Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 873–877, February 1993
Neurobiology

Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing

(working memory/conditional learning/positron emission tomography)

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Communicated by Brenda Milner, September 22, 1992

ABSTRACT **Work with non-human primates had previously demonstrated that the mid-dorsolateral frontal cortex, which comprises cytoarchitectonic areas 46 and 9, plays a critical role in the performance of nonspatial self-ordered working memory tasks, whereas the immediately adjacent posterior dorsolateral frontal cortex (area 8) is critical for the learning and performance of visual conditional associative tasks. The present study used positron emission tomography with magnetic resonance imaging to demonstrate the existence, within the human brain, of these two functionally distinct subdivisions of the lateral frontal cortex. These findings provide direct evidence that, just as in the monkey brain, the human lateral frontal cortex is functionally heterogeneous and that comparable anatomical areas underlie similar functions in the two species.**

Patients who have sustained surgical excisions from the frontal cortex perform well on many standard tests of memory, unlike patients with damage to the limbic region of the mesial temporal lobes, who exhibit a more general memory loss (1). Damage to the frontal cortex, however, impairs specific aspects of mnemonic performance (1). For instance, excisions involving a variable extent of the lateral frontal cortex impair performance on certain working memory tasks, the self-ordered tasks, in which the patients are required to monitor a series of self-generated responses (2). Lesions involving the lateral frontal cortex also impair performance on another class of tasks, the conditional associative learning tasks, in which specific responses have to be carried out conditional upon the presentation of particular exteroceptive cues (3, 4). The frontal cortex is not a homogeneous region of the brain, but rather a large expanse of the cortical mantle, encompassing many different cytoarchitectonic areas that exhibit their own unique pattern of connections with other cortical and subcortical areas.

It has been known for a long time that, in the monkey, lesions confined to a specific part of the mid-dorsolateral frontal cortex, the cortex lining the sulcus principalis, give rise to severe impairments in certain spatial working memory tasks (5). Only in recent years, however, has a specific attempt been made to adapt the nonspatial self-ordered working memory tasks first used with patients for work with the monkey (6, 7). This work has demonstrated a clear dissociation of the effects of lesions located within different parts of the dorsolateral frontal cortex for the performance of the two different classes of tasks referred to above. Monkeys with lesions restricted to the mid-dorsolateral frontal cortex (cytoarchitectonic areas 46 and 9) (Fig. 1*A*) are severely impaired on the self-ordered working memory tasks that had previously been used with patients (6, 7). Such lesions, however, do not significantly affect performance on conditional tasks. By contrast, lesions located just posterior to the mid-dorsolateral frontal cortex have a devastating effect on performance of conditional tasks (8–10) but do not affect performance on the self-ordered tasks (6, 7).

Unfortunately, in work with patients it is not possible to establish the areas within the frontal cortex that are critically involved in particular aspects of cognitive processing because the lesions are not confined to anatomically distinct areas. Until now, the notion of functional differentiation within the human dorsolateral frontal cortex with regard to the cognitive processing required by the above two classes of tasks had to remain a mere conjecture based on work with non-human primates. In recent years, however, positron emission tomography (PET) has provided a unique opportunity to identify, within the human brain, regions underlying specific cognitive activity (11). This can be achieved by measuring changes in regional cerebral blood flow (rCBF), a marker of local neuronal activity, while normal human subjects perform various tasks. In the present study, we used the paired-image subtraction method (12) to test the hypothesis, derived from the animal work, that the mid-dorsolateral region of the human frontal lobe is particularly involved in the performance of the self-ordered tasks that measure certain aspects of working memory, whereas the immediately adjacent cortex plays a major role in the performance of conditional tasks. This work has been presented in abstract form (13).

METHODS

Subjects. Nine right-handed male volunteer subjects (18–38 years old; mean age, 24.5 years) participated in this study. Informed consent was obtained from the subjects and the study was approved by the Ethics Committee of the Montreal Neurological Hospital.

Scanning Methods and Data Analysis. PET scans were obtained with the Scanditronix PC-2048 system, which produces 15 image slices at an intrinsic resolution of 5 mm × 5 mm × 6 mm (14). The regional distribution of cerebral blood flow (rCBF) was measured by means of the water bolus $H_2{}^{15}O$ methodology (15) during 60-sec PET scanning conditions. For each subject, a high-resolution magnetic resonance imaging (MRI) study (64 slices, 2 mm thick) was also obtained from a Philips Gyroscan (1.5 T) and resliced so as to be coregistered with the PET data using a PIXAR three-dimensional (3D) computer (16). Interactive 3D image software was then used to establish an orthogonal coordinate frame based on the anterior commissure–posterior commissure line as identified from the MRI image (17). These coordinates were used to apply a linear resampling of each matched pair of MRI and PET data sets into a standardized stereotaxic coordinate system (18). The PET images were reconstructed with a 20-mm Hanning filter to overcome

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Abbreviations: PET, positron emission tomography; rCBF, regional cerebral blood flow.

