

Dissociation of Frontal and Cerebellar Activity in a Cognitive Task: Evidence for a Distinction between Selection and Search

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Human brain imaging studies have found that increases in functional activation in left-frontal cortex during cognitive tasks are often accompanied by similar increases in right-cerebellar regions. The present study used functional magnetic resonance imaging (fMRI) to investigate the distinctive contributions of these regions using a word stem completion task. Stems with many possible completions (MANY condition) were alternately presented with stems that had few possible completions (FEW condition), and subjects were asked to covertly complete each stem with a word and press a response switch for each successful completion. Prominent increases in activation in the MANY, relative to the FEW, condition were observed in the left middle frontal gyrus (Brodmann areas 9/10) and left caudate nucleus. In contrast, portions of the right-cerebellar hemisphere (posterior quadrangular lobule and superior semilunar lobule) and cerebellar vermis exhibited increases in the FEW, relative to the MANY, condition. This double dissociation suggests that the frontal and cerebellar regions make distinctive contributions to cognitive performance, with left-frontal (and striatal) activations reflecting response selection, which increases in difficulty when there are many appropriate responses, and right-cerebellar activation reflecting the search for responses, which increases in difficulty when even a single appropriate response is hard to retrieve. © 1998 Academic Press

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Functional neuroimaging studies have identified patterns of frontocerebellar coactivation that are important for language, memory, and thought. The coactivation was initially revealed in a positron emission tomography (PET) study finding greater left-frontal and right-cerebellar activation when subjects generated verbs to presented nouns than when they read the nouns aloud (Petersen *et al.*, 1988). The activation was interpreted as reflecting the greater semantic challenge of generating a related word than reading a presented word. After subjects repeatedly generated

verbs to nouns, left-frontal and right-cerebellar activations decreased (Raichle *et al.*, 1994). Thus, left-frontal and right-cerebellar activations increased or decreased in tandem across conditions. Verbal working memory studies have also reported correlated left-frontal and right-cerebellar activations associated with increased working memory demands (Paulesu *et al.*, 1993, 1995; Grasby *et al.*, 1994; Awh *et al.*, 1996; Fiez *et al.*, 1996; Jonides *et al.*, 1997). Although semantic retrieval and verbal working memory involve different processes mediated by different subregions of the left-frontal lobe, they both invoke correlated left-frontal and right-cerebellar activations. Close coupling of frontal and cerebellar regions is also evident in clinical reports of cerebellar hypometabolism occurring after contralateral frontal lobe lesions, i.e., crossed cerebellar diaschisis (Fulham *et al.*, 1992; Tanaka *et al.*, 1992; Miura *et al.*, 1994), and frontal hypometabolism subsequent to cerebellar damage (Boni *et al.*, 1992). Accordingly, cerebellar damaged patients often exhibit signs of frontal lobe damage, as measured by tests of initiation/perseveration and verbal fluency (Appollonio *et al.*, 1993), planning (Botez *et al.*, 1989; Grafman *et al.*, 1992), agrammatism (Silveri *et al.*, 1994), and associative learning (Bracke-Tolkmitt *et al.*, 1989; Canavan *et al.*, 1994; Tucker *et al.*, 1996). Interactions between frontal and cerebellar regions can occur via anatomical pathways that connect the cerebellum with prefrontal cortex (Middleton and Strick, 1994).

Although functional activations in frontal cortex are correlated with those of the contralateral cerebellum, it is not known whether these activations reflect the identical process. No study has provided evidence about what distinguishes the functions of these two anatomically disparate brain regions. The aim of the present study was to dissociate left-frontal and right-cerebellar activations in order to elucidate the distinctive functions of the two regions. To address this problem, we employed a variation of a word stem completion task, a task that has been shown to elicit frontal and cerebellar activation (Buckner *et al.*, 1995), and has been employed in studies of implicit and explicit memory pro-

cesses (Squire *et al.*, 1992; Buckner *et al.*, 1995; Schacter *et al.*, 1996). We used fMRI to compare activations when subjects completed three-letter word stems that had either many possible completions (e.g., STA _____) or few possible completions (e.g., PSA _____) into the first word that came to mind. When subjects complete stems with many possible answers, they may retrieve many words before selecting one response, but for stems with few possible answers, they may have to sustain a longer time searching for a legitimate completion. Given that frontal-lobe damage has been shown to result in response selection deficits (Decary and Richer, 1995), we hypothesized that left-frontal activation reflects how much knowledge is retrieved in task performance, including selection of the appropriate information, and that left-frontal activation would therefore be greater when completing stems with many possible completions. If the right cerebellum is involved in the identical cognitive operation, then right-cerebellar activation would be expected to exhibit the typical pattern of activating in tandem with the left-frontal regions. However, if right-cerebellar activation reflects a different process, e.g., the sustained search for knowledge required to complete the task, then right-cerebellar activation would be greater when completing stems with few possible completions.

MATERIALS AND METHODS

Subjects

Six right-handed female subjects gave their informed consent to participate in this study, which was approved by the Institutional Review Board at Stanford University. The mean age of the subjects was 33.3 years \pm 9.0 (SD).

