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Anatomical organization of the eye fields in the human and non-human primate frontal cortex

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ABSTRACT

There are several eye fields in the primate frontal cortex. The number and location of these oculomotor control zones remain controversial, especially in the human brain. In the monkey, the frontal eye field (FEF) is located in the rostral bank of the arcuate sulcus at approximately the level of the posterior end of the sulcus principalis, the supplementary eye field (SEF) is located on the dorsomedial frontal cortex, and the cingulate eye field (CEF) in the dorsal bank of the cingulate sulcus. In the human frontal cortex, the location of the FEF varies depending on the method used, electrical stimulation or functional neuroimaging, to establish it. Some investigators have argued that the SEF is located on the medial wall of the frontal lobe but its presumed location remains controversial. The location of the CEF in the human brain is not known. The present article reviews electrophysiological and functional neuroimaging evidence regarding the location of these frontal oculomotor areas in the macaque monkey and human brains and, in light of new findings in the human brain, attempts to reconcile the differences observed in the location of these eye fields using the different techniques. Together, these data suggest the existence of at least four eye fields in the frontal cortex, i.e. the FEF, the SEF, the CEF, and a premotor eye field, and suggest that their anatomical relationships are preserved from monkey to human brain.

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Abbreviations: AS, arcuate sulcus; CEF, cingulate eye field; CG-EF, cingulate sulcus eye field; CgS, cingulate sulcus; CS, central sulcus; FEF, frontal eye field; fMRI, functional magnetic resonance imaging; IP-EF, inferior precentral sulcus eye field; IPSd, dorsal branch of the inferior precentral sulcus; IPSv, ventral branch of the inferior precentral sulcus; MaP, marginal precentral sulcus; MeP, medial precentral sulcus; MeP-EF, medial precentral sulcus eye field; PS, sulcus principalis; S, spur of the arcuate sulcus; SF, Sylvian fissure; SEF, supplementary eye field; SFS, superior frontal sulcus; SPdimple, superior precentral dimple; SP-EF, superior precentral sulcus eye field; SPS, superior precentral sulcus; SPSd, dorsal branch of the superior precentral sulcus; SPSv, ventral branch of the superior precentral sulcus.

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1. Introduction

Within the frontal cortex of the macaque monkey, the performance of voluntary saccadic eye movements involves at least three distinct regions: the frontal eye field (FEF) (Bruce et al., 1985), the supplementary eye field (SEF) (Schlag and Schlag-Rey, 1987a,b) and the cingulate eye field (CEF) (Gaymard et al., 1998a). The location of these areas is relatively well known and has been established with electrical microstimulation of the cortex which has shown that the FEF lies in the concavity of the arcuate sulcus (Bruce and Goldberg, 1985; Bruce et al., 1985; Schall, 1997; Tehovnik et al., 2000), the SEF is located on the mediolateral surface of the brain above the upper branch of the arcuate sulcus (Schlag and Schlag-Rey, 1987a), and the CEF is located in the dorsal bank of the cingulate sulcus (Mitz and Godschalk, 1989), within the rostral part of the cingulate motor area (Dum and Strick, 1991; Mitz and Godschalk, 1989; Wang et al., 2004).

In the human brain, however, the location of these areas remains controversial. The localization of the human homolog of the monkey FEF varies depending on the method used to establish it. The results of functional neuroimaging studies suggest that the FEF of the human brain lies within the dorsal premotor cortex at the junction of the superior precentral sulcus (SPS) with the superior frontal sulcus (SFS) (Astafiev et al., 2003; Corbetta et al., 1998; Gagnon et al., 2002; Grosbras et al., 2005; Koyama et al., 2004; Luna et al., 1998; Paus, 1996; Petit et al., 1997; Petit and Haxby, 1999). On the other hand, the few electrical stimulation studies available suggest that the FEF lies in a more ventral and rostral region, in the most posterior part of the middle frontal gyrus (Blanke et al., 2000; Godoy et al., 1990; Penfield and Jasper, 1954; Penfield and Rasmussen, 1950). The localization of the human homolog of the monkey SEF remains unclear. Grosbras et al. (1999) have carried out a functional magnetic resonance imaging (fMRI) study suggesting that the SEF may be located on the medial wall of the frontal lobe, close to the medial paracentral sulcus (Eberstaller, 1890). Finally, the human homolog of the monkey CEF is not known. Because of the lack of studies examining the human CEF, it cannot be excluded that the region of increased activity on the medial surface of the frontal lobe that Grosbras et al. (1999) reported in relation to oculomotor performance may, in fact, be the homolog of the monkey CEF or an extensive region of functional activity including both the CEF and SEF. It is clear from the above comments that there are major problems regarding our understanding of the organization of the eye fields in the frontal cortex of the human brain and their correspondence with those better studied in the macaque monkey brain. The aim of the present article is to review the evidence concerning the location of the eye fields involved in the control of saccadic eye movements in the frontal cortex of the macaque monkey and human brains, highlight the apparent similarities and differences, and attempt to clarify these issues in the light of new findings obtained in our laboratory. Importantly, note that, in the present review, we define an eye field as a brain region where saccadic eye movements can be elicited with electrical microstimulation or where performance of voluntary saccadic eye movements induces an increased signal during functional neuroimaging.

2. Eye fields in the monkey frontal lobe

2.1. Frontal eye field

2.1.1. Electrophysiological studies

In the 19th century, Ferrier (1875) was able to show that electrical stimulation of a large region within the lateral frontal cortex of anaesthetized monkeys elicits controlateral saccadic eye movements (Fig. 1A). This finding was subsequently confirmed by several investigators in the first half of the 20th century (Crosby et al., 1952; Smith, 1949). In the 1960s, Robinson and Fuchs (1969), using 2 mA stimulation, refined the location of this eye field in the awake monkey, showing that it lay in a large region in front of the arcuate sulcus (Fig. 1B). It must be pointed out here that the extent of the frontal eye field as assessed with electrical stimulation is largely dependent on the current used: the higher the current, the greater the spatial extent of the frontal eye field. Thus, the precise location of the eye fields based on the older studies using high electrical currents to stimulate the cortex must be treated with caution.

