Imaging the premotor areas
Nathalie Picard* and Peter L Strick†

Recent imaging studies of motor function provide new insights into the organization of the premotor areas of the frontal lobe. The pre-supplementary motor area and the rostral portion of the dorsal premotor cortex, the ‘pre-PMd’, are, in many respects, more like prefrontal areas than motor areas. Recent data also suggest the existence of separate functional divisions in the rostral cingulate zone.

Introduction
Large regions of the brain located on the lateral surface and on the medial wall of each hemisphere participate in the generation and control of movement. The premotor areas in the frontal lobe have the anatomical substrate to influence motor output, both through connections with the primary motor cortex (M1) and through direct projections to the spinal cord (e.g. [1]). In monkeys, the frontal lobe contains six well-defined premotor areas (Figure 1a). The presence of analogous areas in humans has been inferred from functional imaging studies (Figure 1b) [2,3]. However, the definition of premotor areas in humans is still evolving. Some associations between anatomy and function proposed in the past [2] have been validated by recent imaging data, and other associations are emerging.

In this review, we present the results of salient imaging studies that have helped to increase our understanding of the underlying anatomical and functional organization of the premotor areas. Much recent effort in the field of functional imaging has been to examine brain regions involved in cognitive operations. The interpretation of activations in premotor cortex during cognitive operations depends critically on a clear definition of the location and boundaries of these cortical areas. Thus, one focus of our review synthesizes the new data that is relevant to this issue.

Medial wall
Pre-supplementary motor area and supplementary motor area
In monkeys, it is now established that area 6 on the medial wall of the brain contains two separate areas: the supplementary motor area proper (SMA) in the caudal portion of area 6, and the pre-SMA in the rostral portion (Figure 1a; reviewed in [2,4]). The SMA and pre-SMA are equivalent to fields F3 and F6 described by Matelli et al. [5]. In humans, the level of the anterior commissure (VCA line) [6] marks the border between the two areas. The division of medial area 6 into two distinct fields is based on a collection of anatomical and functional data [2,4]. Because the pre-SMA was born out of a premotor area — the traditional SMA of Woolsey et al. [7] — the common perception is that the pre-SMA is also a motor area. However, the connectivity and physiology of the pre-SMA suggest that it is more like a prefrontal area than a motor area. Prefrontal areas provide cognitive, sensory or motivational inputs for motor behavior, whereas the motor areas are concerned with more concrete aspects of movement (e.g. muscle patterns). Two important differences in the anatomical connections of the SMA and pre-SMA support this view. First, only the SMA is directly connected to M1 and to the spinal cord [1,8–11]. Second, only the pre-SMA is interconnected with the prefrontal cortex [12–14]. These anatomical features, among others, are reflected by differential patterns of activity in the SMA and pre-SMA [4]. In neuroimaging studies, the pre-SMA/SMA distinction is the clearest example of an anatomical and functional dissociation that emerged from the primate model [2]. In the following, we describe recent findings that provide further support for this dissociation.

Initially, studies in monkeys suggested that the pre-SMA has involved in learning sequential movements [15–17]. This motor view of pre-SMA function was supported by the observation that, in humans, activation of the pre-SMA increased in parallel to acquisition of a motor sequence task [18]. In contrast, SMA activation during the same task was related simply to aspects of motor execution. More recent studies by the same group have resulted in a modified view of pre-SMA function. Sakai et al. [19] recently compared pre-SMA activation in closely matched tasks that all required visuo–motor associations, but varied in motor and perceptual sequence components. Activation of the pre-SMA occurred in all tasks related to visuo–motor association demands rather than to sequential components. In fact, pre-SMA activation was greatest in the conditional task, in which non-sequential responses were arbitrarily...
determined by the color of visual cues, and showed a relative decrease in sequential paradigms. This important study shows conclusively that activation of the pre-SMA in these tasks has little to do with motor sequence learning per se. Instead, pre-SMA activation occurs in association with establishing or retrieving visuo–motor associations (see also [20,21]). The activity in the pre-SMA in association with visually cued changes between motor sequences [22,23] may also be due to the role of the pre-SMA in retrieving visuo–motor associations.

