An Anatomical Landmark for the Supplementary Eye Fields in Human Revealed with Functional Magnetic Resonance Imaging

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Together with the frontal and parietal eye fields, the supplementary eye field (SEF) is involved in the performance and control of voluntary and reflexive saccades and of ocular pursuit. This region was first described in non-human primates and is rather well localized on the dorsal surface of the medial frontal cortex. In humans the site of the SEF is still ill-defined. Functional imaging techniques have allowed investigation of the location and function of the SEF. However, there is great variability with regard to the published standardized coordinates of this area. We used here the spatial precision of functional magnetic resonance imaging (fMRI) in order to better localize the SEF in individuals. We identified as the SEF a region on the medial wall that was significantly activated when subjects executed self-paced horizontal saccades in darkness as compared to rest. This region appeared to be predominantly activated in the left hemisphere. We found that, despite a discrepancy of >2 cm found in the standardized Talairach coordinates, the location of this SEF-region could be precisely and reliably described by referring to a sulcal landmark found in each individual: the upper part of the paracentral sulcus.

Introduction

Three main areas in the cortex of primates are known to be specifically dedicated to the performance of eye movements: the frontal eye fields (FEF) in the precentral sulcus; the supplementary eye fields (SEF) on the dorsomedial frontal lobe, in the region of the supplementary motor area (SMA); and the parietal eye field (PEF) in the intraparietal sulcus. Nonetheless, at least in man, the functional status and the anatomical location of these areas remain to be further clarified. As Rizzolatti and others proposed (Rizzolatti, 1998), the organization of the brain may be understood as a constellation of well-delineated areas, interconnected in order to form very specific functional circuits. These authors pointed out the fine connectivity between parietal and frontal areas forming networks dedicated to a particular action or task. In this context it is of great interest to locate precisely the cortical areas so as to allow, in further functional imaging studies, a reliable identification of the elements that constitute the circuits activated in a given task. In the present study we focused on the localization of the SEF in man, using the spatial resolution of functional magnetic resonance imaging (fMRI).

The SEF was first defined by Schlag and Schlag-Rey in the macaque monkey as the bilateral area in the dorsomedial frontal cortex in which an electrical low-current stimulation elicits eye movements, and where unit activity is related to eye movements (Schlag and Schlag-Rey, 1987, 1992; Tanji, 1994; Tehovnik, 1995). More recently, the SEF has been fairly well characterized and localized in non-human primates cortex, by stimulation as well as connectivity studies. In the macaque monkey, the site from which saccades are evoked by small electrical currents (<50 μA) is limited to a small area several millimeters medial to the superior limb of the arcuate sulcus, at the same anteroposterior level as the pre-SMA, but more dorsal and lateral (see Fig. 1) (Huerta and Kaas, 1990). The SEF shares anatomical links with the FEF and the superior colliculus as well as with thalamic nuclei involved in the control of eye movements (Luppino *et al.*, 1991; Matelli *et al.*, 1991). It presents units which discharge during execution and/or preparation of saccades or during conditional learning of saccadic eye movements.

In humans, evidence for the existence of an area on the medial wall linked to eye movements, which can be assimilated to the SEF, has been gathered for a long time. Nevertheless, the anatomical position of the SEF is still ill-defined. First, many reports of eye movements following cortical stimulations can be related to the definition of the SEF established by Schlag and Schlag-Rey in macaque monkeys (Schlag and Schlag-Rey, 1987), i.e. the area of the dorsomedial frontal cortex, in contiguity with the SMA, where stimulation induces saccades. In their extraoperative electrical stimulation study, Penfield and Welch described eye responses elicited from the mesial superior frontal gyrus (Penfield and Welch, 1951). Talairach and Bancaud also demonstrated eye deviations, in association with head movements, when stimulating sites on the interhemispheric surface, anterior to the sites from where upper limb movements were evoked (Talairach and Bancaud, 1966). Several studies have confirmed that low-current stimulation into the frontal medial wall, in both hemispheres, can induce eye movements similar to those they observed when stimulating the frontal eye fields (Godoy *et al.*, 1990; Fried *et al.*, 1991; Lim *et al.*, 1994). Furthermore, oculomotor deficits have been reported in patients with lesions of the medial Brodman area 6, but these lesions included a large part of the SMA (Gaymard *et al.*, 1990, 1993; Israël *et al.*, 1995).

