proper indicates that these frontal areas are involved primarily in motor execution rather than in the internal specification of the verbal responses.

Frontal lobe areas demonstrating modulation for the internally specified verbal responses included the pre-SMA, the left PMAv and the left inferior frontal gyrus (BA 45/46). Each of these areas exhibited stronger activity for word generation compared to word reading. Anatomically, the pre-SMA has extensive and direct connections with the prefrontal cortex (Luppino et al., 1993; Bates and Goldman-Rakic, 1993; Lu et al., 1994) but has only limited and indirect connections with the primary motor area (e.g., Luppino et al., 1993). Because of its connectivity, the pre-SMA appears to be involved at a higher level in the motor control

process, possibly for setting up goals or internally selecting individual actions, all of which are features of internally specified actions. Indeed, the pre-SMA has been associated with various forms of internally specified actions such as self-initiated (e.g., Deiber et al., 1999; Cunnington et al., 2002; Blouin et al., 2003) and self-selected finger movements (Deiber et al., 1996; Hyder et al., 1997; Lau et al., 2004), as well as self-selected covert (Crosson et al., 2001) and overt verbal responses (Alario et al., 2006). Together, these observations provide support for the hypothesis that the pre-SMA is involved in actions that are internally specified, as suggested by Goldberg (1985) and others (e.g., Mushiaki et al., 1991).

The PMAv, which showed a pattern of activity similar to that of the pre-SMA, also receives input from the prefrontal cortex (Matelli et al., 1986; Barbas and Pandya, 1987; Lu et al., 1994), connects to the larynx representation of M1 (Simonyan and Jurgens, 2002) and contributes to the corticobulbar tract (Morecraft et al., 2001). The PMAv is also the target of strong parietal input (e.g., Matelli et al., 1986). In primates, two distinct sectors (rostral and caudal) have been identified in the PMAv based on cytoarchitecture (Matelli et al., 1985; Barbas and Pandya, 1987) and connectivity (Matelli et al., 1989). The rostral PMAv contains mirror neurons, which are neurons with motor and sensory properties (e.g., Gallese et al., 1996). The caudal area appears to be a sensorimotor area involved in goal-directed actions (e.g., Rizzolatti et al., 2002). As was suggested by Goldberg (1985), it is possible that the PMAv is involved in externally specified actions; the sensorimotor properties of many neurons in the PMAv suggest that this area may have a role in sensorimotor transformation, a key process in the planning of externally specified actions. Recently, Crosson et al. (2001) provided support for this hypothesis by showing that activity in the left PMAv decreased for tasks in which the degree of internal specification progressively increased. Surprisingly, in the only task that was fully externally specified (word repetition), no activity in the PMAv was reported. Nevertheless, the authors concluded that the PMAv is important for externally specified actions.

Contrary to the Crosson et al. (2001) study, results from the present study indicate that the PMAv was activated during all tasks, even though in the word-reading task the activation did not reach significance. Nevertheless, results of the present study indicate a significant trend in a direction opposite to that found by Crosson et al. (2001). Activity in the PMA increased as the degree of internal specification progressively increased. Given the similarity of our tasks to those used by Crosson et al. (2001), the difference in activation pattern may be explained by the covert nature of the tasks used by Crosson. The rationale for using covert speech is that it is similar to actual speech production and that the brain activity associated with covert speech is the same as the brain activity for overt speech production, without the motor-related brain activity. However, there is a growing body of literature indicating that covert and overt word production yield different activity patterns (Price et al., 1994; Bookheimer et al., 1995; Barch et al., 1999; Huang et al., 2001; Shuster and Lemieux, 2005). In other words, covert speech is not just speech without movement. In support of the present finding of increased PMAv activity for word generation compared to word reading, Fu et al. (2002) and Abrahams et al. (2003) using overt word generation reported stronger activity in the PMAv when a verbal response is generated compared to simple word repetition. Similarly, Vanlancker-Sidtis et al. (2003) and Warburton et al. (1996) reported increased activity in PMAv for

word generation tasks when compared to overt speech. However, simple word repetition did not result in PMAv activity when compared to rest (Warburton et al., 1996).