The location of this classical frontal eye field, which was referred to as the frontal eye field (FEF) by Foerster (1931), was further specified by Bruce et al. (1985). These investigators showed that microstimulation (i.e. with currents lower than 50 μA) within a limited region of the rostral bank of the arcuate sulcus elicited saccadic eye movements in awake monkeys. This region is located in front of the premotor representation of the arm, hand and mouth (Bruce et al., 1985; Stanton et al., 1989). Although traditionally the FEF has been thought to lie within architectonic area 8, the microstimulation defined FEF was shown to lie in the depth of the anterior bank of the arcuate sulcus, the rostral border being at the transition with area 46 and the caudal border being premotor area 6 (Bruce et al., 1985). Stanton et al. (1989) have also argued that the location of the FEF as defined with low threshold microstimulation exhibits a specific cytoarchitectonic feature, i.e. large neurons in layer V. Indeed, new combined physiological/architectonic studies are now needed to examine the precise relation of the frontal eye field to traditional architectonic areas. Several single unit recording studies have also based the localization of the FEF using such microstimulation parameters (Bruce and Goldberg, 1985; for review, see Bruce et al., 2004; Schall, 2002; Schall and Boucher, 2007; Tehovnik et al., 2000) and the concept of the more restricted classical FEF has been clearly established.

It should be pointed out here that the present review is focussed on the eye fields involved in the control of voluntary saccadic eye movements and does not deal with the small region located ventral to the FEF, in the fundus of the arcuate sulcus, and which is involved with the control of smooth pursuit eye movements (Bruce et al., 1985; Gottlieb et al., 1993; MacAvoy et al., 1991).

2.1.2. Neuroimaging studies

In the past few years, developments in functional magnetic resonance imaging (fMRI) (e.g. Pfeuffer et al., 2007) have permitted assessment of the location of the frontal eye fields in awake

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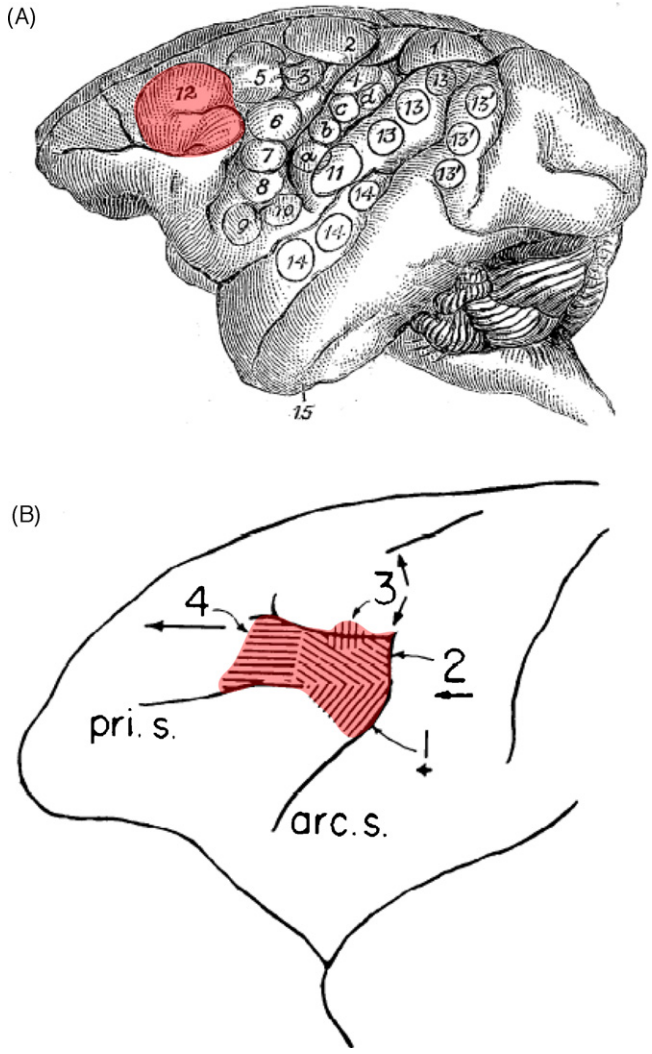


Fig. 1. Location of the FEF as defined by Ferrier (1875) (A), and Robinson and Fuchs (1969) (B). (A) "The circle 12 includes the superior and middle frontal convolution from the antero-parietal sulcus (Huxley), sulcus precentralis (Ecker), to the anterior extremity of the supero-frontal sulcus. The results of stimulation of these convolutions were always so uniform, that the general result of experimentation in ten monkeys may be stated together. The results were: Elevation of the eyebrows and the upper eyelids, turning of the eyes and head to the opposite side, and great dilatation of both pupils. Occasionally on stimulation of the centre for the forward extension of the hand this movement of the eyes and head was called into play. Inferior frontal convolution (including all in advance of the sulcus precentralis). Stimulation of this region gave no results. Antero-frontal region (including all in advance of the anterior extremity of the supero-frontal sulcus, and indicated sometimes by a slight sulcus at right angles to the median fissure) and orbital convolution. These regions were subjected to stimulation in four cases, viz. I, V, VIII, and IX. No results could be observed, either from the antero-frontal or orbital regions. In a later experiment (December 2) on another monkey it was found that stimulation of the frontal part of the brain caused the eyes to move to the opposite side. This was found to be the case with irritation of both right and left hemispheres. The eyelids were not always opened, however, nor was dilatation of the pupils observed. Sometimes also the eyes moved upwards, instead of to the opposite side. Irritation, therefore, of this region gives nothing definite as to their function" (from Ferrier, 1875). (B) "A summary of the four regions which exhibited constant saccadic characteristics. Although regions 1, 2, and 4 produced primarily horizontal movements, it was not unusual to find movements tilted up or down by 30 or even 45 O. In region 3, however, the movements were typically tilted 60 or 75 O up or down. They were 10–20 in. in amplitude, and small displacements of the electrode tip often produced a large change in the amount and direction of tilt" (Reproduced with permission from Robinson and Fuchs, 1969).

monkeys with this methodology. Koyama et al. (2004) carried out an fMRI study in behaving macaque monkeys under conditions involving voluntary saccadic eye movements compared with an ocular fixation control condition. These investigators observed bilateral increases in activity in both the rostral and the caudal banks of the arcuate sulcus, as well as in the spur of this sulcus. This larger region involving the classic FEF in the anterior bank of the arcuate sulcus but, importantly, also extending into its posterior bank and the spur was referred to as the "FEF+". Using a similar protocol, Baker et al. (2006) have also shown increased activity in this larger region than the one observed using electrical microstimulation. Activity increases were observed in the anterior bank of the arcuate concavity, extending onto the adjacent surface area as far as the caudalmost part of the sulcus principalis, and in the posterior bank of the arcuate sulcus spreading into the spur of the arcuate sulcus both above and below it. It should be noted here that the posterior bank of the arcuate sulcus is clearly agranular cortex belonging to premotor area 6. Thus, in addition to the electrical microstimulation studies which concluded that the classical FEF lies just in front of the premotor cortex in the anterior bank of the arcuate sulcus (Bruce et al., 1985), these functional neuroimaging studies suggest that the posterior bank of the arcuate sulcus and the cortex within and around the spur, which belong to the architectonic premotor area 6 (see Fig. 2) may be part of an extended oculomotor control region. These findings are very important, as we will see later, in view of the apparent discrepancies in the location of the frontal eye field in the human and monkey frontal cortex.