Functional imaging studies of saccades – using positron emission tomography (PET) and fMRI – have confirmed the importance of a specific region of the dorsomedial area 6 for the control of eye movements. This region has been named SEF, by analogy with the field described in non-human primates. SEF activation has been described for voluntary saccades, either self-paced (Petit *et al.*, 1993, 1996), visually guided or memory guided (Fox *et al.*, 1985; Darby *et al.*, 1996; Anderson *et al.*, 1994; O'Sullivan *et al.*, 1995; Petit *et al.*, 1996; Luna *et al.*, 1998), for executed as well as imagined saccades (Lang *et al.*, 1994; Law *et al.*, 1997), and in antisaccades tasks (O'Driscoll *et al.*, 1995; Sweeney *et al.*, 1996; Doricchi *et al.*, 1997). However, there is a variability in the published standardized coordinates of at least 26 mm for both hemispheres (see Table 1), even for studies that used very similar paradigms. This variability could reflect real differences in the functional localization of the SEF between individuals and the loss of information in combining data from several individuals. This variability could also be a consequence of the process of data normalization into standard stereotactic space, which does not always respect individual anatomical

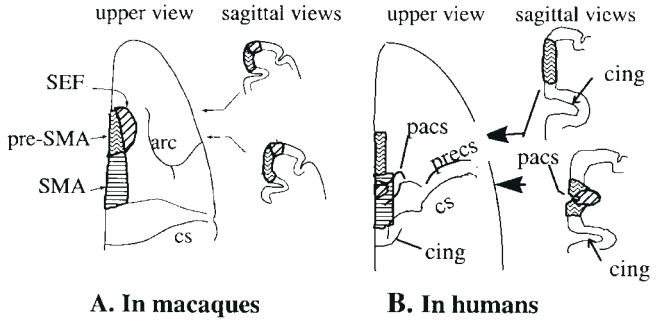

Figure 1. SEF localization relative to SMA and pre-SMA in macaque monkeys (*A*, adapted from Tanji *et al.*, 1994) and in the humans (*B*, extrapolated from our data). arc, arcuate sulcus; cing, cingulate sulcus; cs, central sulcus; pacs, paracentral sulcus; precs, precentral sulcus.

landmarks, especially local sulcal topography (Rademacher *et al.*, 1993). For example, Zilles reported that: 'based on his experience with 15 human brains, the Talairach and Tournoux atlas has a problem with the most dorsal cortex, resulting in an error of greater than 1 cm. Since this distance is approximately that of one gyrus in the human cerebral cortex, the possibility for serious anatomic errors must be considered carefully' (Wise *et al.*, 1996). The precise localization of human SEF remain to be clarified taking into account these considerations.

A recent fMRI study (Luna *et al.*, 1998) has already provided a description of the cortical oculomotor circuit, more precise than the descriptions given by PET studies. Luna and collaborators investigated activation in dorsal frontal and parietal cortex during a visually guided saccades task compared to fixation. They described foci of activation in FEF, SEF and different zones in parietal cortex (PEF), and discussed the anatomical homology with the macaque monkey oculomotor areas. Their study gives a useful overview of the dorsal oculomotor fields in the human dorsal cortex involved in reflexive, visually guided saccades. However, as the SEF appears to be a part of the SMA region, it may be useful to study it in the light of the knowledge we have about this latter area. The SMA, sometimes named a 'supra-motor' area, is known to be especially involved in the control of endogenous sequences of movement (Halsband, 1994; Tanji *et al.*, 1994). Electrophysiological data from non-human primates and experimental and clinical studies in humans all arrive at the conclusion that the SMA is crucially involved when a correct motor sequence is determined on the basis of internalized information. For instance, Fried *et al.* observed, when stimulating the SMA in patients, that this region is more involved in the intention to perform a motor act, rather than in simply monitoring the muscular contraction (Fried *et al.*, 1991). A vast corpus of studies has already underlined and discussed the physiological distinction between reflexive and self-paced motor acts (Passingham, 1993; Pierrot-Deseilligny *et al.*, 1995, Deubel, 1995). SMA lesions in humans do not affect reflexive saccades to peripheral visual targets (Gaymard *et al.*, 1990, 1993, Paus *et al.*, 1991, Heide and Kompf, 1998), whereas sequencing memory-guided saccades is severely impaired. Considering these facts it seemed to us of great importance to study the SEF using a task where the oculomotor acts are endogenous, preventing external visual trigger.