Additional studies have extended the involvement of the pre-SMA to associations based on auditory stimuli [24••,25] (Figure 2a). Visual and auditory versions of a conditional choice reaction time paradigm generated pre-SMA activations of equal magnitude [25]. Thus, the contribution of the pre-SMA to sensory–motor associations is modality-independent. In addition, the contribution of the pre-SMA appears to be effector-independent. Similar regions are activated in conditional manual motor [24••,25] and oculomotor tasks [21] (Figure 2b). This is consistent with the poor somatotopic organization of the pre-SMA [2] and supports the view that the pre-SMA operates at a more abstract level. In contrast, SMA activation displayed only movement-related activation in visual or auditory tasks.

It must be emphasized that pre-SMA activation during conditional motor behaviors was not due to response selection or preparation [19,24••]. In fact, activation patterns of the pre-SMA during non-conditional behavior suggest that its contribution to sensory–motor association is detached from motor aspects of the task. For example, the pre-SMA displayed sustained activation, independent of motor preparation, during working memory delays of a match to sample task [26] (Figure 2c). In addition, the pre-SMA showed transient activation associated with shifts of attention to visual object features (shape, color, location) in a card sorting task [27]. Attending to various features of visual stimuli was found to activate the pre-SMA equally in another context [28]. These results suggest that pre-SMA function is more closely related to processing or maintenance of relevant sensory information than response selection or production.

Overall, neuroimaging studies leave no doubt that the pre-SMA is fundamentally different from the SMA. Activation of the SMA, caudal to the VCA line, is observed primarily in relation to aspects of movement behavior. In contrast, pre-SMA activation, rostral to the VCA line, is associated with cognitive aspects of a variety of tasks (see also [29–34]). These findings, together with anatomical results, suggest that the pre-SMA might be functionally considered a region of prefrontal cortex.

Figure 1

Motor areas of the frontal lobe in monkeys (a) and homologous areas in the human (b).
In humans, the border between areas 6 and 4 on the lateral surface is located in the anterior bank of the central sulcus [65]. For illustration, the border is drawn on the surface of the hemisphere along the central sulcus (bottom, white dotted line). Except for the most medial portion, M1 does not occupy the precentral gyrus. Pictures of the monkey brain courtesy of Richard P Dum; pictures of the human brain reproduced with permission from [93].
Anatomical and functional distinction of the SMA and the pre-SMA in three different tasks. (a) Top: activation in the SMA and pre-SMA during an auditory conditional task; bottom: selective activation in the pre-SMA during an auditory-motor association task. Reproduced with permission from [24**]. (b) Top: Activation in the supplementary eye field (SEF) during visually guided saccades; bottom: selective activation of the pre-SMA for a mixed condition of compatible and incompatible (Stroop-like) conditional saccades. Reproduced with permission from [21]. (c) Top: motor-related activations in the SMA and CCZ; bottom: sustained activation during working memory delay in the pre-SMA and RCZ. Reproduced with permission from [26].

Two theories predominate about the overall function of this region of cortex: 'conflict monitoring' [43] and 'attention/selection for action' [44]. The first theory emphasizes the evaluative function of the RCZ, whereas the second emphasizes its motor function ([45*], but see also [46]). How do these two theories and functions relate to the motor area(s) in the RCZ? We propose that they reflect the properties of two different functional regions: conflict monitoring within the RCZa and selection for action within the RCZp. For example, a series of imaging studies that were carefully designed to control conflict monitoring, found activation in the ‘anterior cingulate’ cortex [43,45*,47,48*]. On average, the sites of these activations were located 24 mm ± 7 mm (mean ± standard deviation) anterior to the VCA line (Table 1). This location corresponds to the RCZa, which may correspond to the CMAr of monkeys [2]. In contrast, when some of the same investigators used a similar paradigm that did not specifically dissociate conflict monitoring from response selection, they found response-related activation in the area of the ‘anterior cingulate’ cortex, located 1 mm anterior to the VCA line [49]. This site corresponds to the RCZp, which may correspond to the CMAv of monkeys [2].