Stimuli

The stimuli consisted of 144, uppercase, three-letter sets (stems) that were generated from a Macintosh computer (Apple Computer, Inc., Cupertino, CA) using PsyScope software (Cohen *et al.*, 1993). For half the stems, the letters formed the beginning of relatively few words (FEW condition) and for the other half, the letters formed the beginning of many, at least 10 different, words (MANY condition). Based on the database of Kucera and Francis (1967), the median \pm interquartile deviation of the number of completions for the FEW stems was 3 \pm 1.0, whereas for the MANY stems it was 74 \pm 26.5. This difference was significant (Mann-Whitney $U = 5184$, $P < 0.0001$).

Two analyses, based on frequency values of Kucera and Francis (1967), were conducted to assess the frequencies of all possible word completions for the stems. The first analysis was based on the mean word frequency per stem. For these data, the median \pm

interquartile deviation was 4.0 \pm 4.64 for the FEW stems and 10.09 \pm 5.60 for the MANY stems. This difference was significant (Mann-Whitney $U = 4050$, $P < 0.0001$). The second analysis was based on the median frequency of completions for each stem. The median \pm interquartile deviation for these values was 2.5 \pm 2.75 for the FEW stems and 2.0 \pm 0.0 for the MANY stems. This difference, which was in the opposite direction to that found using the mean frequency per stem, was also significant (Mann-Whitney $U = 3131.5$, $P = 0.031$). To investigate further which of these analyses was more likely to reflect the stem completion behavior of subjects, stem completion responses were tape-recorded in a separate behavioral study from six subjects, and median word frequency for FEW and MANY stems was obtained for each subject. The mean \pm SD of the median frequencies was 6.83 \pm 1.33 for the words completed for the FEW stems and 14.67 \pm 6.55 for the MANY stems. A paired t test indicated that word frequencies for the MANY stem completions was significantly greater than those for the FEW stems ($t(5) = 3.00$, $P = 0.03$). These data suggest that the first analysis of differences in all possible FEW and MANY stem completions, based upon the mean frequency per stem, more accurately predicts the completion behavior of subjects than the analysis based on median frequencies per stem.

The stems were visually presented to the subject in the scanner by back-projecting the images, via a magnet-compatible projector (Resonance Technology, Inc., Van Nuys, CA), onto a screen located above the subject's neck. Visual images were viewed from a mirror mounted above the subject's head.

Task

Subjects were presented with a stem every 2.5 s, and each stem was on for 0.5 s. To avoid artifacts from head motion associated with overt speech during an MRI scan, subjects were instructed to covertly complete the stem into a real word and, once they had successfully generated a valid completion, to then immediately press a fiber-optic-based switch with their right hand. The switch therefore provided information regarding stem completion success and response times. Eight alternating blocks (18 stems/block) of FEW and MANY stems were presented continuously over a 6-min scan. Whether FEW or MANY stems were presented first was counterbalanced across subjects, and subjects were not cued as to which type of stem they were seeing.

Data Acquisition and Analysis

Imaging was performed with a 1.5 T whole body MRI scanner (General Electric Medical Systems Signa, Rev. 5.5, Waukesha, WI), using a custom built quadrature "top hat" elliptical bird cage head coil (Hayes and

Mathias, 1996). Head movement was minimized using a "bite-bar" that was formed with the subject's dental impression, and further corrected using the method of Woods *et al.* (1992). A T2* sensitive gradient echo spiral sequence (Meyer *et al.*, 1992) was used for functional imaging with parameters of TR = 630 ms, TE = 40 ms, and flip angle = 66°. Four interleaves were obtained for each image, so total acquisition time per image was 2.52 s. Seven 6-mm-thick slices (inplane resolution of 2.35 mm, 1 mm interslice interval) were acquired in an oblique axial plane that was rotated 25° with respect to the AC-PC line, as illustrated in Fig. 1. This angle optimized acquisition of both cerebellar and frontal lobe structures. A total of 144 images per slice were acquired continuously for the duration of each experiment. T1-weighted anatomy images were acquired in the same plane as the functional images using a spin-echo pulse sequence with parameters of TR = 500 ms, TE = 20 ms, NEX = 1, matrix = 256 × 192. Pixels that were found to be significantly activated during the functional scan were overlaid on these structural images. T2-weighted anatomy images were also obtained in the sagittal plane and in an oblique coronal plane that was parallel to the brainstem using a fast spin echo pulse sequence and the following parameters: TR = 3000 ms, TE = 85 ms, echo train length = 8, NEX = 1, matrix = 256 × 192, 5-mm-thick, 0-mm interslice interval. The latter acquisitions were used for remapping the functional data onto different planes. Remapping was performed by extracting the scanner coordinates for each slice from the image header and computing the transformation needed to map functional data from the acquired sections to the other planes (see Fig. 2). Because the oblique axial acquisition plane is different from the anterior commissure–posterior commissure-based axial plane found in pub-

lished neuroanatomical atlases, such as that of Talairach and Tourneaux (1988), the sagittal plane was used for inspecting frontal lobe activation loci and estimating their Talairach coordinates. The oblique coronal sections were used for inspecting cerebellar hemispheric activations.