Considering all these data, the aim of the present study twofold: (i) to investigate dorsomedial frontal activation during self-paced saccades in darkness, discarding any environmental cues; (ii) to use fMRI with a 5 mm spatial resolution to better localize this activation. We compared an individual anatomical approach to a standardized normalization approach and searched for anatomical landmarks to localize the SEF in humans.

Table 1
Talairach coordinates of the peak of activation of foci in the supplementary eye field from several PET and fMRI studies

Reference	Type of saccades task	*x*	*y*	*z*
Anderson *et al.* (1994)	saccades toward a memorized target versus fixation	left	–2 to +4	
O'Driscoll *et al.* (1995)	antisaccades versus saccades	–1.9	9.8	44
O'Sullivan *et al.* (1995)	saccades toward a memorized target versus fixation	–2	8	52
		8	–12	60
Sweeney *et al.* (1996)	antisaccades versus visually guided saccades	8	–22	64
	saccades toward a memorized target versus visually guided saccades	–2	–18	56
Doricchi *et al.* (1996)	antisaccade versus fixation	12	–2	48
	antisaccades versus visually guided saccades	18	2	48
Petit *et al.* (1996)	self-paced saccades in darkness versus rest	8	4	52
Law *et al.* (1997)	visually guided saccades versus fixation	–4	–8	52
	imagined saccades versus fixation	0	–2	56
Dejardin *et al.* (1998)	self-paced saccades versus rest	–6	–16	56
Luna *et al.* (1998)	visually guided saccades versus fixation	0	0	54
		0	0	48

Materials and Methods

Subjects and Task

Five right-handed healthy volunteers (S1–S5; aged 20–30; two males, three females) participated in this study after giving their written informed consent. Three were left eye dominant and the two others were right eye dominant. All were free of any neurological antecedent and had good vision. This study was part of a project accepted by the local ethical committee.

Subjects were scanned during two experimental conditions, 'saccades' and 'rest'. During the 'saccades' condition they were asked to perform self-paced regular horizontal saccadic eye movement in darkness. They were instructed to maintain amplitude and frequency constant and maximal without being uncomfortable. During the 'rest' condition, still in darkness, they were asked to relax, to keep their eye open without making movements. Before the scanning session, the volunteers were trained for a few minutes to perform this task; we checked using an electro-oculogram (EOG) that they performed it correctly.

Imaging

Experiments were performed on a 3 T whole-body imager (Bruker) equipped with a quadrature birdcage RF coil and a head-gradient coil insert designed for echo-planar imaging (EPI). Subjects layed supine and had their head fixed with the help of foam. Functional images were collected using a T_2^*-weighted gradient-echo EPI sequence: sets of 18 contiguous 5 mm thick axial slices were acquired every 3.67 s (echo time = 40 ms, voxel size = 4 × 4 × 5 mm^3). Sets of high-resolution images (gradient-echo inversion recovery sequence, voxel size = 1 × 1 × 2.5 mm^3) were acquired at the end of the scanning session for anatomical identification. An experiment session consisted of nine blocks of 26 s, alternatively saccades and rest. The first block was a rest condition. Performance was followed online with EOG, using carbon electrodes compatible with the magnetic environment. The EOG recordings were low-pass filtered, and used to assess the frequency and the mean amplitude of saccades.