The results of other imaging studies can be interpreted within the same anatomical-functional framework. Two groups of investigators, using single subject analysis, found multiple foci of activation in the ‘anterior cingulate’ cortex during word generation tasks that involved response selection [37,42] (Figure 3a). In both instances, the major site of activation was located largely within the RCZp. Tasks that can be interpreted as involving both conflict processing and response selection (versions of Go/NoGo and STOP tasks) evoked distinct sites of activation in the ‘anterior cingulate’ cortex [50*,51]. In a Go/NoGo task, different cues (e.g. green or red stimuli) each determine a particular response (Go or NoGo). Thus, this task is similar to a conditional visuo–motor association task. Because only one cue is presented for each response to produce (no interference) and because a cue is always associated with a single response,

uncertainty in the definition of the cingulate motor areas remains. However, on the basis of results from recent experiments, consistent patterns of activation are found in the CCZ, and a new view of the RCZ is emerging.

The CCZ, which appears to be comparable to the CMAd of monkeys, is activated primarily in relation to movement execution ([2,3,26,38**], see also [39]). Painful stimuli activate an area in or near the CCZ ventral to the area associated with movement execution [38**]. Thus, different functional areas may exist for movement and for painful stimuli. The site of movement-related activation in the CCZ is remarkably similar across studies. For example, in two different studies, finger movements activate virtually identical sites in the CCZ [26,38**] (Figure 2c). In addition, activation in the CCZ is consistently separable from that in the SMA. These observations reinforce the view that the CCZ is distinct from the SMA, despite the proximity of the two areas and their tendency to be co-activated during manual tasks [40]. In the monkey, the functional dissociation of the CMAd from the SMA occurs under specific behavioral conditions [41]. Thus, future studies are likely to find important functional differences between the human CCZ and SMA.

Recent studies confirm that movement leads to activation in the RCZ, rostral to the VCA line [26,38**]. Movement-related activation in this region is best demonstrated in analyses of single subjects [3,37,38**], presumably because of anatomical variability. The activation in these studies is clustered near the cingulate sulcus or its ramifications. Similarly, the RCZ activation associated with a word generation task is located in or near the cingulate or paracingulate sulci and never extends onto the cingulate gyrus [37]. Thus, some motor and cognitive functions may share a common substrate within the RCZ. In contrast, activations related to attention or arousal are located at more rostral and ventral locations [38**,42], which are probably outside the RCZ on the cingulate gyrus proper.
conflict is negligible in Go/NoGo tasks in which response selection is required. Activation in the RCZ during the Go/NoGo task was located, on average, 7.5 ± 9 mm in front of the VCA line (Table 1). This site falls within the RCZp [2]. In addition, activation in the RCZp was larger during the Go/NoGo task than during the STOP task. In STOP tasks, a cued Go response is prevented by the delayed presentation of a second cue signaling NoGo. Thus, STOP tasks present a high degree of response conflict because contradictory instructions determine the subject's response. The RCZ activation in STOP tasks, like that in other high conflict tasks, was located in a separate focus 25 mm rostral to the VCA line (in the RCZa) [50•] (Table 1).

In sum, these data support the existence of at least three functional areas in the anterior portion of the cingulate sulcus: the CCZ and two subdivisions within the RCZ. The CCZ appears to be activated during simple motor tasks, whereas the RCZa and the RCZp appear to be differentially involved in conflict monitoring and response selection. Overall, proposals about the RCZ are founded on a relatively small number of studies. Further research is necessary to fully define the function(s) of these cortical regions.

Lateral surface

The dorsal part of the lateral premotor cortex

In monkeys, the dorsal part of the lateral premotor cortex (PMd) has been divided into rostral (F7, PMdr) and caudal (F2, PMdc) subdivisions [5,52], on the basis of anatomical and physiological differences (Figure 1a). These differences are analogous to those that generate the pre-SMA/SMA split. In fact, in a number of important respects, the caudal portion of the PMd has much in common with the SMA proper. Both areas project to the primary motor cortex and directly to the spinal cord [1,8,52,53]. Neither area has substantial interconnections with prefrontal cortex [14]. Neurons in both regions are primarily involved in aspects of motor control [4]. In contrast, the rostral portion of the PMd has much in common with the pre-SMA. Neither of these areas projects to the primary motor cortex or to the spinal cord [1,8,52,53]. Instead, both regions are interconnected with areas of prefrontal cortex and with the reticular formation [4,14,54]. Interestingly, neither the pre-SMA nor the PMd appears to have substantial interconnections with the SMA proper or with the caudal portion of the PMd [11,13,55]. Furthermore, the results of neuronal recording and functional imaging studies suggest that the pre-SMA and the rostral portion of the PMd are more involved in cognitive than in motor processes (see below). On the basis of these findings, we believe that there is heuristic value in adopting a new terminology to refer to these cortical areas.