For data analysis, image reconstruction was performed offline by transferring the raw data to a Sun SparcStation (Sun Microsystems, Inc., Mountain View, CA). The data were resampled into a Cartesian matrix and then processed with a 2d FFT. The reconstructed image files were then Gaussian filtered spatially using a FWHM of 4.8 mm. Time series of each pixel were correlated with a reference waveform and transformed into a Z score map, SPM[Z] (Friston *et al.*, 1994). The waveform was calculated by convolving a square wave representing the time course of the alternating conditions (MANY–FEW or FEW–MANY) with a data-derived estimate of the hemodynamic response function. SPM[Z] map averaging was used to analyze patterns of functional activation across subjects. Averaging was performed by first manually tracing the perimeter of each section using an anatomy image of a representative subject to form a template for that slice. Then each subject's functional map at each section was transformed into the region specified by the template as previously described (Desmond *et al.*, 1995b). This procedure consisted of the following steps: (1) translating, scaling, and rotating the functional map to match the centroid and dimensions of the template; (2) defining a matching set of points around the perimeter of the functional map and that of the template; (3) creating a grid of points from the perimeter points of the functional map and a corresponding grid of the template such that a one-to-one mapping existed for the grid points in each set; and (4) mapping the values from the grid points of the functional image to the grid points of the template. The resulting averaged functional maps were then intensity thresholded at a $P < 0.05$ level (two-tailed) and each slice was subjected to a cluster analysis procedure (Xiong *et al.*, 1995) to correct for multiple statistical comparisons, using a spatial extent threshold that yielded a $P < 0.05$ significance level over the entire image (taking into account the 4.8-mm FWHM spatial smoothing and the 2.35-mm inherent resolution of the images, a smoothness FWHM of $(4.8^2 + 2.35^2)^{1/2} = 5.3$ mm was used for the cluster analysis procedure).

RESULTS

Behavioral data collected during the scan revealed that subjects pressed the response switch to indicate a successful completion significantly more often, $t(5) = 11.07$, $P < 0.0001$, for stems with MANY completions ($99.1 \pm 1.7\%$, mean \pm SD, of the MANY stem trials)

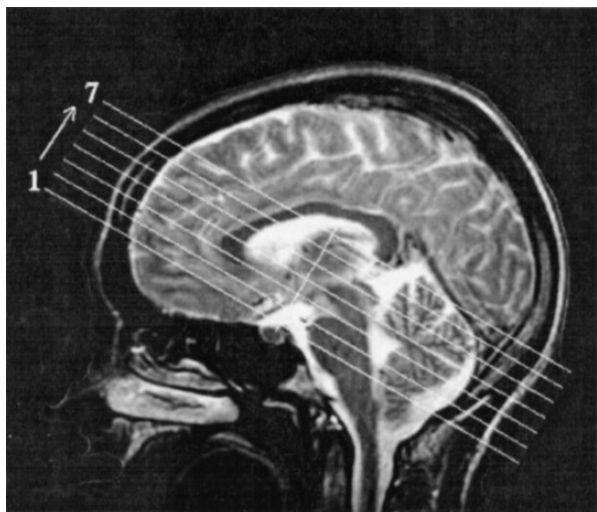


FIG. 1. Midline sagittal section illustrating the locations of the seven planes acquired during the fMRI experiment.