Data Processing and Analysis

Functional magnetic resonance images were first corrected for movement and temporally smoothed with a low-pass Gaussian kernel of 10 s full width at half-maximum (FWHM). The first four images were discarded to ensure that steady-state signal was reached. Individual functional maps were obtained by computation of the autocorrelation peak of the MR

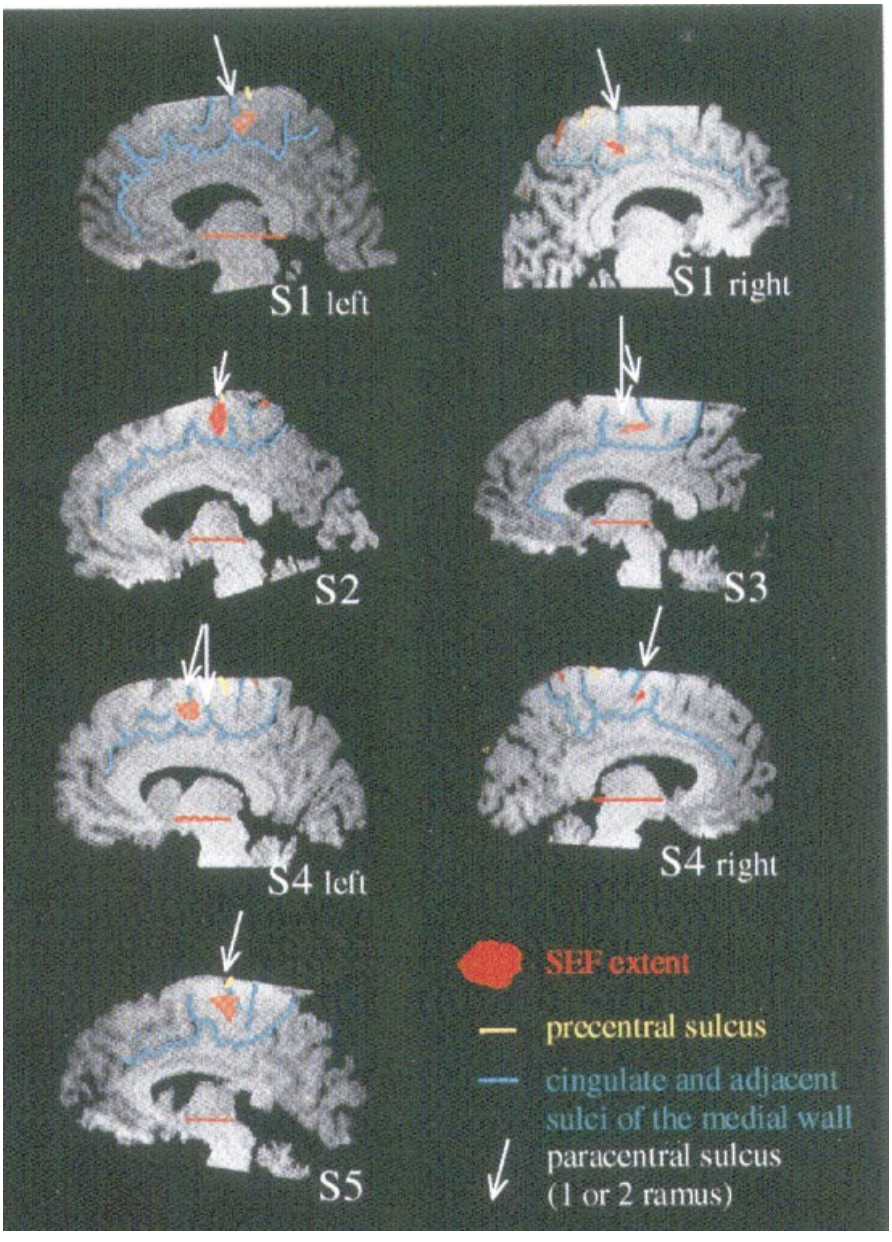

Figure 2. Sagittal views (generated with Voxtool) of hemispheres where significant SEF activation was detected. The SEF extent is reported in red. It was always located in the end of the descending branch of the paracentral sulcus (white arrows).

