Eye movement control by the cerebral cortex

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Purpose of review

This review focuses on eye movement control by the cerebral cortex, mainly in humans. Data have emerged based on the important contribution of recent techniques such as transcranial magnetic stimulation and functional magnetic resonance imaging, which provide complementary results to those of the classical lesion and electrical stimulation studies.

Recent findings

The location of the human frontal eye field and its role in pursuit eye movement control were recently detailed. Cumulative evidence for the role of the dorsolateral prefrontal cortex in unwanted reflexive saccade inhibition, short-term spatial memory and prediction suggests that this area controls decisional processes governing ocular motor behaviour. The organization of spatial memory in the dorsolateral prefrontal cortex (short-term), the parahippocampal cortex (medium-term) and the hippocampal formation (long-term) is also reviewed with the results of recent transcranial magnetic stimulation studies. The relatively complicated anatomy of the posterior parietal cortex in humans is briefly described followed by some additional results concerning the location of the parietal eye field – within the posterior half of the intraparietal sulcus – and its role in visuo-spatial integration and attention. The other areas involved in spatial attention are also examined in the light of several recent contributing reports. Lastly, there are also new functional magnetic resonance imaging findings concerning the posterior cingulate cortex, which appears to be mainly involved in the control of externally guided eye movements and attentional mechanisms.

Summary

Many new findings on the organization of saccades and pursuit eye movements at the cortical level have recently been reported. Furthermore, eye movements are increasingly used as a tool to elucidate relatively complex neuropsychological processes such as attention, spatial memory, motivation and decisional processes, and a considerable number of reports dealing with these questions have been observed.

Keywords

attention, cingulate cortex, eye movements, frontal eye field, parietal eye field, spatial memory

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Abbreviations

ACC	anterior cingulate cortex
CEF	cingulate eye field
DLPFC	dorsolateral prefrontal cortex
FEF	frontal eye field
fMRI	functional magnetic resonance imaging
IPS	intraparietal sulcus
PCC	posterior cingulate cortex
PEF	parietal eye field
PEM	pursuit eye movement
PHC	para-hippocampal cortex
PPC	posterior parietal cortex
SEF	supplementary eye field
SPL	superior parietal lobule
TMS	transcranial magnetic stimulation

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Introduction

Eye movement research in humans has noticeably advanced in recent years mainly thanks to new investigative methods such as transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI), with currently a considerable increase in the number of published studies using the latter. What are the advantages and disadvantages of these two methods compared with the classical lesion and electrical stimulation studies? First, they can both be used in normal subjects, who are clearly easier to explore than patients with either small focal lesions or a pathology warranting direct electrical stimulation of their cerebral cortex. Secondly, they also provide clear advantages in terms of spatial resolution for fMRI, which is in the order of a few millimetres, and temporal resolution for TMS, which is around a few milliseconds (Table 1) [1]. However, these new methods are unlikely to replace completely the older methods in eye movement research since lesion studies remain the best involvement markers, determining which areas are crucial in the control of a given paradigm [2]. In lesion studies, this point may be inferred when a significant deficit is observed after a small lesion of a cerebral area. By contrast, fMRI studies are much less reliable in establishing such a point, because activation may falsely appear in certain areas or, above all, not be really crucial to the execution of the paradigm. This problem is also encountered in experimental electrophysiological studies, which also often require the use of muscimol in a cerebral area (resulting in a temporary functional lesion) in order to validate the crucial feature of an activity observed in this area for the control of the studied paradigm. TMS is not the best involvement marker either, due to difficulty in controlling stimulation intensity, which may be insufficient. Finally, in humans,

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Table 1. Effectiveness of methods currently used to study the functioning of human cerebral areas

	Involvement marker: WHAT?	Spatial resolution: WHERE?	Temporal resolution: WHEN?
Lesion studies	Good	Mild	None
Electrical stimulation studies	Mild	Mild	Mild
Transcranial magnetic stimulation studies	Mild	Weak	Good
Functional MRI studies	Mild	Good	Mild

MRI, magnetic resonance imaging.

these different methods are really complementary to our understanding of how the cerebral cortex controls a paradigm. This complementation explains the recent rapid advance in our knowledge of eye movement organization, and even of the role of some neuropsychological processes in preparing the movement generally when, for example, saccades are used as a tool or model for motricity. This review will, therefore, mainly focus on the latest advances in our knowledge of the control of human eye movements at the cortical level. The roles of some areas located in the frontal lobe, the parietal lobe and the cingulate cortex will be reviewed, successively, before a brief concluding overview of the main pathways existing between them.

Frontal lobe

In the frontal lobe, three main areas are involved in eye movement control [2]: the frontal eye field (FEF), the supplementary eye field (SEF) and the dorsolateral prefrontal cortex (DLPFC).

The frontal eye field

The FEF is involved in the preparation and triggering of all intentional saccades, which are internally triggered towards a target already present (intentional visually guided saccade), not yet present (predictive saccade), no longer visible (memory-guided saccade) or located in the opposite direction (antisaccade) [2]. This area is less involved in the triggering of reflexive visually guided saccades (often called 'pro-saccades'), which are externally triggered towards a suddenly appearing peripheral target and are mainly dependent upon the parietal eye field (PEF). The FEF also controls pursuit eye movements (PEMs), along with the posterior parieto-temporal areas. Recent findings on the FEF mainly concern its location and its role in the control of PEMs.