Table 1

<table>
<thead>
<tr>
<th>Ref</th>
<th>Task Type</th>
<th>Type</th>
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<th>y</th>
<th>z</th>
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<td>29</td>
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<td>-8</td>
<td>22</td>
<td>32</td>
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<td>22</td>
<td>43</td>
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<td>[50•]</td>
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<td>37</td>
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<td>42</td>
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<td>[51]</td>
<td>Go/NoGo vs STOP task</td>
<td>Selection</td>
<td>-6</td>
<td>0</td>
<td>42</td>
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Figure 3

Anatomical and functional division of the RCZ. (a) Activation during free word generation. The dashed line separates activations located in the pre-SMA and in the RCZ. Reproduced with permission from [37]. (b) Activation related to conflict monitoring. Brain images from the two studies were matched in size in the anterior-posterior axis. Dotted lines in (b) represent the estimated locations of levels indicated in (a). Activations related to conflict monitoring are located at the rostral edge of activations found during word generation. This topography suggests that the RCZa is involved in conflict monitoring (evaluative function) whereas the RCZp is involved in response selection. Note that all cingulate activations are in sulci, not on the cingulate gyrus, supporting the view that they overlap with cingulate motor areas. Reproduced with permission from [43].
We suggest that the rostral portion of the PMd (F7) be termed the pre-PMd, and that the caudal portion of the PMd (F2) be termed the PMd proper. This terminology more clearly reflects the parallels between these areas and the pre-SMA and SMA proper.

Recent studies in monkeys further support the distinction between the pre-PMd and the PMd proper. Parietal cells that project to the pre-PMd convey eye movement signals, whereas those that project to the PMd convey hand movement signals [56,57]. The two subdivisions can be further characterized on the basis of their differential involvement in oculomotor control [58]. Eye movements are evoked by stimulation of pre-PMd, whereas predominantly limb and body movements are evoked from the PMd. Similarly, neurons in the pre-PMd are more active during a saccade task than during a limb movement task. In contrast, the reverse is the case for neurons in the PMd. Thus, there is ample evidence that the pre-PMd and the PMd are anatomically and physiologically distinct [59**].

The functional distinction between the pre-PMd and the PMd has not always been obvious in imaging studies of human subjects. However, we have found that a consistent pattern emerges when activation related to hand movement is used as an ‘anchor point’ and activations in premotor cortex, relating to other more cognitive types of movement in the same subjects, are measured in relation to this point. The data in Table 2 illustrates that, in a recent group of studies, movement performance tasks produced activations more caudally in the PMd than more cognitively demanding tasks. Movement-related activations were located on average 8.1 mm rostral to the center of M1 activation in the same subjects [31,32,60–64]. This value is strikingly similar to the location of the hand representation on the precentral gyrus. In humans, the precentral gyrus corresponds to the premotor cortex (area 6) [65], which is 8.8 mm anterior to the hand representation in the central sulcus [66]. Over a relatively large number of studies, the average of the absolute coordinates for movement-related activation in the PMd and the location of the hand representation on the precentral gyrus [66] are very similar (Table 2). Conversely, activations related to higher-order processing (e.g. conditional visuo–motor associations, response selection or motor imagery) are located in the pre-PMd an average of 22.9 mm anterior to movement-related activation in M1 [25,31,61,67].

The rostro-caudal gradient of activation across the pre-PMd–PMd is most convincingly demonstrated within subjects [24**,25,31,59**,61,67–69] (Figure 4). For example, activation that specifically relates to sensory–motor association in an auditory conditional task is restricted to the rostral edge of area 6 [24**]. The site of this activation is likely to be in the pre-PMd, rather than in the PMd. Similarly, activation in other conditional motor tasks is located in the pre-PMd, 18–26 mm anterior to movement-related activation in M1 [25,67] (Table 2). In addition, rostral portions of area 6 in the pre-PMd are activated during the presentation of visual cues or movement imagination, whereas caudal portions of area 6 in the PMd are activated during movement preparation or execution [59**,61,69]. This interpretation is compatible with the response properties of neurons seen in recording studies of
awake trained monkeys [59**,70,71]. The PMd contains a high proportion of neurons that display set- and move-set related activity. In contrast, neurons in the pre-PMd are more responsive to sensory cues, and fewer are active in relation to movement. Thus, neuroimaging studies and neuron properties indicate that the PMd is primarily involved in aspects of movement preparation or generation (see also [72,73]), whereas the functions of the pre-PMd are more closely related to cognitive processes than to motor processes.