signal time-course on a pixel by pixel basis. This approach enables robust, phase-independent detection of a periodic temporal response (Paradis *et al.*, 1997). Three-dimensional clusters of more than two voxels (160 mm^3) showing an autocorrelation peak >0.25 and Z score >4 (activation versus rest) were retained as activated. These thresholds were determined to correspond to an estimated uncorrected P-value of 2×10^{-4} based on an analysis of 45 000 brain voxels acquired in the rest condition (null hypothesis), in the same subjects, during the same acquisition session, and with the same acquisition sequences and parameters as the experimental images. Activated clusters were superimposed on anatomical slices. For each volunteer, the cortical anatomy was carefully studied using a three-dimensional reconstruction software (Voxtool General Electric, software that allows navigation in three-dimensional brain images). Major sulci were identified and the SEF was defined in relation to these anatomical landmarks.

To carry out a normalization approach, we used the SPM 96 package (Wellcome Department of Neurology, London). Functional volumes were normalized into the standard space defined by the Montreal Neurological Institute (MNI) template, and spatially smoothed with a 4 mm FWHM gaussian filter (Friston *et al.*, 1995). Statistical parametric maps were calculated using a multilinear regression analysis based on a hemodynamic modelization of the two states of the experiment and including global signal change and low frequencies as confounding covariates (Worsley and Friston, 1995). Activated clusters were determined by thresholding the [saccades – rest] contrast map at $Z > 3.1$ ($P < 0.001$ uncorrected; no correction for multiple comparison was performed in the whole brain since we focused on a single area).

Results

EOG Recording

During scanning, all volunteers executed, in darkness, voluntary self-paced saccades that were symmetric with respect to the midsagittal plane. As measured with EOG, the mean (±SD) frequency of these saccades was 0.98 ± 0.39 Hz. Saccades