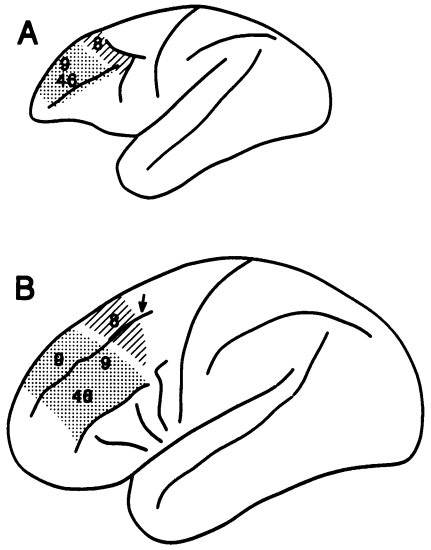

FIG. 1. (A) Outline of the lateral surface of the brain of the monkey illustrating the location of areas 46 and 9 (the mid-dorsolateral frontal cortex) and area 8 of the posterior dorsolateral frontal cortex. (B) Outline of the human brain illustrating the location of the same cytoarchitectonic areas. The arrow indicates the superior frontal sulcus.

residual anatomical variability persisting after the stereotaxic standardization. These PET images were then normalized for global CBF value, and the mean state-dependent change in CBF was obtained (19). The mean state-dependent change volume was converted to a t-statistic volume by dividing each voxel by the mean standard deviation in normalized CBF for all intracerebral voxels (20). Individual MRI images were subjected to the same averaging procedure, such that composite stereotaxic image volumes were obtained for t-statistic and MRI volumes. The transformed volumes were 128 × 128 × 80 voxels in extent and sampled at 1.34 × 1.72 × 1.50 mm in the x, y, and z dimensions, respectively. Anatomical and functional images were merged (17), a procedure that allows (*i*) direct localization of t-statistic peaks, identified by an automatic peak-detection algorithm, on the MRI images and (*ii*) the anatomical correlation of extended zones of activation that cannot be expressed in terms of isolated peaks. Mapping the subject's own MRI image into stereotactic space overcomes some of the difficulties associated with using a standard atlas alone to identify anatomical correlates of PET responses in areas of high anatomical variability (e.g., frontal lobe) (17).

For this work, two search strategies were employed: an exploratory and a directed search. For the exploratory search—i.e., for all peaks within the grey matter volume of 600 cm^3 or 200 resels—the threshold for reporting a peak as significant was set at $t = 3.50$, corresponding to an uncorrected probability of $P < 0.0002$ (20). For the directed search within the dorsolateral frontal cortex for predicted activation foci in particular cytoarchitectonic areas, we selected a search volume of ≈150 cm^3 or 50 resels. The threshold for significance was set at $t = 3.00$, corresponding to an uncorrected probability of $P < 0.0013$.

Testing Procedure. The subjects were scanned for 60 sec with PET under three conditions of testing. In all three scanning conditions, the subjects were presented with a series of cards, one card at a time. The same set of eight abstract designs was printed on each card, but the position of these designs varied randomly from card to card. At the top of each card, there was a stripe that could appear in any one of eight different colors. The stimuli used and the mode of response were identical in all three conditions, the only difference being in the cognitive requirements of the tasks that the subjects had to perform. A control condition was administered first. Just before scanning began, the experimenter pointed to one of the designs and, during scanning, the subjects were required to point to this particular design on each card presented. In the self-ordered condition, the same cards were used as in the control condition, but now the subjects were required to point to a different design on each card presented until all eight designs had been selected. The subjects were told that they could point to these designs in any order they wished, but without pointing to any one design more than once. They were also told that when eight cards had been presented, a blank white card would appear, indicating that they were to start, from the beginning, selecting a new sequence of these designs on the cards that were to follow. A blank card was inserted after each set of eight cards in all conditions, the only difference being that in the other conditions the subjects were informed that the white card had no significance. In this condition, the subjects had to maintain an on-going record of the stimuli that they had already selected, constantly monitoring their prior selections as they were preparing each pointing response. The third scanning condition involved the performance of a conditional task. The same cards were again used but now the subjects were required to point to a different design conditional upon the color of the stripe appearing at the top of each card. Each one of the eight colors was the cue for only one of the eight designs and the subjects had learned these associations between the colors and the designs just prior to scanning. Training on this task was conducted as follows. The cards were presented one at a time and the subject pointed to various designs on the card until the correct design for the particular color cue shown on the card was discovered. The experimenter told the subject whether he had pointed to the correct design after each response. Training continued in this manner until the subject made no errors over 16 consecutive presentations of cards.