2.1.3. Stimulation versus neuroimaging studies: reconciling the two sets of data

As we have seen above, the main difference between the electrical microstimulation and functional neuroimaging techniques in mapping the frontal eye fields in the monkey is that, whereas microstimulation has shown elicited saccadic eye movements from the anterior bank of the arcuate sulcus (FEF), functional neuroimaging has shown activity increases within both the anterior and posterior banks of the arcuate sulcus (FEF+). In addition, Moschovakis et al. (2004) have carried out a [^{14}C]-2-deoxyglucose functional imaging study in monkeys performing a saccade task and clearly demonstrated that saccade-related activation was located in both the anterior and the posterior banks of the arcuate sulcus, including its spur. This difference in findings between electrical stimulation and functional neuroimaging may be due to several factors. First, the 50 μA threshold broadly used in microstimulation studies to map the FEF in the monkey is arbitrary and may underestimate the extent of this region. Second, the posterior bank of the arcuate sulcus is often not explored in detail in many of the FEF studies. It should here be noted that there is some evidence from microstimulation and electrophysiological recording that a part of the agranular premotor cortical area 6 may be involved in the performance of saccadic eye movements (Fujii et al., 1998, 2000; Preuss et al., 1996). Thirdly, some of the difference in results between microstimulation and fMRI studies may be partly explained by the fact that eye blinking occurs commonly during the performance of saccadic eye movements (Evinger et al., 1994) and some of the activity observed in fMRI studies may have been due to blinking. Interestingly, Bruce et al. (1985) have shown that the microstimulation of the posterior bank of the arcuate sulcus, which is part of premotor area 6, evokes eye blink responses. Thus, the extensive region of increased activity during saccadic eye movements observed in functional neuroimaging studies involving both the anterior and posterior banks of the arcuate concavity (i.e. the "FEF+") could refer to a combination of activity due to the performance of the saccadic eye movements and the associated eye blinking responses. These results suggest that the anterior bank of the arcuate sulcus belonging to a special part of area 8 and the posterior bank of the arcuate sulcus and the spur which belong to area 6 may be involved in the performance of saccadic eye

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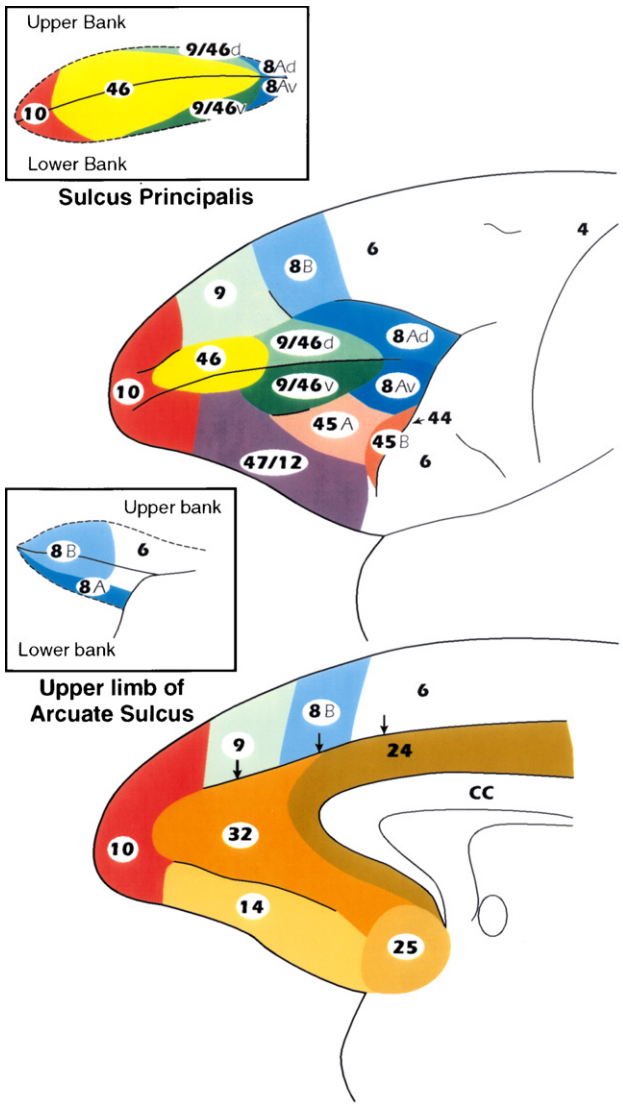


Fig. 2. Architectonic map of the lateral and medial surfaces of a monkey brain (Petrides and Pandya, 1994).

movements. It has been suggested that premotor cortex may play a role in blinking movements (Bruce et al., 1985) and in coordinating eye–arm movements (Fujii et al., 2000), but the respective role of these two regions in the control of saccadic eye movements remains to be elucidated.