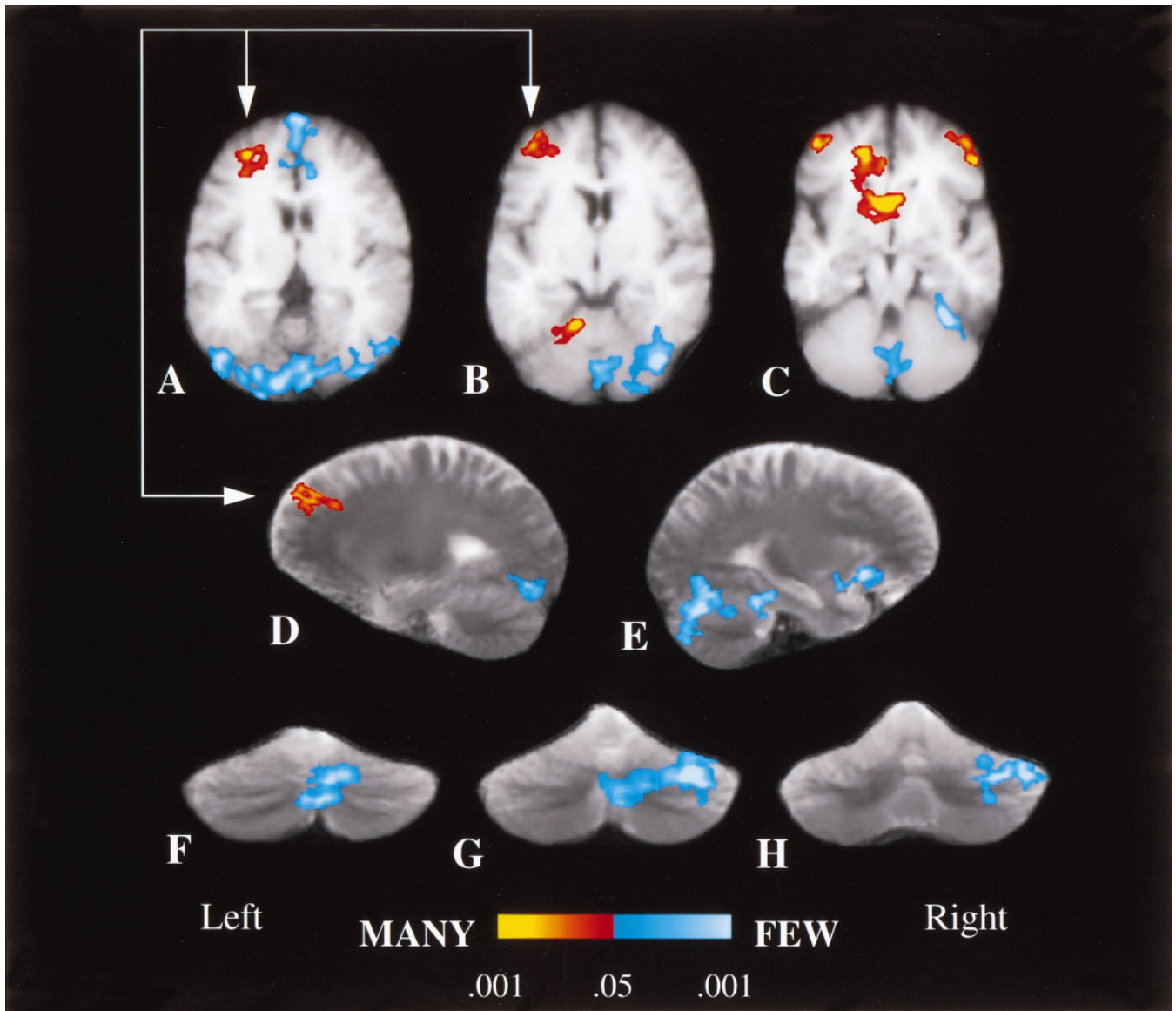


FIG. 2. Averaged fMRI activation over 6 subjects depicted on averaged T1-weighted oblique axial sections (top row, obtained using the angled approach depicted in Fig. 1), averaged T2-weighted sagittal sections (middle row), and averaged T2-weighted oblique coronal sections (bottom row, taken parallel to the floor of the 4th ventricle). A, B, and C represent in-plane sections 6, 5, and 3, respectively, depicted in Fig. 1. D depicts a left sagittal view located 25 mm from midline. E depicts a right sagittal view located 30 mm from midline. F, G, and H depict the cerebellum at 35, 30, and 25 mm, respectively, posterior to the floor of the 4th ventricle. Regions depicted in red–yellow represent areas that exhibited increased activation when subjects completed MANY, relative to FEW, stems, whereas regions in blue–light blue represent areas that exhibited increases during the FEW, relative to MANY, condition. The color scale at the bottom of the figure represents the significance levels (two-tailed P values) of the averaged Z score intensities (corrected for multiple comparisons at an overall significance of $P < 0.05$ per image). The right side of the brain is depicted on the right side of the figure for the oblique axial (top row) and oblique coronal (bottom row) sections. The left-frontal activation indicated by arrows on A and B is indicated by arrow on sagittal D.

than for stems with FEW completions ($82.9 \pm 3.1\%$ of the FEW stem trials). Mean median response times were 709.6 ± 175.4 ms for FEW stems and 626.4 ± 114.3 ms for MANY stems; the difference approached significance ($t(5) = -2.27$, $P = 0.0727$). Thus, subjects completed stems with many possible completions more often and more quickly than stems with few possible completions.

Regions of functional activation averaged across the six subjects are illustrated in Fig. 2. Relative to the FEW condition, increases in activation during MANY stem completion was observed in the left middle frontal gyrus at a relatively superior and medial location (Figs. 2A, 2B, and 2D; Brodmann area 9/10; Talairach coordinates $-25, 44, 27$), and to a lesser extent, at a more inferior and lateral position (Brodmann area 10/46;

coordinates $-47, 42, 1$). A less extensive activation was also observed in the right middle frontal gyrus (Fig. 2C; Brodmann area 10; coordinates $+31.5, 53, 15$). Increased activation during the MANY condition was also observed in the left cingulate gyrus (Fig. 2C; Brodmann areas 24/32; coordinates $-9, 37, 5$), the left caudate nucleus (Fig. 2C; coordinates $-5, 14, 0$), the left postcentral gyrus (Brodmann area 43; coordinates $-47, -13, 16$), and in the left anterior quadrangular lobule of the cerebellum (Fig. 2B).

In contrast to these regions, increases in activation during the FEW relative to MANY stem completion condition were observed in several portions of the cerebellar vermis, including the declive (Fig. 2F; Larsell's lobule VI), folium and tuber vermis (Fig. 2F; VII), and pyramid (Fig. 2G; VIII), as well as in large portions of the right-cerebellar hemisphere (Figs. 2F–2H), including the posterior quadrangular lobule (HVI), the superior semilunar lobule (superior HVIIA), and, to a lesser extent, the inferior semilunar lobule (inferior HVIIA). Increased activation during the FEW condition was also observed in the right inferior frontal gyrus (Fig. 2E; Brodmann area 47, coordinates $30, 25, -5$), along the midline in the superior frontal gyrus (Fig. 2A; Brodmann area 8, coordinates $\pm 3, 44, 34$), and bilaterally in the fusiform gyrus (Fig. 2D; Brodmann area 37/19, coordinates $\pm 40, -70, -7$; also right Brodmann area 37, coordinates $+30, -37, -11$).

To confirm the double dissociation in frontal and cerebellar activation during the FEW and MANY stem blocks, right-cerebellar and left-frontal regions of interest (ROIs) were identified based on the activations found in the averaged functional maps. Then for each subject, the mean signal intensity during the FEW and MANY stem blocks (averaged across all blocks) was obtained for the left-frontal and right-cerebellar ROIs. An analysis of variance on these data revealed no main effects, but a significant REGION \times STEM-TYPE interaction ($F_{1,5} = 15.36, P = 0.011$) was found. Comparisons of the means revealed that signal intensity for the MANY stems was significantly greater than that of the FEW stems for the left frontal ROI ($F_{1,5} = 8.3, P = 0.035$), whereas intensity for MANY stems was significantly less than that of the FEW stems for the right cerebellar ROI ($F_{1,5} = 7.08, P = 0.045$).