RESULTS

In the control task, the subjects were required to look for a particular stimulus and point to it. These same looking and pointing responses were also required in the two experimental tasks, except that the latter tasks had the following additional requirements. During the performance of the self-ordered task, the subjects had to maintain, within working memory, the stimuli that they had already selected so as not to select them again. By contrast, during the performance of the conditional task, the subjects were required to retrieve from long-term memory the particular stimuli that were correct on the basis of the color cues presented.

To address the question of whether there would be significant activation within the human dorsolateral frontal cortex related to the performance of the self-ordered task, normalized CBF in the control task was subtracted from that in the self-ordered task. There was significant activation within the right mid-dorsolateral frontal cortex (area 46) (Fig. 2) as well as a weaker response within this region in the left hemisphere (see Table 1). The same question was also addressed in another comparison in which activation in the conditional task was subtracted from that in the self-ordered task. In this comparison, the reference state is activation during the performance of the conditional task, which is known to involve another region of the frontal cortex (10), and it should thus provide another strong test of the hypothesis that the mid-dorsolateral frontal cortex is specifically involved in the self-ordered task. The significant foci obtained when this subtraction was carried out are shown in Table 2. There were now four activation peaks within the right mid-dorsolateral

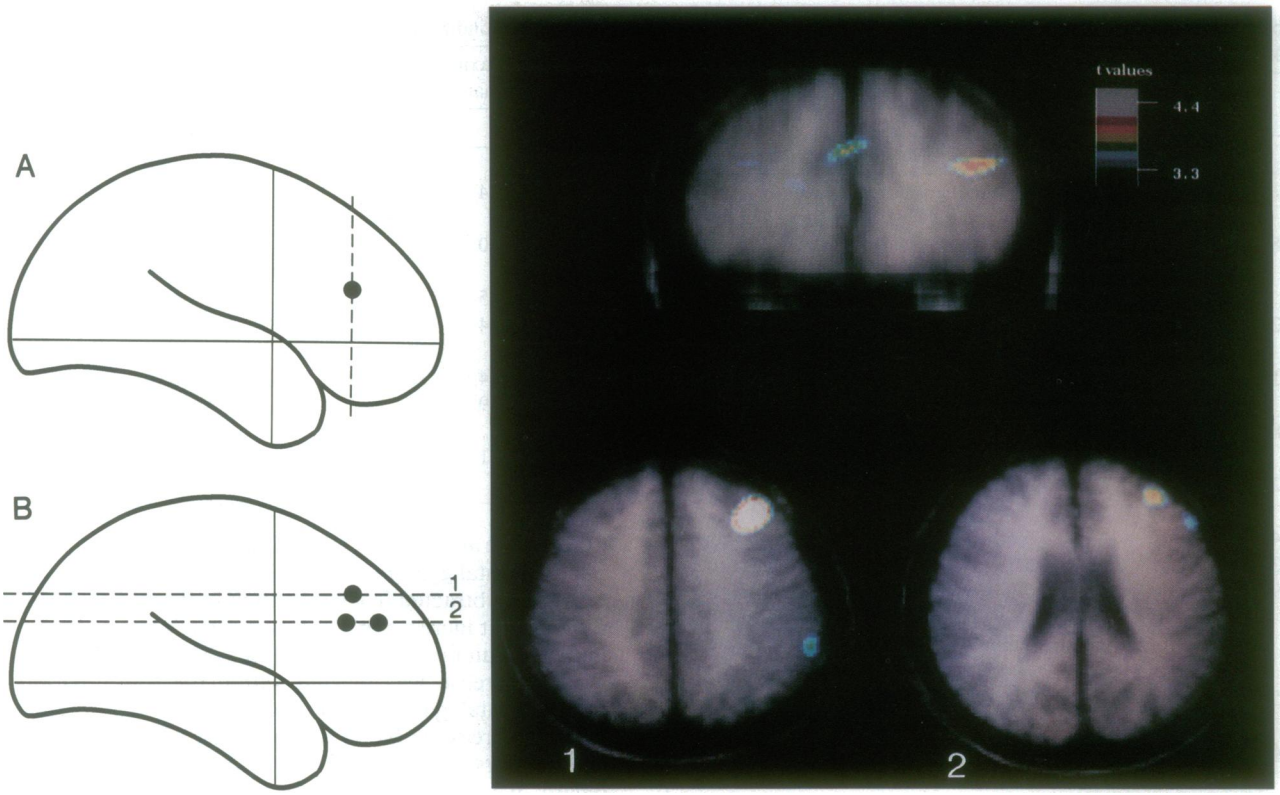

FIG. 2. Merged PET-MRI sections illustrating rCBF increases averaged for all nine subjects. The schematic outlines of the brain indicate the level (interrupted lines) of the sections presented. The subject's left is on the left side in these sections. (*A*) Self-ordered minus control task. Coronal section showing activation within the right mid-dorsolateral frontal cortex (area 46). (*B*) Self-ordered minus conditional task. Horizontal sections showing activation within the mid-dorsolateral frontal cortex. The coordinates (*x*, *y*, *z*) of the foci shown in *A* were 35, 32, 21 and those shown in *B* were 32, 32, 36 (1: upper horizontal section) and 48, 29, 24 and 31, 42, 24 (2: lower horizontal section).

Table 1. Self-ordered task minus control task

Stereotaxic coordinate				
x	*y*	*z*	*t* statistic	Brain area
				Left hemisphere
−38	10	40	4.47	Mid-dorsolateral frontal cortex (area 9)