2.2. Supplementary eye field

2.2.1. Electrophysiological studies

Brinkman and Porter (1979) were the first to suggest the existence of an eye field, with a surface area of 4 mm^2, close to the medial wall in the caudal part of the dorsolateral region of the frontal lobe, above the superior branch of the arcuate sulcus. Schlag and Schlag-Rey (1987a) later named this region the supplementary eye field (SEF) and reported it to have a surface area of 42 mm^2 (see Fig. 3). Since then, several stimulation and unit recording studies have confirmed the existence of the SEF in the monkey (Bon and Lucchetti, 1991, 1992; Chen and Tehovnik, 2007; Chen and Wise, 1995a,b, 1996, 1997; Coe et al., 2002; Fujii et al., 1995, 2002; Hanes et al., 1995; Huerta and Kaas, 1990; Isoda and Tanji, 2002; Lee and Tehovnik, 1995; Martinez-Trujillo et al., 2003a,b, 2004; Missal and Heinen, 2001, 2004; Mitz and Godschalk, 1989; Moorman and Olson, 2007; Mushiake et al., 1996; Olson and Gettner, 1995, 1999, 2002; Olson et al., 2000; Olson and Tremblay, 2000; Pouget et al., 2005; Russo and Bruce, 1993, 1996, 2000; Schall, 1991a,b; Schlag-Rey et al., 1997; Schlag and Schlag-Rey, 1987a,b; Schlag et al., 1992; Sommer and Tehovnik, 1999; Tehovnik, 1995; Tehovnik and Lee, 1993; Tehovnik et al., 1994, 1999, 1998, 2000; Tehovnik and Sommer, 1997; Tian and Lynch, 1995; Tremblay et al., 2002; Ventura et al., 2002). It is interesting to note that, across studies, the precise location and the surface extent of the SEF exhibits variability, ranging from 4 to 70 mm^2 in extent, involving the rostrodorsal part of area 6 above the superior branch of the arcuate sulcus (area F7 of Matelli et al., 1991) and extending sometimes into the medial wall of the brain (Tehovnik and Lee, 1993; for review, see Tehovnik, 1995). Thus, the SEF cannot be precisely located on the basis of obvious anatomical landmarks such as the rostral end of the superior branch of the arcuate sulcus, since sometimes it spreads further anterior or further posterior, forcing investigators to microstimulate this region to establish precisely its location prior to studies of its function. The significant difference in the reported size of the SEF region most probably depends on the strength of the stimulation current and the behavioural paradigm used.

2.2.2. Neuroimaging studies

Only one fMRI study carried out on behaving monkeys reported increased activity in the SEF (Baker et al., 2006). In this fMRI study of macaque monkeys performing voluntary saccades, the SEF was located on the dorsomedial aspect of the lateral frontal cortex, above the rostral end of the superior branch of the arcuate sulcus. The activated region was smaller than the one observed in many electrical stimulation studies. In addition, in the [^{14}C]-2-deoxyglucose functional imaging study carried out by Moschovakis et al. (2004), saccade-related activation was found on the dorsomedial frontal cortex at a distance of about 4 mm from the medial wall, starting at the level of the rostral end of the superior branch of the arcuate sulcus and extending posteriorly on a surface area 10 mm long × 2 mm wide.

2.3. Cingulate eye field

Several motor areas exist within the cingulate sulcus. Dum and Strick (1991), based on projection patterns to the primary motor cortex (M1) and the spinal cord, subdivided the cingulate motor cortex in two main regions: the rostral and the caudal cingulate motor areas (CMAr and CMAc). The CMAc is itself subdivided into a dorsal and a ventral part (CMAd and CMAv). CMAd is found in architectonic area 6, CMAv in area 23c, and CMAr in area 24c. In addition, it has been shown that the cingulate motor cortex projects to the FEF and the SEF (Bates and Goldman-Rakic, 1993; Huerta and Kaas, 1990). Specifically, Wang et al. (2004) have shown that two regions of the cingulate cortex project to the FEF, suggesting the existence of rostral and caudal cingulate eye fields. According to these authors, the rostral CEF is located rostral to CMAr and the caudal CEF is adjacent to CMAc. Using microstimulation, Mitz and Godschalk (1989) have also demonstrated the presence of a region in the dorsal bank of the cingulate sulcus where saccadic eye movements can be elicited, in area 24c posterior to the genu of the corpus callosum, just ventral to the SEF. Finally, in the [^{14}C]-2-deoxyglucose functional imaging study by Moschovakis et al. (2004), saccade-related activation was found in a large region of the cingulate cortex. More experiments would be required to assess the exact number and location of the monkey CEFs as well as their functional roles (see Schall and Boucher, 2007 for the possible role of the anterior cingulate cortex in the control of saccadic eye movements).

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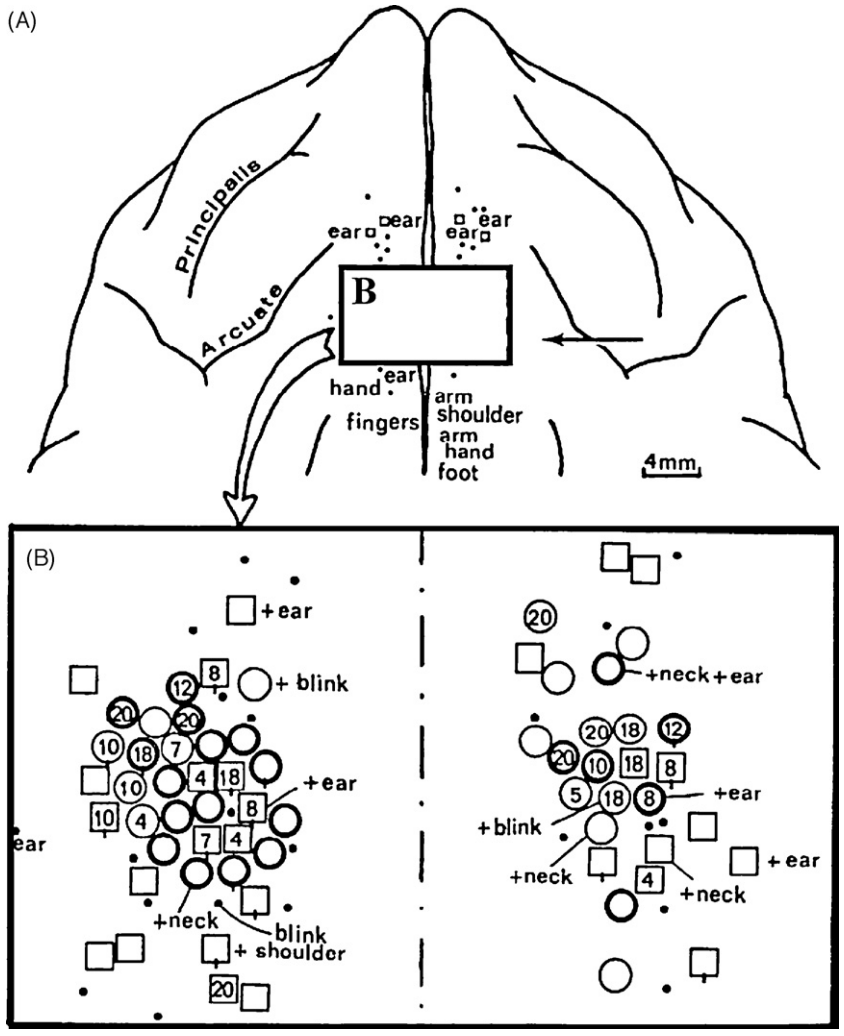