A more important question, however, raised by Blank et al. (2002) is whether word generation or word retrieval tasks reflect language processes per se or cognitive processes associated with the experimental task. In their study employing both word generation and propositional speech, Blank et al. (2002) reported activity in the left PMAv for word generation but not for propositional speech, a task that involves the formulation of a response that conveys a message. It is possible, as suggested by Blank et al. (2002), that activation in the left PMA is related to executive or memory-related cognitive processes reflecting the meta-linguistic nature of word generation. Differences in attention level and memory related processes for word reading compared to word generation, in particular, can potentially account for the difference in the pattern of activity in the left PMA. However, Tamas et al. (1993) reported activity increase in the PMA for propositional speech (relating the details of the previous day) compared to rest. One possible difference between the findings of Tamas et al. (1993) and Blank et al. (2002) is that Blank contrasted propositional speech to serial counting and the recitation of nursery rhymes whereas/although the Tamas study contrasted propositional speech with rest. Our perspective, consistent with results from nonspeech motor tasks (Dirnberger et al., 1998; Sakai et al., 2000; Hunter et al., 2003) is that all expressive tasks rely to some degree on internally specified response selection, which activates PMAv to some extent. However, in studies of single word generation or retrieval, the selection process is being maximally activated by the experimental task. In contrast, during more natural conditions such as relating past experiences, the response selection process is used less extensively because retrieval is less frequently activated because selection involves actions that encompass more than single lexical items (phrases, for example). That is, word generation or retrieval during discourse is not engaged for each word but involves chunks of words and phrases. This difference would explain why PMA was not significantly activated in the Blank et al. (2002) study. Reciting rhymes and serial counting would more substantially recruit the retrieval process and, when contrasted with propositional speech, would eliminate any PMA activation. We view word generation to a cue as maximizing the normal process of the retrieval during verbal expression.

In addition to the pre-SMA and left PMAv changes associated with word generation, a similar pattern of activity was found in the left inferior frontal gyrus. Our result suggests that the ventrolateral prefrontal cortex, and more specifically the inferior frontal gyrus (Brodmann area 45), is involved in the internal selection of verbal responses. Similar findings have been reported when comparing word generation to word reading (Phelps et al., 1997; Crosson et al., 2001; Buckner et al., 1995). Other studies, however, using similar tasks, have reported more dorsal clusters of activity (Friston et al., 1991; Buckner et al., 1995). In the finger movement literature, interestingly, the area that is the most commonly associated with internal selection of actions is the dorsolateral prefrontal area, corresponding to BA 46/10 (Frith et al., 1991; Hyder et al., 1997; Rowe et al., 2000), not the inferior frontal gyrus. Although the present result suggests that the internal selection of a verbal response is tied to the inferior frontal gyrus, further studies are necessary to replicate this finding and further examine whether this activity is related to the selection of a verbal response or other aspects of verbal response planning.

Conclusion

In summary, the present study refines and extends the hypothesis originally proposed by Goldberg (1985) on the participation of a number of frontal lobe areas for externally and internally specified verbal responses. The primary motor area and SMA-proper are involved in externally specified verbal responses but show no preferential activity for internally specified verbal response generation. It appears that the inferior frontal gyrus, in and around Broca's area, and the pre-SMA, areas not originally considered by Goldberg (1985), contributes to the internal specification of verbal responses (see also Alario et al., 2006; Crosson et al., 2001). Furthermore, the left PMAv appears to play a role in the internal generation of verbal responses, a finding consistent with its neuroanatomical connections to prefrontal areas and more recent theoretical perspectives (Rizzolatti et al., 2002). However, the activity in PMAv for word reading also suggests that this area contributes to the execution of speech motor actions possibly reflecting a functional heterogeneity consistent with its complex neuroanatomical connections.

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