−35	30	22	3.52	Mid-dorsolateral frontal cortex (area 46)
−7	34	26	3.74	Anterior cingulate cortex (area 32)
−3	29	29	3.99	Anterior cingulate cortex (area 32)
−32	−47	36	4.43	Posterior parietal cortex
−24	−56	40	4.76	Posterior parietal cortex
				Right hemisphere
35	32	21	4.18	Mid-dorsolateral frontal cortex (area 46)
23	8	44	3.81	Posterior premotor cortex
9	24	40	3.52	Anterior cingulate cortex (area 32)
23	−56	33	4.07	Posterior parietal cortex
16	−56	30	4.03	Posterior parietal cortex

Activation foci in this and the other tables represent peaks of statistically significant (see text) increases in normalized CBF. The stereotaxic coordinates are expressed in mm. *x*, Medial-to-lateral distance relative to the midline (positive = right); *y*, anterior–posterior distance relative to the anterior commissure (positive = anterior); *z*, is the superior–inferior distance relative to the anterior commissure–posterior commissure line (positive = superior).

frontal cortex and one activation peak within the left mid-dorsolateral frontal cortex.

The second question of interest was whether there would be activation related to the performance of the conditional task at a location just posterior to the mid-dorsolateral frontal cortex. We wished to see whether there would be activation within the region considered as area 8 cortex, as would be predicted from the available work with non-human primates (21) for the particular conditional task that was used. To address this question, activation in the control task was subtracted from activation in the conditional task. The significant foci obtained from this subtraction are shown in Table 3. The only significant lateral frontal focus now observed was located in the posterior dorsolateral frontal cortex, within the region which, according to the Talairach and Tournoux stereotaxic atlas (18), is occupied by area 8. There were no activation foci within the mid-dorsolateral frontal cortex as a result of this subtraction. The activation focus within area 8 was located at the depth of the superior frontal sulcus (Fig. 3). Cytoarchitectonic area 8 on the lateral surface of the frontal lobe extends from the midline down to the superior frontal sulcus and occupies a variable extent of the cortex just below the sulcus (see Fig. 1*B*).

Further evidence supporting the involvement of area 8 in the performance of the conditional task was obtained when activation in the self-ordered task was subtracted from the conditional task. There was only one significant activation focus within the frontal lobe and this was located within area 8 in the depth of the superior frontal sulcus in the left hemisphere (Table 2).