Fig. 3. Location of the SEF as defined by Schlag and Schlag-Rey (1987a). "Mapping of motor responses to stimulation. (A) Dorsal view of frontal pole of monkey brain; rostral end is up. (B) Enlarged view of rectangular area outlined in A. Types of responses mapped at sites of microelectrode penetrations. Circles: fixed-vector saccades. Heavy circles: amplitude 4 O. Squares: converging saccades. Numbers: threshold values when lower than 20 PA. Small vertical bars appended to circles and squares: latencies lower than 50 ms. Dots: no saccades evoked. Other types of movements observed are specified. Map includes all identified tracks in 4 brains, with reference to location of arcuate angle. When several saccadic responses were found along the same tracks, the values indicated refer to the lowest threshold, amplitude, and latency" (Reproduced with permission from Schlag and Schlag-Rey, 1987a).

3. Eye fields in the human frontal lobe

3.1. Frontal eye field

3.1.1. Electrophysiological studies

In the early part of the 20th century, Foerster (1931) attempted to identify the homolog of the monkey FEF in the human frontal lobe using electrical stimulation in epileptic patients undergoing brain surgery and concluded that this region was in the posterior part of the middle frontal gyrus. Subsequently, Rasmussen and Penfield (1948) demonstrated that stimulation of a region larger than the one described by Foerster evoked saccadic eye movements. This region involved the caudalmost parts of the inferior, middle, and superior frontal gyri, as well as the rostral part of the precentral gyrus. More recently, it has been shown that the FEF defined by low threshold electrical stimulation is located just anterior to the superior precentral sulcus, rostral to the premotor representation of the arm (Blanke et al., 2000; Godoy et al., 1990; Lobel et al., 2001; Yamamoto et al., 2004).

3.1.2. Neuroimaging studies

In functional neuroimaging studies based on group analysis (i.e. the averaging of signal across several brains), a region of increased activity in relation to saccadic eye movements has consistently been found at the intersection of the superior precentral sulcus with the superior frontal sulcus (Astafiev et al., 2003; Corbetta et al., 1998; Ettinger et al., 2008; Gagnon et al., 2002; Grosbras et al., 2005; Koyama et al., 2004; Luna et al., 1998; Paus, 1996; Petit and Haxby, 1999). This region, which has been interpreted as the homolog of the macaque monkey FEF, appears to be located much more dorsal and caudal than one might have expected from macaque monkey studies and also more caudal than the one identified in electrical stimulation studies of the human brain.

In addition, functional neuroimaging studies revealed other increases in activity related to the performance of saccadic eye movements in the premotor cortex (area 6), in the middle precentral gyrus. A few studies have associated this region to the blinking inherent to the performance of such a task but its functional role remains poorly understood (Kato and Miyauchi, 2003a,b). Interestingly, this result is similar to the one observed in fMRI studies in the monkey. It is, therefore, possible that some of the increased activity observed in the posterior bank of the arcuate sulcus and in the spur in the monkey in neuroimaging studies (Baker et al., 2006) may relate to the increased activity observed in the dorsal branch of the inferior precentral sulcus in

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the human brain since both refer to Brodmann's area 6. However, further studies examining electrical stimulation with cytoarchitectonic analysis in the monkey and examination of the architecture of the regions where activation related to eye movements in humans will be needed to establish any firm conclusions about the architectonic areas within which the frontal eye fields lie.

3.1.3. Stimulation versus neuroimaging studies: reconciling the two sets of data

Interestingly, as in the monkey, electrical stimulation and functional neuroimaging provide somewhat different results regarding the location of the FEF in the human brain. This discrepancy could be partly due to the fact that the extent of the FEF in stimulation studies depends on the electrical current used (as in the monkey) and the relatively limited region that is inevitably explored, but also to the fact that group analyses commonly used in neuroimaging studies provide only an approximate general location of the activity peaks. In a recent fMRI study, we examined the location of the FEF in individual subjects and tried to relate it to the local morphological variability in individual brains. This research demonstrated that the FEF was consistently located within the ventral branch of the superior precentral sulcus, *below* the point of intersection between the superior precentral sulcus and the superior frontal sulcus (Amiez et al., 2006). Our results indicated that, because of the significant local variation in the morphology of human brains, group analysis commonly used in fMRI studies can only provide a general approximate location of any functional peak and does not allow relating the precise location of activity increases to specific sulci or gyri. The individual subject analysis that we carried out relating variability in sulcal morphology and functional activation showed that the FEF in the human brain, as in the monkey, lies slightly anterior and ventral to the premotor hand representation. Our results are consistent with the electrical stimulation studies in the human brain showing the FEF to lie in the caudal part of the middle frontal gyrus close to and within the ventral branch of the superior precentral sulcus (Blanke et al., 2000; Godoy et al., 1990; Lobel et al., 2001; Yamamoto et al., 2004).

As pointed out above, there has been a tendency to interpret the increased activity observed in the human brain in neuroimaging studies at the intersection between the caudal end of the superior frontal sulcus and the superior precentral sulcus as the homolog of the monkey classic FEF observed in the arcuate sulcus concavity. It has always appeared paradoxical that this peak in the human brain is located much more dorsal and caudal than one might have expected from macaque monkey studies. It is widely assumed that the macaque FEF lies in area 8, although microstimulation studies have shown that it extends quite deep in the anterior bank of the arcuate sulcus reaching its fundus where the architecture is dysgranular, an area that clearly is not part of the granular area 8. Thus, even in the monkey the FEF may lie in a special part of the cortex at the intersection between granular area 8 and agranular area 6. Furthermore, there has been a systematic bias to search for the FEF in the anterior bank of the arcuate sulcus and to make only a few penetrations in the posterior bank where agranular premotor cortex (area 6) is found (for review, see Schall, 2002; Schall and Boucher, 2007; Tehovnik et al., 2000). Given that functional neuroimaging studies in the monkey clearly show that a large part of area 6 contains eye field representations, one should be careful in relating the increased activity found at the intersection between the superior precentral sulcus and the caudal end of the superior frontal sulcus in the human brain to the classic monkey FEF lying in the anterior bank of the arcuate concavity. Further functional and architectonic investigations in both species will be required before firm conclusions can be reached.