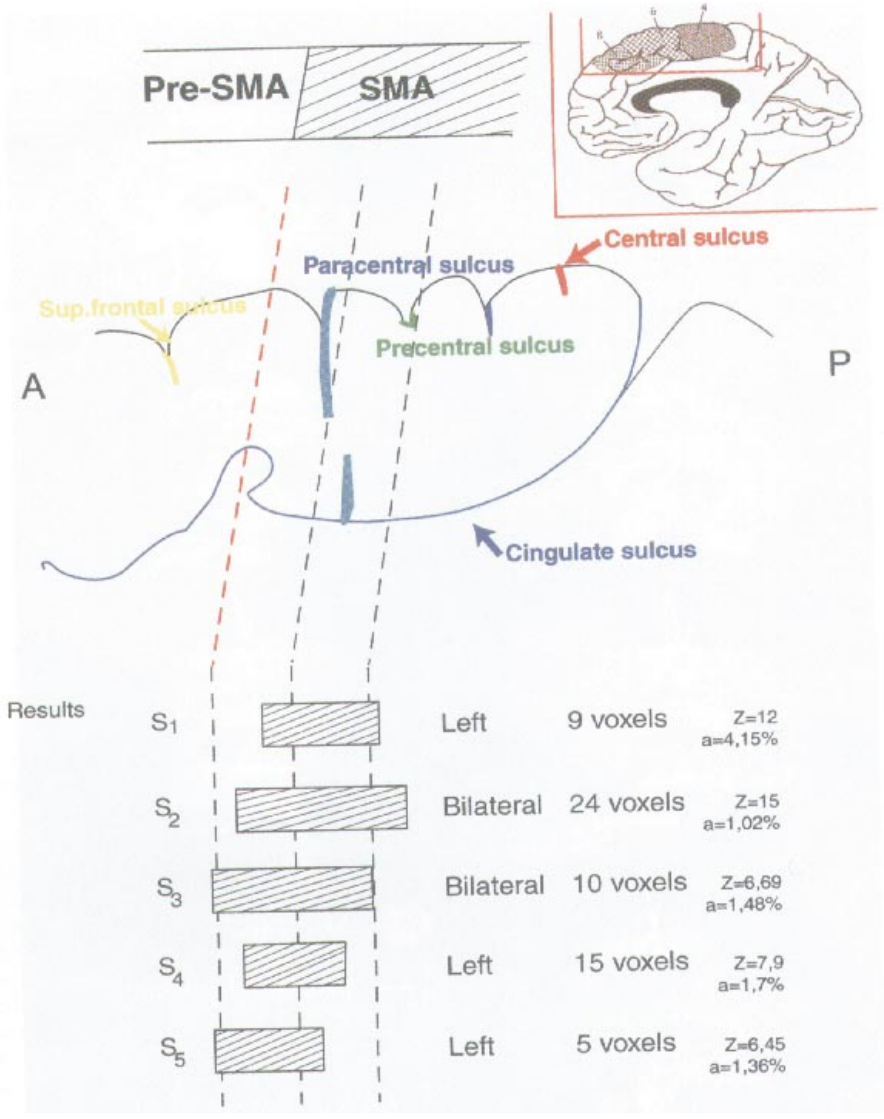

Figure 3. Schematic drawing of the SEF extent relative to main sulci of the medial wall. The lower bars represent the antero-posterior extent of the activation in the SEF. a = percentage signal change.

amplitude ranged between 30° and 50°, and were regular for all volunteers.

Cortical Network for Saccades

When saccades and rest conditions were compared, we found foci of significant activation ($Z > 4$, ac > 0.25) in the cortical regions that have been previously described as participating in the control of voluntary saccadic eye movements (Petit *et al.*, 1993; Pierrot-Deseilligny *et al.*, 1995). All subjects showed activation in the precentral gyrus which corresponds to the FEF. In the five subjects, we observed foci of activation in the posterior parietal cortex, mainly in the superior parietal gyrus (P1) and in the lateral part of the intraparietal sulcus. In three subjects these parietal foci of activation tended to be either more extended or more significant in the left hemisphere. In two subjects there was additional activation of the precuneus bilaterally. In two subjects there was activation in the bilateral fusiform gyrus. In four out of five subjects we observed significant activation in the right striatum. The cerebellar vermis was activated bilaterally in one subject, but in the other subjects this structure was not imaged entirely.

In this paper we focused our analysis on the SEF region. For two out of five subjects the significant activation in the region of the dorsomedial frontal cortex corresponding to the SEF was bilateral; for the three others the SEF activation was limited to the left hemisphere. When the activation was bilateral, it was more extended and reached higher *Z*-scores in the left than in the right hemisphere. Across the seven foci considered, the number of voxels per SEF region ranged between 5 and 14 (400 and 1120 mm^3, see Fig. 3).

Anatomical Localization of the SEF

Individual analysis of non-normalized images revealed that, in every case, the SEF focus was located on the medial wall, above the cingulate sulcus, between the VCA line (perpendicular to the CA–CP line, which crosses the anterior commissure) and the deep superior precentral sulcus. For all volunteers the focus was located in the banks of the upper part of the paracentral sulcus

Table 2
Talairach (x, y, z) coordinates of activation peaks in the SEF regions (comparison between saccades and rest condition: Student's t-test $P < 0.001$) obtained with SPM software

	Left hemisphere			Right hemisphere		
S1	–4	–20	52	8	–32	48
S2	–8	–24	52	×		
S3	–4	–2	54	×		
S4	–12	–12	48	0	–36	48
S5	–12	–4	48	×		

(see Figs 2 and 3), in the left as well as in the right hemisphere. The paracentral sulcus is one of the main sulci of the medial wall. It is located closely anterior to the end of superior precentral sulcus (when this later sulcus is present on the interhemispheric surface), and it marks the anterior border of the paracentral lobule. According to the atlas of Ono, in most cases the paracentral sulcus is either a sulcus from the lateral surface (descending paracentral sulcus) or divided into a descending part and an ascending branch originating from the cingulate sulcus (Ono *et al.*, 1990). This latter pattern was the one observed in all the 10 hemispheres (see Fig. 2). The SEF focus was located around the end of the descending branch. We found that the paracentral sulcus is a stable landmark for the SEF.