DISCUSSION

Subjects completed stems with many completions more often and more quickly than stems with few completions. The differential demands of the kinds of stem completion yielded a double dissociation between left-frontal and right-cerebellar regions that in prior studies have always shown associated activations. Left-

frontal regions were more active when subjects completed stems with many than with few possible completions, whereas right-cerebellar regions were more active when subjects completed stems with few than with many completions. These results do not challenge the many prior findings indicating that left-frontal and right-cerebellar regions regularly interact in verbal performance, but rather indicate for the first time that these two regions make distinctive contributions to that interaction and provide some clues about the nature of those unique contributions. Specifically, the present study indicates that left-frontal activations reflect selection of response, whereas cerebellar activations reflect search for response.

Left-Frontal Activation

Left-frontal activation was greater when subjects completed stems with many than with few possible completions. Although only one response was required for each stem, it is likely that more words were considered and more selection had to be made among competing candidate responses when stems had many rather than few possible completions. Indeed, greater activation in the MANY condition reveals the covert, incidental, and perhaps partial retrieval of candidate completions that were not selected as the one required completion. The left-frontal activation cannot be accounted for by task difficulty per se because performance was easier with MANY stems—subjects performed 16% more accurately and 84 ms more quickly with MANY than with FEW stems.

The specific location of left-frontal activation in the present study, i.e., Brodmann area 9/10, in the middle-frontal gyrus differs from left-frontal areas activated in related studies, but this is likely due to the nature of the contrast between two highly similar stem completion conditions. Buckner *et al.* (1995) reported increases in left inferior frontal gyrus (Brodmann area 45) when comparing stem completion with a fixation baseline. The left inferior frontal gyrus is also the major locus of activation in many semantic tasks, including generation (Petersen *et al.*, 1988; McCarthy *et al.*, 1993) and classification tasks (Kapur *et al.*, 1994; Demb *et al.*, 1995; Desmond *et al.*, 1995b; Gabrieli *et al.*, 1996). These generation and classification studies make comparisons between conditions that differ substantially in phonological, lexical, and semantic demands. Many of these differences are absent in our comparison between two kinds of stem completion. The middle-frontal locus of activation in the present study is nearly identical to that reported by Price *et al.* (1996) when comparing activation for a letter-feature detection task in real words versus pronounceable pseudowords. Because

neither stem completion nor letter-feature detection requires overt semantic analysis, these results suggest that the middle-frontal activation is related to nonsemantic lexical processes invoked by stems with many relative to few completions or by real words versus meaningless letter strings.

The present findings suggest that left-frontal activation increases across tasks as a function of the amount of verbal information retrieved and the selection of task-relevant information. In most studies, amount and selection are correlated, with more selection required as more information is retrieved. In the present study, MANY stems may have accessed many completions and required selection of one completion. In the letter-feature detection task, real words would access more knowledge than nonwords and require selection of relevant information (letter shapes rather than word meaning or associations). Verb generation requires more semantic information than noun reading because more information is required to generate an appropriate verb than to read a presented noun. At the same time, there are always more alternative verbs to select among (EAT, SLICE, BAKE) than the one presented noun (CAKE) (Petersen *et al.*, 1988). Similarly, there is more left-frontal activation when subjects must generate the typical color or use of an object than the name of that object (Martin *et al.*, 1995). Generating typical color or use requires more semantic information than naming the object because most objects have one identity but can appear in more than one color and have more than one use. Thus, a common principle emerging across different tasks is that greater left-frontal activation occurs for the task that involves more knowledge and more selection of an appropriate response from that knowledge. At present, it is unknown whether amount and selection of information are inherently correlated or whether those two processing dimensions can be dissociated. Amount and selection may be inevitably intertwined because greater amounts of retrieved knowledge require more selection to isolate the knowledge salient for task response.

The present results show that a subtle increase in the demand for response selection within a stem-completion task can have a substantial influence on left-frontal activation. This finding is consistent with a report of greater left-frontal activation (cerebellum was not included in their scan) in three different semantic tasks during high selection relative to low selection conditions (Thompson-Schill *et al.*, 1997), and is also in accord with a broad range of findings indicating that dorsolateral prefrontal cortex is important for response selection on many tasks (Cohen and Servan-Schreiber, 1992; Kimberg and Farah, 1993; Decary and Richer, 1995). It may be that different frontal regions mediate response selection for different domains. Indeed, the focus of left-frontal activation in the present study

occurred in the middle rather than the inferior gyrus where activations are more pronounced in semantic tasks.

Right-Cerebellar Activation

Right-cerebellar activation was greater when subjects completed stems with few than with many possible completions. These results conflict with two possible explanations for cerebellar involvement in cognition. The first is a motor explanation; that is, consistent with traditional views of cerebellar function, cerebellar activation in cognition is related to preparing for the motor output requirements of the task. Thus, to the extent that selection is occurring and the frontal lobe is engaged in processing more possible alternative responses, the cerebellum would have to prepare for these alternatives, and its activation would be expected to increase. A second explanation—based upon evidence of crossed cerebellar diaschisis as well as correlated functional activation of frontal and contralateral cerebellar regions—is that regardless of motor output, the cerebellum is a slave system that supports frontal lobe computations, but does not provide a unique contribution to cognitive operations.