3.2. Supplementary eye field

3.2.1. Electrophysiological studies

Foerster (1931), using electrical stimulation in patients undergoing brain surgery, was the first to identify a region related to eye movement within the dorsomedial aspect of the frontal cortex in the human brain. Similar observations were subsequently made by Penfield and Jasper (1954), Penfield and Rasmussen (1950), and Penfield and Welch (1951) who suggested that an eye-related region may be located in Vogt's area 6aα (Vogt and Vogt, 1919), rostral to the supplementary motor area. These data have been recently replicated and extended, suggesting that a SEF may be located rostral to the supplementary motor area (Fried et al., 1991; Godoy et al., 1990; Yamamoto et al., 2004).

3.2.2. Neuroimaging studies

Using fMRI and single-subject analysis, Grosbras et al. (1999) showed a large increase in activity related to the performance of saccadic eye movements on the medial wall of the human brain, in the paracentral sulcus as defined by Ono et al. (1990). Thus, the SEF appears to be located within the sulcus that forms the rostral border of the paracentral lobule. The study by Grosbras and colleagues raises two issues. First, the paracentral sulcus used as a landmark by Grosbras et al. (1999) has been inconsistently labeled as the medial precentral or the paracentral sulcus by Ono et al. (1990). In a detailed study of the morphology of the posterior precentral region of the human brain, Germann et al. (2005) were able to dissociate consistently the medial precentral sulcus from the medial paracentral sulcus in individual subjects. Consequently, given the ambiguity in the definition of the sulcal landmark used to define the location of the SEF (Grosbras et al., 1999), one might expect some ambiguity in the location of the SEF. Second, close examination of the results in individual subjects in the Grosbras et al. study (see Fig. 2 in Grosbras et al., 1999) suggests that the location of the activity can often be linked to the cingulate sulcus in addition to the paracentral sulcus. It is therefore possible that the region of increased activity reported by Grosbras et al. (1999) as the SEF might encompass the SEF, the eye field located in the cingulate sulcus (CEF) or both the SEF and CEF.

3.3. Cingulate eye field

There is some evidence from a positron emission tomography study by Paus et al. (1993) that the performance of saccadic eye movements in response to conditional visual cues induced increased activity in two regions of the cingulate cortex, within the cingulate sulcus. Furthermore, a study assessing oculomotor behaviour in patients with lesions including the cingulate cortex revealed deficits in the control of eye movements when the posterior part of the anterior cingulate cortex was damaged (Gaymard et al., 1998b). Thus, the presence of one or more eye fields in the human cingulate sulcus as well as their location remains controversial.

3.4. Evidence of the existence of four eye fields in the human frontal lobe

In order to define more precisely the location of the different eye fields in the human brain, we carried out an fMRI study while subjects performed a saccadic eye movement task and an ocular fixation task (Fig. 4). The data analysis was carried out on a subject by subject basis in order to establish the increase in activity in relation to the local morphological variability in the sulcal and gyral pattern of individual brains. The results concerning the frontal eye field have been previously published (Amiez et al., 2006). In order to determine the location of the brain regions

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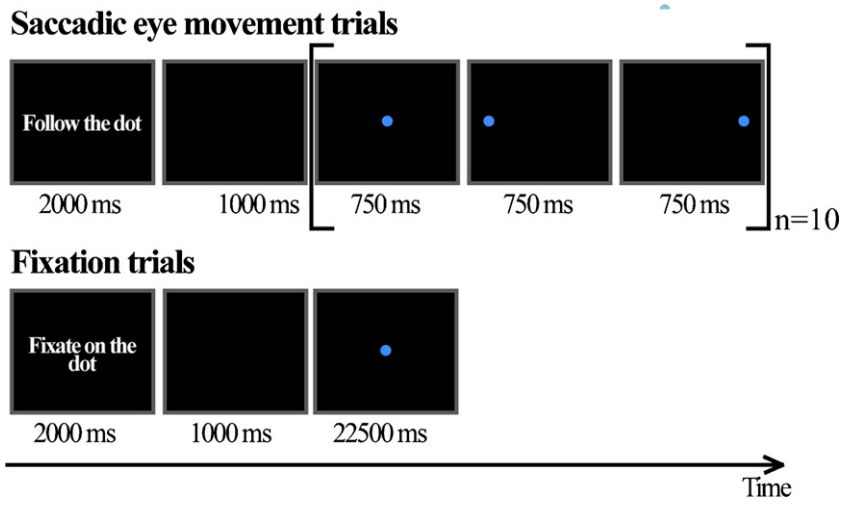


Fig. 4. Saccadic eye movement paradigm reproduced from Amiez et al. (2006). "Saccadic eye movement task and ocular fixation control task. The sentences "Follow the dot" and "Fixate on the dot" instructed the subject to perform saccadic eye movements or to fixate, respectively. During the saccadic eye movement trials, a dot was presented in one of three possible locations on the screen (i.e., left, center or right) for 750 ms in each location for a total of 22.5 s. The subjects had to perform a saccade to follow the dot to its current location on the screen. During the ocular fixation trials, the subjects had to fixate on the dot presented in the center of the screen for 22.5 s" (Reproduced with permission from Amiez et al., 2006).