Table 2
Talairach coordinates [6] of activation sites in the PMd relative to movement-related activations in M1†.

<table>
<thead>
<tr>
<th>Refs</th>
<th>Contrast</th>
<th>Type</th>
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<th>(\Delta y)</th>
<th>(\Delta z)</th>
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<td>-54, -18, -16</td>
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<td>-2</td>
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<td></td>
<td>Choice RT (auditory mode): time uncertainty-control</td>
<td>Higher-order</td>
<td>-50, -42, 16</td>
<td>22</td>
<td>-6</td>
<td></td>
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<tr>
<td></td>
<td>Choice RT (auditory mode): dual uncertainty-control</td>
<td>Higher-order</td>
<td>-52, 18, 16</td>
<td>24</td>
<td>0</td>
<td></td>
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<td></td>
<td>Choice RT (visual mode): (control-rest)∩(response uncertainty-rest)∩(time uncertainty-rest)∩(dual uncertainty-rest)</td>
<td>Movement-related</td>
<td>-36, -16, 50</td>
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<td></td>
<td>Choice RT (visual mode): response uncertainty-control</td>
<td>Higher-order</td>
<td>-50, -8, 16</td>
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<td>Choice RT (visual mode): time uncertainty-control</td>
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<td>-42, -20, 16</td>
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<td>Choice RT (visual mode): dual uncertainty-control</td>
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<td>-52, 18, 16</td>
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<td>-4</td>
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<td>[31]</td>
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<td>(finger movement-rest)-(imagined movement-rest)</td>
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<td>(imagined movement-rest)-(imagined movement-rest)</td>
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<td>Event-related: instruction &amp; delay periods</td>
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<td>[62]</td>
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<td>[67]</td>
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<td>-33, -34, -23</td>
<td>-33, -27, 55</td>
<td>24</td>
<td>-7</td>
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Average† (n=14) | Movement-related | 37.3, -14.4, 38.2, -22.2, 8.1 | 2.4 |
Standard deviation† | 60.3 | 10.9, 9.3, 7.4 | 4.0, 5.9, 6.5 | 6.5 | 5.8 |
Average† (n=13) | Higher-order | 43.9, 5.0, 50.6 | 22.9 | 4.8 |
Standard deviation† | 10.1, 3.7, 5.1 | 2.4 | 7.9 |

[66] | High resolution fMRI & 3D reconstruction: finger movement-rest | Movement-related | -35.5, -14.6, -36.6, -23.4, 8.8 | 8.5 |
Average (n=5) | 65.3 | 56.8 |
Standard deviation | 6.0, 4.5, 5.6 | 7.6, 4.1, 9.4 |

Table 2 legend:

*Only hand movement tasks were considered in this comparison.

The ventral part of the lateral premotor cortex

In monkeys, the ventral part of the lateral premotor cortex (PMv) lies in area 6 below the spur of the arcuate sulcus (Figure 1a). The PMv, like the PMd proper, is densely interconnected with M1. In addition, the portion of the PMv in and adjacent to the caudal bank of the arcuate sulcus contains neurons that project directly to the spinal cord [1,53]. There is general agreement that the PMv in humans lies ventral to the frontal eye field (FEF). However, the precise location and boundaries of the PMv in humans is uncertain [3,74•].
Matelli et al. [75] suggest that the PMv of monkeys consists of two cytoarchitectonic fields, F4 and F5 (Figure 1a). The connections of F4 with posterior parietal cortex and the responses properties of F4 neurons have led Rizzolatti et al. [76] to suggest that F4 is involved in 'transforming object locations into appropriate movements towards them' (see also [77]). This hypothesis has not been explored by imaging studies in humans. Furthermore, the location or even the existence of a human equivalent of the monkey F4 remains to be established.