The increased right-cerebellar activation during the FEW stem condition is inconsistent with both the motor and the frontal-slave explanations, both of which predict that contralateral cerebellar activation should increase in concert with the left-frontal lobe during the MANY condition. [A variation of the motor explanation, that the cerebellum prepares for the finger press response, would also predict cerebellar increases during the MANY condition because subjects successfully completed more stems, and consequently pressed more, during the MANY condition. In addition, activation due to finger movement is located considerably more anterior and medial to the locations found in the present study (Desmond *et al.*, 1995a, 1997b)]. Our results therefore suggest that the cerebellum has a unique contribution to cognitive processes that is independent of the motor requirements of response preparation. The exact nature of this contribution is unclear, but one possibility that could link motor control aspects of cerebellar function with cognition is that cerebellar activation reflects greater subvocal articulatory rehearsal processes corresponding to the sustained demand for working memory needed while searching for completions for FEW stems. This explanation would be consistent with the slightly longer response latencies observed for these stems. The activations in posterior vermis and right HVI and superior HVIIA are similar to cerebellar activations we have observed during a Sternberg verbal working memory task (Desmond *et al.*, 1995a, 1997b).

In addition to the increased need for working memory resources required for the search for responses, the

FEW stem condition may also require more error corrections in order to reject similar but incorrect matches that would likely occur more often for FEW than MANY stems. Thus, the right cerebellar activations may also reflect such error correction operations. This explanation would be consistent with the case study reported by Fiez *et al.* (1992) of a patient with a large lesion in the right-cerebellar hemisphere. This patient was found to produce "a large number of inappropriate responses across a variety of rule-based generation tasks" (Fiez *et al.*, 1992) such as verb generation.

Other Possible Influences on Activations

Although stems were chosen on the basis of the number of word completions, both the stems and their completions are likely to have a number of correlated differences besides the number of completions. For example, our analyses of the frequency characteristics of the stem completions suggest that more high-frequency words are available for selection in the MANY stem condition than in the FEW stem condition. The effect of word frequency on stem completion activation is unknown, but if high-frequency words are those which are more likely to have been seen recently by subjects, then it is plausible that the word frequency effect would resemble that observed during priming. Priming studies of word stem completion have shown reductions of activation in occipital regions when stems presented can be completed by recently seen words (Squire *et al.*, 1992; Buckner *et al.*, 1995). Although our increased activation in fusiform areas during the FEW condition is consistent with these priming results, the similar activation patterns for the FEW stems that we observed in the cerebellum along with opposite patterns in left frontal areas are not consistent.

A second possibility is that the MANY and FEW conditions may have resulted in differences in the number of phonologically regular completions. Data reported by Fiez and Petersen (1998) and Herbster *et al.* (1997) indicate that activation in left-frontal lobe may be greater for pronunciation of low-frequency exception words than for low-frequency regular words, although the regions implicated tend to be located in the left-frontal operculum rather than in middle-frontal regions observed in the present study. In the Herbster *et al.* study (1997), activation in right lateral cerebellum was found during pronunciation of regular words relative to a repetitive speaking control condition. However, direct comparisons of regular vs irregular word pronunciation resulted in differences only in the left inferior frontal gyrus, with irregular word pronunciation showing greater activation than that of regular word pronunciation. Although further investigations are needed, these findings do not favor phono-

logical regularity as the main source of the difference between the FEW and MANY conditions.

Activations in Other Regions

The present study focused on dissociating left-frontal and right-cerebellar processes, but several other activations were noted. Of particular interest were the left-cingulate and left-caudate activations that shadowed the left-frontal activation for MANY relative to FEW stems. Cingulate and basal ganglia areas have been associated with selective attention and mental effort (Posner and Petersen, 1990; Pardo *et al.*, 1991; Braver *et al.*, 1997) but the present results indicate that these areas are more involved in the effort required for selection per se—consistent with the response-selection role of the striatum hypothesized by Wallesch (Wallesch, 1985; Wallesch and Papagno, 1988)—than that involved in sustained search. These results, therefore, distinguish between striatal and cerebellar interactions with prefrontal cortex. The bilateral fusiform activation for FEW relative to MANY stems may reflect the longer visual inspection required for the more difficult-to-complete FEW stems. The additional activations are difficult to interpret at present, but must be additional components of the two networks that support search or selection for *le mot juste*.

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REFERENCES

- Appollonio, I. M., Grafman, J., Schwartz, V., Massaquoi, S., and Hallett, M. 1993. Memory in patients with cerebellar degeneration. *Neurology* **43**: 1536–1544.
- Awh, E., Jonides, J., Smith, E. E., Schumacher, E. H., Koeppel, R. A., and Katz, S. 1996. Dissociation of storage and rehearsal in verbal working memory: Evidence from positron emission tomography. *Psychol. Sci.* **7**: 25–31.
- Boni, S., Valle, G., Cioffi, R. P., Bonetti, M. G., Perrone, E., Tofani, A., and Maini, C. L. 1992. Crossed cerebello-cerebral diaschisis: a SPECT study. *Nucl. Med. Commun.* **13**:824–831.
- Botez, M. I., Botez, T., Elie, R., and Attig, E. 1989. Role of the cerebellum in complex human behavior. *Ital. J. Neurol. Sci.* **10**:291–300.
- Bracke-Tolkmitt, R., Linden, A., Canavan, A. G. M., Rockstroh, B., Scholz, E., Wessel, K., and Diener, H. C. 1989. The cerebellum contributes to mental skills. *Behav. Neurosci.* **103**: 442–446.
- Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., and Noll, D. C. 1997. A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage* **5**:49–62.