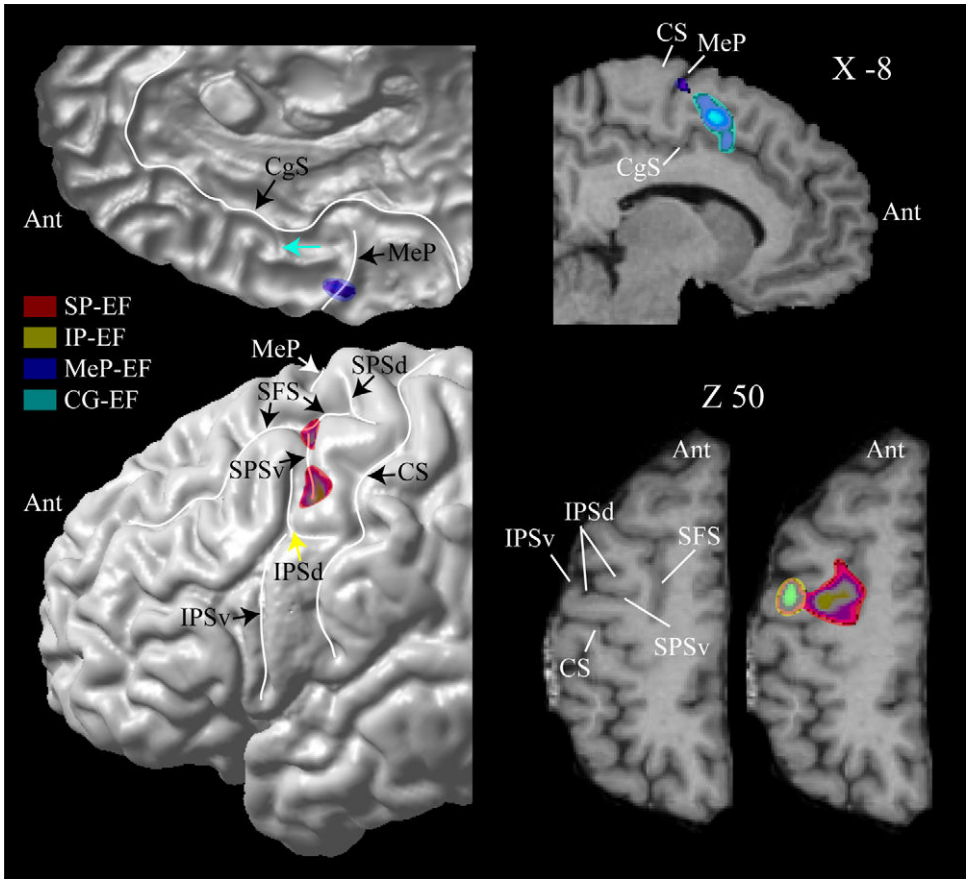


Fig. 5. Location of the SP-EF, IP-EF, MeP-EF, and CG-EF in a typical subject. The foci of activity within the SP-EF, IP-EF, MeP-EF, and CG-EF resulting from the comparison between saccadic eye movements and fixation are represented on a lateral and a medial view of the cortical surface rendering in standard stereotaxic space of the left hemisphere of a typical subject (left diagrams). The light blue and the yellow arrows indicate the point of the cingulate sulcus and the dorsal branch of the inferior precentral sulcus in the depth of which the CG-EF and the IP-EF are located, respectively. The diagrams on the right side represent sagittal and horizontal sections. The data demonstrate that the SP-EF is located in the ventral branch of the superior precentral sulcus, the IP-EF is located in the dorsal branch of the inferior precentral sulcus, the MeP-EF is located within the medial precentral sulcus and spreads out in front of this sulcus, and the CG-EF is located in the vertical branch of the cingulate sulcus. *Abbreviations*: CS, central sulcus; MeP, medial precentral sulcus; MaP, marginal precentral sulcus; SFS, superior frontal sulcus; SPSd, dorsal branch of the superior precentral sulcus; SPSv, ventral branch of the superior precentral sulcus; IPSd, dorsal branch of the inferior precentral sulcus; IPSv, ventral branch of the inferior precentral sulcus; CgS, cingulate sulcus.

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involved in the performance of saccadic eye movements, we compared differences in activity based on the comparison of a saccadic eye movement condition with an ocular fixation condition (Amiez and Petrides, 2008). In order to assess the exact location of the peaks of activity in relation to local morphological features, we examined the peaks observed at the group level also in each individual brain. We refer to the peaks of activity increases observed by the sulcus within which they were observed, and not on a priori judgments of the macaque monkey areas to which they may correspond (e.g. FEF, SEF, CEF). Four regions of increased activity were observed. There was an eye field (EF) peak consistently located in the ventral branch of the superior precentral sulcus (SP-EF) which was originally reported by Amiez et al. (2006), an eye field region located in the dorsal branch of the inferior precentral sulcus (IP-EF), a peak located rostral to the medial precentral sulcus (MeP-EF) at the border of the lateral and medial surfaces of the brain, and a peak in the vertical branch of the cingulate sulcus (CG-EF), anterior to the medial precentral sulcus. The location of these eye-related peaks, the SP-EF, the IP-EF, the MeP-EF, and the CG-EF, are represented in a typical subject in Fig. 5.

These results clearly demonstrate the existence of four distinct activity increases in the frontal lobe in the human brain. Two of them are located on the lateral surface of the frontal cortex (i.e. the SP-EF and IP-EF), one of them at the border between the medial and the lateral surfaces of the frontal cortex (i.e. MeP-EF), and one on the medial wall of the frontal cortex, within the cingulate sulcus (i.e. CG-EF). Our data demonstrate that these regions can be located reliably on the basis of the sulcal and gyral pattern in each individual brain.

Two issues must be considered here. First, since we observed two increases in activity on the lateral surface of the frontal cortex, is the SP-EF or the IP-EF the human homolog of the monkey FEF? Concerning the SP-EF, we can reasonably conclude that it corresponds to the FEF that is usually reported in neuroimaging studies of the human brain (Astafiev et al., 2003; Corbetta et al., 1998; Gagnon et al., 2002; Gitelman et al., 2002; Grosbras et al., 2005; Kato and Miyauchi, 2003a,b; Koyama et al., 2004; Luna et al., 1998; Paus, 1996; Petit and Haxby, 1999). Concerning the IP-EF, previous studies suggested that this region within premotor area 6 may be involved in eye blinking processes (Kato and Miyauchi, 2003a,b). The stereotaxic coordinates ($x = -51$, $y = -1$, $z = 40$) provided by Kato and Miyauchi (2003a) corresponds to the activity focus that we observed ($x = -52.1$, $y = -3.9$, $z = 44$). We can therefore hypothesize that our IP-EF might correspond to the eye blinking area within the premotor area 6, but further studies are needed to clarify this issue.

Second, we clearly show two distinct regions, close to each other, on the medial wall of the frontal lobe. Thus far, except for the neuroimaging study showing activity in the cingulate cortex in oculomotor behaviour in the context of a conditional task (Paus et al., 1993), only one activity focus has been reported in the medial wall in neuroimaging studies of saccadic eye movements. This activity focus has been referred to as the SEF (Gagnon et al., 2002; Grosbras et al., 1999; Heinen et al., 2006; Koyama et al., 2004; Petit and Haxby, 1999). In the monkey, the SEF has always been reported on the mediolateral surface of the brain, whereas in the human brain its presumed homolog has been reported to be on the medial surface and not extending on the lateral surface (for review, see Tehovnik et al., 2000).