Stereotaxic Coordinates of the SEF (Table 2)

Transformation into Talairach space and analysis with the SPM software yielded similar results for the cortical activation in the saccades condition when compared to rest. Across the five volunteers, the Talairach coordinates of the maximal pixel of the SEF region were stable in the mediolateral (x) direction (–4 to –12 mm for the left hemisphere; 0 to +8 in the right hemisphere) and in the vertical (z) position (+48 to +52 mm in both hemispheres). However in the antero-posterior direction, y-coordinates were quite variable among subjects: –2 to –24 mm (mean –12.4 ± 9.6 SD) in the left hemisphere, and –32 and –36 mm in the right hemisphere.

Discussion

In common with other studies of the neural correlates of saccadic eye movements in human (cf. Introduction), we observed, using fMRI of self-paced saccades in darkness compared with rest, the involvement of an eye field located on the human medial wall, in the SMA region. As discussed in the Introduction this area may legitimately be identified as the human SEF. It is activated as a part of a circuit which involved mainly FEF bilaterally, posterior parietal cortex and the striatum. We observed that the activation of the SEF was more important in the left hemisphere. An important anatomical landmark for the exact location of this area turned out to be the paracentral sulcus.

A Reference to Locate the SEF: Anatomical Landmarks are More Precise than Stereotaxic Coordinates

The main contribution of the present study is to provide a stable landmark for the SEF. It indeed appears that the paracentral sulcus, and especially its descending branch, allows the location of this functional area on the medial wall. This result provides a systematic demonstration of the observation recently made by Luna *et al.* that the SEF is adjacent to the paracentral sulcus (Luna *et al.*, 1998). Until now, studies about the localization of the SEF in humans referred to the Talairach system and its main reference, the VCA line. Here, we show that, with respect to the VCA line, the position of the paracentral sulcus and thus of the SEF varies significantly among individuals, as well as between hemispheres. The coordinates of the SEF in our group varied by >2 cm in the antero-posterior direction, despite a very accurate localization made by referring to anatomical landmarks. This fact might explain the differences in Talairach coordinates given in the literature for the localization of the human SEF. The interindividual, and even interhemispheric, variability in the topography of the paracentral sulcus has already been noted in anatomical studies (Ono *et al.*, 1990, Rademacher *et al.*, 1993).

Our finding also provides further evidence that gross anatomical landmarks could have a functional significance. This is in agreement with theories linking functional development with the anatomy in the cortex (Welker and Campos, 1963; Van Essen, 1997). This is a source of information that completes, and can be linked with, data of the relations between cytoarchitectonic borders and cerebral sulci (Rademacher *et al.*, 1993). Other authors have already attempted to anatomically localize functional regions with some success [area V5 (Watson *et al.*, 1993), visual areas (Sereno *et al.*, 1995), hand motor area (Yousry *et al.*, 1997)]. In the present case, the reliable location of the SEF with the upper paracentral sulcus will enable future neuroimaging studies to clearly identify this area based on anatomical analysis, and will help functional interpretation of activation in the frontal medial wall.

Dominance of the Left SEF for Endogenous Saccades

We observed a clear dominance of the left hemisphere in the SEF activation when subjects performed endogenous saccadic eye movements. This cannot have been related to subject's ocular dominance (in the three subjects in whom significant SEF activation was only in the left hemisphere, two were right eye dominant and one left eye dominant), or to gender because unilateral and bilateral activation was observed in both males and females. Luna *et al.* did not report such an interhemispheric difference when studying visually guided saccadic eye movements (Luna *et al.*, 1998). This asymmetry might therefore be due to a physiological specificity of endogenously driven behavior. A PET study by Petit *et al.* noted (but without discussion) that the left SEF was dominant for the execution of self-triggered saccades (Petit *et al.*, 1993). A group analysis of cortical blood flow measurement during self-paced saccades compared with rest showed greater activation in the left hemisphere (Dejardin *et al.*, 1998). Gaymard *et al.* observed that left SMA lesions, but not right lesions, lead to severe impairment in sequencing memory-guided saccades (Gaymard *et al.*, 1993). Thus, the left SEF seems to be predominantly involved in the generation of voluntary internally generated saccades (without visual trigger). The right SEF may be required for additional aspects of visuomotor behavior that imply visual guidance.