- Buckner, R. L., Petersen, S. E., Ojemann, J. G., Miezin, F. M., Squire, L. R., and Raichle, M. E. 1995. Functional anatomical studies of explicit and implicit memory retrieval tasks. *J. Neurosci.* **15**: 12–29.
- Canavan, A. G. M., Sprengelmeyer, R., Diener, H. C., and Hoemberg, V. 1994. Conditional associative learning is impaired in cerebellar disease in humans. *Behav. Neurosci.* **108**: 475–485.
- Cohen, J. D., MacWhinney, B., Flatt, M., and Provost, J. 1993. PsyScope: A new graphic interactive environment for designing psychology experiments. *Behav. Res. Methods Instr. Comp.* **25**: 257–271.
- Cohen, J. D., and Servan-Schreiber, D. 1992. Context, cortex, and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychol. Rev.* **99**:45–77.
- Decary, A., and Richer, F. 1995. Response selection deficits in frontal excisions. *Neuropsychologia* **33**: 1243–1253.
- Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., and Gabrieli, J. D. E. 1995. Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *J. Neurosci.* **15**:5870–5878.
- Desmond, J. E., Gabrieli, J. D. E., Ginier, B. L., Demb, J. B., Wagner, A. D., Enzmann, D. R., and Glover, G. H. 1995a. A functional MRI (fMRI) study of cerebellum during motor and working memory tasks. *Soc. Neurosci. Abstr.* **21**:1210.
- Desmond, J. E., Gabrieli, J. D. E., Stone, M., Wagner, A. D., and Glover, G. H. 1997a. An fMRI study of cerebellum and frontal cortex during a word stem completion task. *Soc. Neurosci. Abstr.* **23**:210.
- Desmond, J. E., Gabrieli, J. D. E., Wagner, A. D., Ginier, B. L., and Glover, G. H. 1997b. Lobular patterns of cerebellar activation in verbal working memory and finger tapping tasks as revealed by functional MRI. *J. Neurosci.* **17**: 9675–9685.
- Desmond, J. E., Sum, J. M., Wagner, A. D., Demb, J. B., Shear, P. K., Glover, G. H., Gabrieli, J. D. E., and Morrell, M. J. 1995b. Functional MRI measurement of language lateralization in wada-tested patients. *Brain* **118**: 1411–1419.
- Fiez, J. A., and Petersen, S. E. 1998. Neuroimaging studies of word reading. *Proc. Natl. Acad. Sci. USA* **95**:914–921.
- Fiez, J. A., Petersen, S. E., Cheney, M. K., and Raichle, M. E. 1992. Impaired non-motor learning and error detection associated with cerebellar damage. A single case study. *Brain* **115**:155–178.
- Fiez, J. A., Raife, E. A., Balota, D. A., Schwarz, J. P., Raichle, M. E., and Petersen, S. E. 1996. A positron emission tomography study of the short-term maintenance of verbal information. *J. Neurosci.* **16**: 808–822.
- Friston, K. J., Jezzard, P., and Turner, R. 1994. Analysis of functional MRI time-series. *Hum. Brain Map.* **1**: 153–171.
- Fulham, M. J., Brooks, R. A., Hallett, M., and Di Chiro, G. 1992. Cerebellar diaschisis revisited: pontine hypometabolism and dentate sparing. *Neurology* **42**: 2267–2273.
- Gabrieli, J. D. E., Desmond, J. E., Demb, J. B., and Wagner, A. D. 1996. Functional magnetic resonance imaging of semantic memory processes in the frontal lobes. *Psychol. Sci.* **7**: 278–283.
- Grafman, J., Litvan, I., Massaquoi, S., Stewart, M., Sirigu, A., and Hallett, M. 1992. Cognitive planning deficit in patients with cerebellar atrophy. *Neurology* **42**: 1493–1496.
- Grasby, P. M., Frith, C. D., Friston, K. J., Simpson, J., Fletcher, P. C., Frackowiak, R. S., and Dolan, R. J. 1994. A graded task approach to the functional mapping of brain areas implicated in auditory-verbal memory. *Brain* **117**: 1271–1282.
- Hayes, C., and Mathias, C. 1996. Improved brain coil for fMRI and high resolution imaging. In *International Society for Magnetic Resonance in Medicine, 4th Annual Meeting*, p. 1414, New York.
- Herbster, A. N., Mintun, M. A., Nebes, R. D., and Becker, J. T. 1997. Regional cerebral blood flow during word and nonword reading. *Hum. Brain Map.* **5**: 84–92.
- Jonides, J., Schumacher, E. H., Smith, E. E., Lauber, E. J., Awh, E., Minoshima, S., and Koeppe, R. A. 1997. Verbal working memory load affects regional brain activation as measured by PET. *J. Cog. Neurosci.* **9**: 462–475.
- Kapur, S., Craik, F. I. M., Tulving, E., Wilson, A. A., Houle, S., and Brown, G. M. 1994. Neuroanatomical correlates of encoding in episodic memory: Levels of processing effect. *Proc. Natl. Acad. Sci. USA* **91**: 2008–2011.
- Kimberg, D. Y., and Farah, M. J. 1993. A unified account of cognitive impairments following frontal lobe damage: The role of working memory in complex, organized behavior. *J. Exp. Psych. Gen.* **122**: 411–428.
- Kucera, H., and Francis, W. N. 1967. *Computational Analysis of Present-Day American English*. Brown Univ. Press, Providence, RI.
- Martin, A., Haxby, J. V., Lalonde, F. M., Wiggs, C. L., and Ungerleider, L. G. 1995. Discrete cortical regions associated with knowledge of color and knowledge of action. *Science* **270**: 102–105.
- McCarthy, G., Blamire, A. M., Rothman, D. L., Gruetter, R., and Shulman, R. G. 1993. Echo-planar magnetic resonance imaging studies of frontal cortex activation during word generation in humans. *Proc. Natl. Acad. Sci. USA* **90**:4952–4956.
- Meyer, C. H., Hu, B. S., Nishimura, D. G., and Macovski, A. 1992. Fast spiral coronary artery imaging. *Magn. Reson. Med.* **28**: 202–213.
- Middleton, F. A., and Strick, P. L. 1994. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science* **266**:458–461.
- Miura, H., Nagata, K., Hirata, Y., Satoh, Y., Watahiki, Y., and Hatazawa, J. 1994. Evolution of crossed cerebellar diaschisis in middle cerebral artery infarction. *J. Neuroimaging* **4**:91–96.
- Pardo, J. V., Fox, P. T., and Raichle, M. E. 1991. Localization of a human system for sustained attention by positron emission tomography. *Nature* **349**: 61–64.
- Paulesu, E., Connelly, A., Frith, C. D., Friston, K. J., Heather, J., Myers, R., Gadian, D. G., and Frackowiak, R. S. 1995. Functional MR imaging correlations with positron emission tomography. Initial experience using a cognitive activation paradigm on verbal working memory. *Neuroimaging Clin. N. Am.* **5**: 207–225.
- Paulesu, E., Frith, C. D., and Frackowiak, R. S. 1993. The neural correlates of the verbal component of working memory. *Nature* **362**:342–345.
- Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., and Raichle, M. E. 1988. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* **331**:585–589.
- Posner, M. I., and Petersen, S. E. 1990. The attention system of the human brain. *Annu. Rev. Neurosci.* **13**: 25–42.
- Price, C. J., Wise, R. J., and Frackowiak, R. S. 1996. Demonstrating the implicit processing of visually presented words and pseudo-words. *Cereb. Cortex* **6**:62–70.
- Raichle, M. E., Fiez, J. A., Videen, T. O., MacLeod, A. M., Pardo, J. V., Fox, P. T., and Petersen, S. E. 1994. Practice-related changes in human brain functional anatomy during nonmotor learning. *Cereb. Cortex* **4**: 8–26.
- Schacter, D. L., Alpert, N. M., Savage, C. R., Rauch, S. L., and Albert, M. S. 1996. Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. *Proc. Natl. Acad. Sci. USA* **93**:321–325.
- Silveri, M. C., Leggio, M. G., and Molinari, M. 1994. The cerebellum contributes to linguistic production: A case of agrammatic speech following a right cerebellar lesion. *Neurology* **44**:2047–2050.