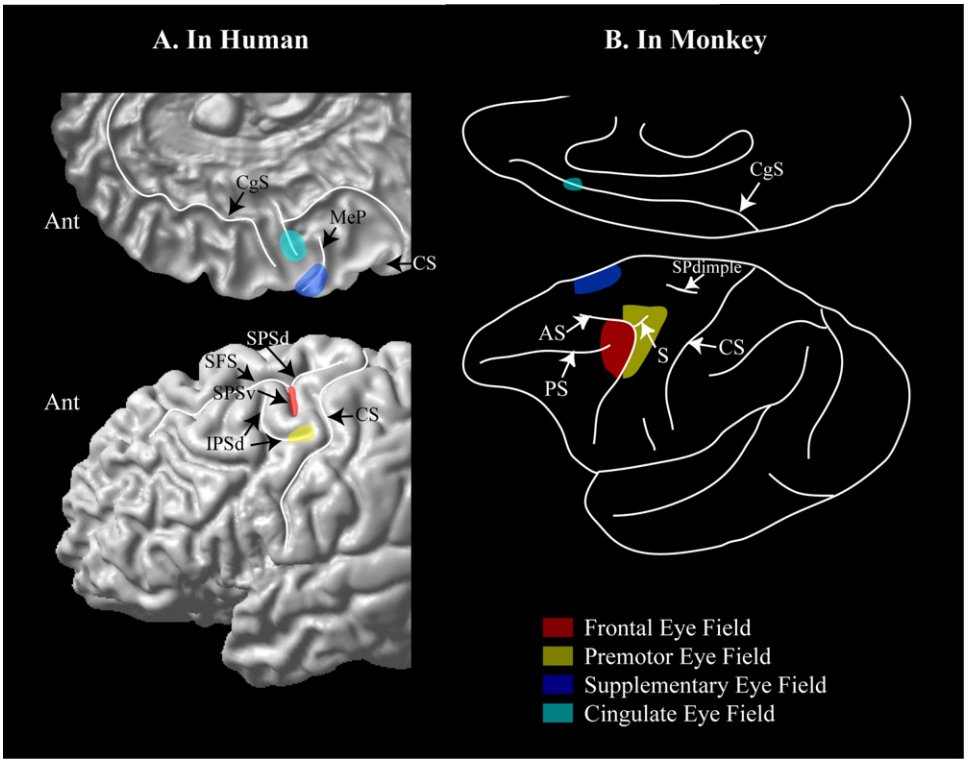


Fig. 6. Location of the SP-EF/FEF, MeP-EF/SEF, CG-EF/CEF, and the IP-EF/premotor eye field in human/monkey. (A) Location of the SP-EF, the IP-EF, the MeP-EF, and the CG-EF represented on the cortical surface rendering in standard stereotaxic space of the left hemisphere of the lateral and the medial surfaces of one standard human brain. The red, yellow, dark blue, and light blue regions indicate the location of the SP-EF, the IP-EF, the MeP-EF, and the CG-EF, resulting from the comparison between visuo-motor hand conditional trials and ocular fixation trials. *Abbreviations*: CS, central sulcus; SFS, superior frontal sulcus; SPSd, dorsal branch of the superior precentral sulcus; SPSv, ventral branch of the superior precentral sulcus; MaP, marginal precentral sulcus; IPSd, dorsal branch of the inferior precentral sulcus; CgS, cingulate sulcus. (B) Location of the FEF, SEF, CEF, and the premotor eye field represented on the left hemisphere of one standard monkey brain based on neuroimaging studies (Baker et al., 2006; Koyama et al., 2004). The red, yellow, dark blue, and light blue regions indicate the location of the FEF, the premotor eye field, the SEF, and the CEF. *Abbreviations*: CS, central sulcus; PS, principalis sulcus; AS, arcuate sulcus; SPdimple, superior precentral dimple; CgS, cingulate sulcus; S, spur.

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It must be emphasized here that the distinction between two eye fields in the medial surface of the human brain can be difficult because of the organization of the human cingulate sulcus, which can be a simple single sulcus or a double sulcus and, furthermore, may be segmented or not (Vogt et al., 1995). When the cingulate sulcus is simple, area 24 occupies the ventral bank of the cingulate cortex and area 32 occupies the dorsal bank of the cingulate cortex, as in the monkey (Petrides and Pandya, 1994). However, when the cingulate sulcus is double (i.e. two parallel sulci), area 24 occupies the first sulcus located closer to the corpus callosum and area 32 occupies the sulcus located on top of this sulcus. Thus, in the case of a double cingulate sulcus, the cingulate cortex occupies a large part of the medial wall, approaching the SEF. It is of interest here that Moschovakis et al. (2004) have shown that both areas 24 and 32 demonstrated saccade-related activation in their [^{14}C]-2-deoxyglucose functional imaging study in the monkey and that both areas projected to extraocular motoneurons, indicating their role in the performance of saccadic eye movements.

Consequently, single-subject analysis is of importance to study the dissociation between the SEF and the CEF using functional neuroimaging. Indeed, our study shows two peaks related to eye movement performance on the medial wall of the frontal lobe (see Figs. 5 and 6). We suggest that our MeP-EF might correspond to the human homolog of the monkey SEF, as it is located at the border between the lateral and the medial surfaces of the brain, and that our CG-EF may correspond to the human homolog of the monkey CEF. In addition, we show here that the SEF is consistently located in the medial precentral sulcus, and not in the paracentral sulcus as previously described (Grosbras et al., 1999). Our results suggest that the peak of activity described as the human homologue of the SEF by Grosbras et al. may correspond to an extensive region of medially located activity that includes the homologs of both the SEF and the CEF.

4. Conclusions: comparison of the macaque monkey with the human frontal eye fields

In the monkey, on the antero-posterior axis, the CEF is found on the medial wall ventral and slightly anterior to the SEF which is itself slightly anterior and dorsal to the classic FEF. In turn, the classic FEF in the anterior bank of the arcuate concavity lies immediately anterior to the premotor eye field (see Fig. 6B). In the human, based on our data, we show that the CEF (MNI y coordinate = −3, z coordinate = 56) is located anterior and ventral to the SEF (MNI y coordinate = −9, z coordinate = 70.5), which is located slightly anterior and dorsal to the FEF (MNI y coordinate = −9.8, z coordinate = 54.4) (see Fig. 6A). The premotor eye field (MNI y coordinates = −3.9, z coordinates = 44), by contrast, is located anterior and ventral to the FEF. Altogether, these data suggest that the anatomo-functional relationships between the FEF, the premotor eye field, the SEF, and the CEF, are relatively well preserved from monkey to human.

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