The cytoarchitectonic areas quoted in the tables for particular stereotaxic coordinates are based on the Talairach and Tournoux atlas (18). We have also sectioned and stained a human brain for cytoarchitectonic and myeloarchitectonic

Table 2. Difference between self-ordered task minus conditional task and conditional task minus self-ordered task

Stereotaxic coordinate				
x	*y*	*z*	*t* statistic	Brain area
Self-ordered task minus conditional task				
				Left hemisphere
−38	30	33	3.23	Mid-dorsolateral frontal cortex (area 9)
				Right hemisphere
32	32	36	5.38	Mid-dorsolateral frontal cortex (area 9)
31	42	24	4.08	Mid-dorsolateral frontal cortex (area 46)
48	29	24	3.60	Mid-dorsolateral frontal cortex (area 46)
42	37	3	3.82	Mid-dorsolateral frontal cortex (area 46)
34	10	51	5.68	Posterior premotor cortex
52	−35	45	5.19	Posterior parietal cortex
39	−49	48	5.04	Posterior parietal cortex
Conditional task minus self-ordered task				
				Left hemisphere
−15	30	38	3.15	Superior frontal sulcus (area 8)
−4	−30	30	3.56	Posterior cingulate cortex (area 23)
−42	−6	6	3.53	Insula
				Right hemisphere
4	−56	18	3.53	Posterior cingulate cortex (area 23)

studies. We have carried out histological examination of sections of this brain at levels that corresponded as closely as possible to the average MRI sections running through the activation foci observed in the lateral frontal cortex. This examination indicated that the activation focus in the depth of the superior frontal sulcus observed during the performance of the conditional task is located in a section of the sulcus occupied by area 8 and that the regions activated within the mid-dorsolateral frontal cortex are occupied by typical frontal granular cortex that is the hallmark of areas 9 and 46.

DISCUSSION

A major question addressed by the present investigation was whether there would be significant functional activation of the human mid-dorsolateral frontal cortex during the performance of the self-ordered task. The mid-dorsolateral frontal cortex, in the human brain and monkey brain, comprises cytoarchitectonic areas 46 and 9 (Fig. 1). These areas constitute the typical primate frontal granular cortex, where a well-defined granular layer IV can be identified. In the human brain, these areas occupy the middle parts of the superior and middle frontal gyri (Fig. 1*B*). When activation in the control task was subtracted from activation in the self-ordered task, a significant increase in rCBF was observed within the right mid-dorsolateral frontal cortex (area 46) (Fig. 2*A*). The focus of this increase was located within the lower part of the middle frontal gyrus, just above the inferior frontal sulcus. A smaller increase in blood flow was also observed within the left mid-dorsolateral frontal cortex (area 46) (Table 1). In this regard, it is important to note that the stimuli used in the present investigation were abstract designs—i.e., stimulus material known to be preferentially processed by the right hemisphere (22). An activation focus within the left dorsolateral frontal cortex was also observed in the posterior part of the middle frontal gyrus, a region that Brodmann considered to be part of area 9 (Table 1).

Table 3. Conditional task minus control task

Stereotaxic coordinate				
x	*y*	*z*	*t* statistic	Brain area
				Left hemisphere
−16	24	39	4.09	Caudal superior frontal sulcus (area 8)
−5	30	21	3.54	Anterior cingulate cortex (border 24 and 32)
−34	−45	36	4.28	Posterior parietal cortex
−27	−54	39	4.28	Posterior parietal cortex
				Right hemisphere
19	−54	35	3.77	Posterior parietal cortex
5	−59	29	4.14	Medial parietal cortex
				Midline
0	−31	29	3.91	Posterior cingulate cortex (area 23)

The key role of the mid-dorsolateral frontal cortex in the cognitive activity underlying performance of the self-ordered task was also demonstrated when activation in the conditional task was subtracted from the self-ordered task. Since these tasks measure different aspects of frontal cortical function, as shown by the lesion work in the monkey (6, 7, 9, 10), this subtraction should provide further evidence regarding any specific contribution of frontal cortical areas 46 and 9 to the self-ordered task. There were now four significant activation foci within the right mid-dorsolateral frontal cortex (areas 46 and 9) (Fig. 2*B* and Table 2), emphasizing once more the predominant involvement of the right mid-dorsolateral frontal cortex in this particular working memory task in which abstract designs were used.