- Squire, L. R., Ojemann, J. G., Miezin, F. M., Petersen, S. E., Videen, T. O., and Raichle, M. E. 1992. Activation of the hippocampus in normal humans: A functional anatomical study of memory. *Proc. Natl. Acad. Sci. USA* **89**:1837–1841.
- Talairach, J., and Tournoux, P. A. 1988. *A Co-planar Stereotaxic Atlas of the Human Brain*. Thieme, Stuttgart.
- Tanaka, M., Kondo, S., Hirai, S., Ishiguro, K., Ishihara, T., and Morimatsu, M. 1992. Crossed cerebellar diaschisis accompanied by hemiataxia: A PET study. *J. Neurol. Neurosurg. Psychiatry* **55**:121–125.
- Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., and Farah, M. J. 1997. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proc. Natl. Acad. Sci. USA* **94**:14792–14797.
- Tucker, J., Harding, A. E., Jahanshahi, M., Nixon, P. D., Rushworth, M., Quinn, N. P., Thompson, P. D., and Passingham, R. E. 1996. Associative learning in patients with cerebellar ataxia. *Behav. Neurosci.* **110**:1229–1234.
- Wallesch, C. W. 1985. Two syndromes of aphasia occurring with ischemic lesions involving the left basal ganglia. *Brain Lang.* **25**:357–61.
- Wallesch, C. W., and Papagno, C. 1988. Subcortical aphasia. In *Aphasia* (F. C. Rose, R. Whurr, and M. A. Wyke, Eds.), pp. 256–287. Whurr, London.
- Woods, R. P., Cherry, S. R., and Mazziotta, J. C. 1992. Rapid automated algorithm for aligning and reslicing PET images. *J. Computer Assisted Tomogr.* **16**:620–633.
- Xiong, J., Gao, J. H., Lancaster, J. L., and Fox, P. T. 1995. Clustered pixels analysis for functional MRI activation studies of the human brain. *Hum. Brain Map.* **3**:287–301.