The F5 portion of the PMv has received more attention. Rizzolatti et al. [76] have described two types of neurons in monkey F5 that have unique responses to visual stimuli: 'canonical' and 'mirror' neurons [4,76,78,79]. Canonical neurons respond to the visual presentation of three-dimensional objects of different size and shape. The motor responses of these neurons are limited to specific goal-directed actions towards these three-dimensional objects. Canonical neurons are largely found in the portion of the PMv that is buried in the bank of the arcuate sulcus. Mirror neurons are active when a monkey watches someone else perform a specific action, and when the monkey executes a similar action. Mirror neurons are largely found in the portion of the PMs that is on the cortical surface, caudal to the arcuate sulcus.

The unique properties of mirror neurons have prompted the search for the equivalent of F5 in human subjects. Neuroimaging studies have generated conflicting results on this issue. In a recent meta-analysis, Grèzes and Decety [74•] failed to find conclusive evidence for neuronal activation in inferior frontal areas, including ventral portions of area 6, during action observation. In contrast, other studies have reported activation of area 44 during imitation and observation of finger movements [80,81], as well as when objects are gripped and manipulated [60,82,83]. This has led some investigators to suggest that area 44, which has traditionally been considered part of Broca's area, is the human equivalent of the monkey F5 [76,84].

Other results raise doubts over this conclusion. Amunts et al. [85] found considerable variation in the location of the border between area 44 and rostral-ventral area 6, and noted that this border cannot be determined solely on the basis of gyral and sulcal landmarks. Area 44 is strongly activated during tasks that involve silent or covert speech (e.g. [86–88]). Thus, it is possible that activation of area 44 during action observation, in some cases, reflects internal verbalization of the observed action (e.g. [74•]). This view is compatible with the absence of activation in Broca's area during the observation of meaningless hand gestures that cannot be named [89,90]. However, verbalization alone cannot account for all activations related to action observation, which are also found in parts of premotor cortex clearly outside of Broca's area [74•,89–91].

A recent report by Buccino et al. [91] indicates that observation of recognizable face, hand or foot actions resulted in a somatotopically organized pattern of activation that involved all of the prefrontal cortex on the lateral surface (i.e. both the PMd and the presumed PMv). These authors also observed activation in or near Broca's area in the action observation tasks. Thus, the relationship between the activation in area 44 and that observed in portions of area 6 is unclear. Importantly, these results indicate that the human PMv can't be identified solely by the presence of activation during movement observation tasks. In summary, on the basis of previous data, it is not possible to establish a definite correspondence between the functional subdivisions of the monkey PMv and the inferior frontal areas in humans.

Conclusions
The data presented in this review help to clarify the location and boundaries of the premotor areas in the frontal lobe of humans. For many of these areas, there is a clear correspondence with a specific premotor area in the monkey. For other regions, such as the motor fields in inferior frontal cortex, the correspondence with areas in the monkey brain remains to be established. Two regions have generally been considered to be motor fields: the rostral part of area 6 on the medial wall of the hemisphere (pre-SMA), and the rostral part of area 6 on the dorsal surface (pre-PMd). However, both these areas display activation that is more closely related to cognitive than to motor processes. Thus, it might be more appropriate to consider the pre-SMA and the pre-PMd as functional components of prefrontal cortex, rather than as premotor areas. In other cases, cognitive and motor functions appear to have a common anatomical substrate. The RCZa, which may correspond to the CMAr of monkeys, is involved in 'conflict monitoring'. The RCZp, which may correspond to the CMAv of monkeys, appears to be involved in response selection. Other premotor areas, including the SMA proper, the PMd proper and the CCZ, are involved in various aspects of movement generation and control. Overall, we feel that it is important to continue to seek correspondences between motor areas in the monkey and human cortex, as this will result in important insights into the functional organization of the frontal lobe.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
**of outstanding interest


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This meta-analysis shows the involvement of the dorsal and ventral premotor cortex in movement execution and imagination. However, the data reviewed does not support the involvement of inferior frontal areas in movement observation. Three hypotheses regarding PMv location are examined [3]: area 6 on the precentral gyrus adjacent and inferior to the FEF; opercular area 6; area 44. The review suggests that activation in Broca’s area is primarily related to overt or covert verbal processes. On the other hand, inferior area 6 was frequently activated during motor execution or imagery.