No lateralization was observed in activation of the FEF. Lesion studies suggest that if a difference existed between left and right FEF it would concern the direction of the saccades, deficits being observed in contralesional saccades (Pierrot-Deseilligny *et al.*, 1991; Schiller and Chou, 1998). Our study implies left- and right-sided saccades equivalently.

The discrepancy regarding the hemispheric specialization in the SEF between visually guided and self-paced saccades is accompanied by a discrepancy in the posterior parietal cortex involvement. Luna *et al.* noted that the number of voxels activated was greater in the right than in the left inferior parietal lobule (lateral bank of the intraparietal sulcus) (Luna *et al.*, 1998). They explained this hemispheric asymmetry by referring

to the known specialization of the right hemisphere for the control of visuospatial attention. This is in accordance with reports of deficits in patients with right posterior parietal lesions for visually guided saccades (Pierrot-Deseilligny *et al.*, 1991). When subjects performed endogenous (i.e. not visually guided) saccades we did not observe such an asymmetry. Instead the left posterior parietal cortex tended to be dominant, especially in the region of the superior parietal lobule. We can therefore hypothesize that a left-sided circuit including SEF and posterior parietal modules is particularly important for endogenously guided eye movements in darkness, whereas the right hemisphere would be more involved when oculomotor acts are integrated into a visuomotor behavior requiring visual guidance.

'Anatomo-physiology' of the SEF in the Context of the SMA

The previous observation and discussion is in accordance with the hypothesis that the SMA plays a crucial role in endogenous movements. A large number of anatomical studies has suggested that the mesial area 6 is parcelled into several subregions that differ structurally and functionally. It is to be expected that an eye field would be found in this region. It is also important to locate it to allow between-studies comparisons. Compared to the sites of SMA-proper and pre-SMA, the location of the SEF in humans is not in exact correspondence with the site described in monkeys (see Introduction). The SEF in man, as we observed, lies along the interhemispheric surface (and not on the dorsal surface of the precentral gyrus convexity as in macaque monkeys) in the anterior part of the region usually described as the SMA-proper, and posterior to the VCA line, which is usually considered as being the posterior limit of the pre-SMA (Picard and Strick, 1996). Vorobiev *et al.* reported secondary but significant cytoarchitectonical differences between a caudal (SMAc) and a rostral (SMAr) part of the SMA proper (Vorobiev *et al.*, 1998). This observation was in accordance with regional cerebral blood flow measurements showing that the SMAc is activated preferentially for movement execution, whereas SMAr is activated preferentially when subjects imagine the same movement without performance or when they observe another person performing the action (Stephan *et al.*, 1995). The site we describe here for the SEF would be located in the anterior part of the SMAc, near the SMA 'face zone'. Such a location is consistent with the idea of a somatotopic organization of the human SMAc (see Introduction) [for review see Kurata (Kurata, 1992)], although a specific study would be necessary to address the issue of the relative position of the SEF and the parts of the SMA involved in other skeletal movements. However, there is evidence that the SEF is a cortical area distinct from the SMA. In particular, receptor distribution and cytoarchitectonic studies have underlined that the SEF in humans exhibits anatomo-functional features that differ from those of the SMA. Rather, the SEF shares more similarities with the FEF and the prefrontal cortex (pronounced lamination, high density of NMDA receptors) (Zilles *et al.*, 1995; Wise *et al.*, 1996).

Conclusion

In summary, we conclude that (i) an area on the frontal medial wall, the SEF is activated by the execution of endogenous saccades in darkness; (ii) this activation is greater in the left hemisphere than in the right; (iii) anatomical landmarks such a sulci may be more accurate than normalization methods and mapping procedures referring to the Talairach space for identification of cortical areas; and (iv) the human SEF can be reliably localized across individuals by referring to the paracentral sulcus.

Notes

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