In the monkey, lesions located just posterior to the mid-dorsolateral frontal cortex—i.e., within areas 8 and rostral 6—impair severely the performance of conditional tasks (8–10) without in any way affecting performance of the self-ordered tasks (7). More specifically, it has been shown that the performance of conditional tasks in which the appropriate visual stimuli must be chosen depending on the

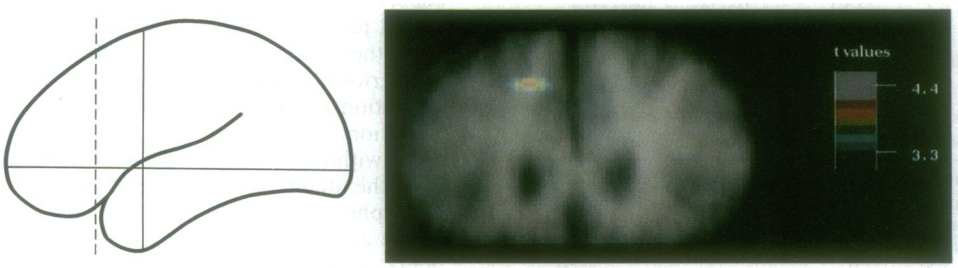

FIG. 3. Conditional minus control task. Merged PET-MRI coronal section showing activation within the depth of the posterior part of the superior frontal sulcus (area 8). The interrupted vertical line indicates the level of the coronal section illustrated.

particular visual cues presented are impaired by lesions limited to area 8 (21). Area 8 is the part of the posterior dorsolateral frontal cortex that is closely linked anatomically (23) and physiologically (24) with the visual and oculomotor systems. The failure on the visual conditional tasks following lesions to this area has been interpreted as evidence that it plays a major role in the selection of specific visual stimuli to become the target of visual search, based on the particular cues present at any given moment in time (21).

In the human brain, a comparable area (area 8 of Brodmann) occupies parts of the superior and middle frontal gyri at a location just posterior to the mid-dorsolateral frontal cortex (25). In the present study, there was only one significant increase within the lateral frontal cortex for the conditional task (see Table 3). This increase was observed in the left hemisphere within the depth of the posterior part of the superior frontal sulcus (Fig. 3), a region that falls within area 8 (Fig. 1*B*). The mid-dorsolateral frontal cortex was not activated in this subtraction, underscoring the specificity of activation within the frontal cortex depending on the cognitive requirements of the task performed.

It must be noted that the classical frontal eye field occupies only a small part of the cytoarchitectonically defined area 8—i.e., its ventralmost portion that lies at the border of area 8 with area 6 (24, 26). Cytoarchitectonic area 8 encompasses various other physiologically defined regions that exert higher-order control on visual behavior (27). The impairment on visual conditional tasks following lesions of area 8 reflects the loss of this control (21). It is important to note that the focus of activation within area 8 observed in the present investigation lies anterior to the area shown to be activated by saccadic eye movements in earlier PET studies and that was considered to be the human frontal eye field (28). The fact that only area 8 in the left hemisphere was activated in the present study is most probably related to the use of color stimuli as the conditional cues. Such stimuli are readily encoded in verbal terms by human subjects and this aspect of processing may have placed greater demands on area 8 within the language-dominant left hemisphere (4).

A few other cortical regions (i.e., cingulate, posterior premotor, and posterior parietal cortex) were coactivated with the lateral frontal areas that were the focus of the present investigation (Tables 1–3). These cortical regions are known to be anatomically interconnected with the lateral frontal cortex (23). In previous PET studies, activation of the posterior premotor (29) and the anterior cingulate cortex* has been observed in relation to motor control and the parietal cortex in relation to spatial visual processing (30). Activation of the anterior cingulate has also been interpreted as critical to the selection process between competing alternatives (31). The activation observed in these regions in the present study can be seen as a reflection of a close functional interaction existing between the particular frontal systems involved during the performance of the present tasks and these other regions. The coactivation in PET studies of a limited number of areas underlines the fact that specific cognitive processing occurs within a distributed but specific system.

The findings of the present investigation provide strong evidence that, just as in the monkey brain, there exist within the human lateral frontal cortex two distinct functional systems. The mid-dorsolateral frontal cortex (areas 46 and 9) is an integral part of a distributed neural circuit underlying certain aspects of working memory (5–7). The dorsolateral frontal cortex that lies just posterior to this region is an essential component of a neural circuit that mediates an aspect of the higher-order control of behavioral responses involving the selection of appropriate stimuli depending on particular environmental contingencies (9, 10).

*Paus, T., Petrides, M., Evans, A. C. & Meyer, E., National Meeting of the American Association for the Advancement of Science, Feb. 11–16, 1992, Boston, p. 251 (abstr.).

We thank the staff of the McConnell Brain Imaging Center for their technical assistance. This work was supported by the McDonnell-Pew Program in Cognitive Neuroscience and Medical Research Council (Canada) Special Project Grant SP-30 (coordinator: Dr. A. Gjedde). Color reproductions were supported by G. E. Medical Services.

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