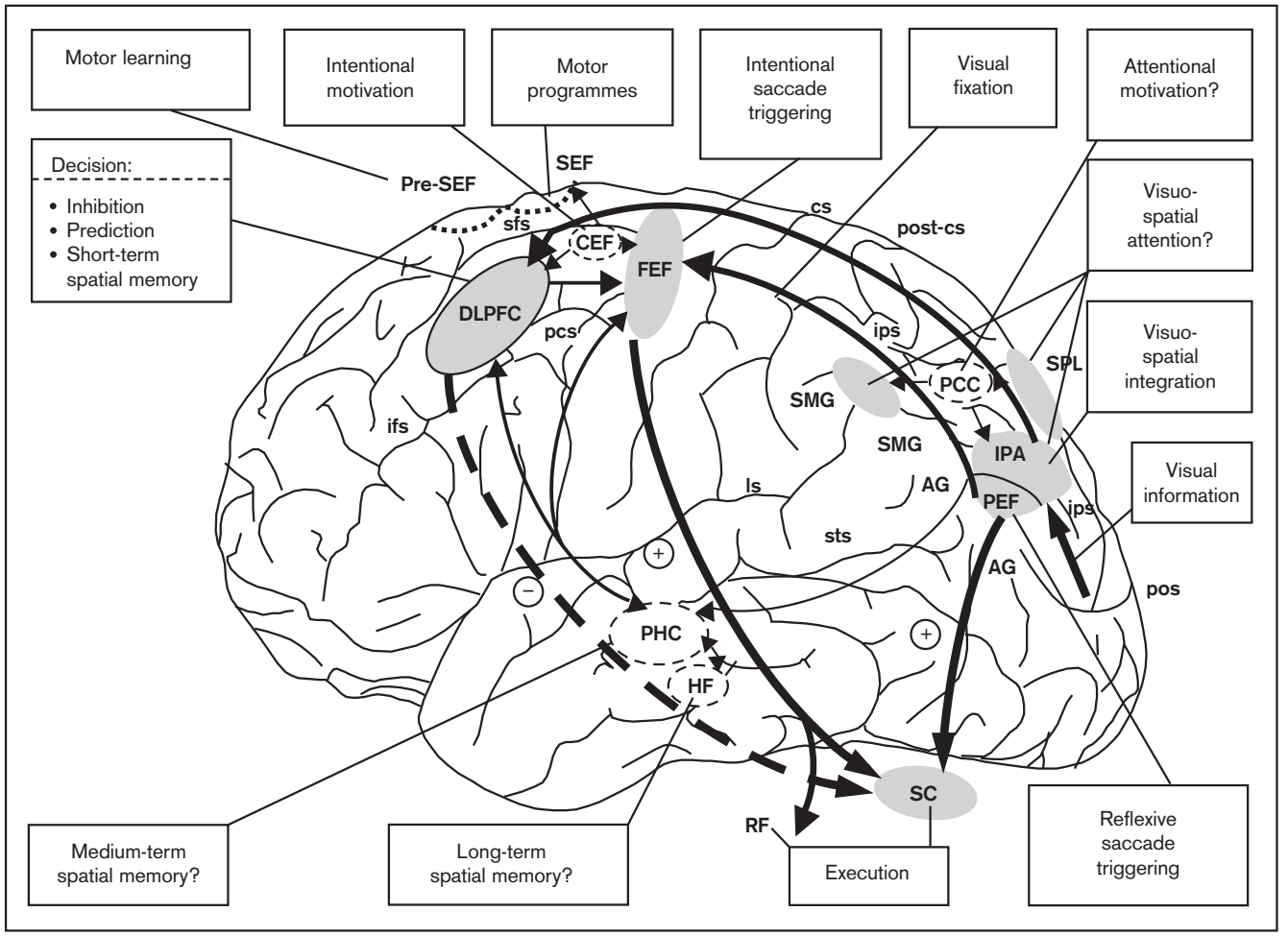
Location

Studies using fMRI have delimited the location of the FEF mainly to the intersection between the precentral sulcus and the superior frontal sulcus (Fig. 1) [3]. Thanks to a recent fRMI study [4], using 3-tesla, the saccade-related area of the FEF has been localized to the upper portion of the anterior wall of the precentral sulcus, and the pursuit-related area to a deeper region along the anterior wall, the fundus and the deep part of the posterior wall. This finding shows a high degree of homology in the organization of the FEF in humans and monkeys [5,6•]. Furthermore, by using labelled tissue sections in post-mortem human brains, it has been shown that the area defined by fMRI studies within the precentral sulcus may be classified by chemoarchitectural criteria as a motor cortex, a result which was expected considering the FEF's functions in PEM control and saccade triggering [7•]. In the precentral sulcus, besides the main locus of the FEF, located at the junction with the superior frontal sulcus, another locus of activation is often observed in fMRI studies along the lateral part of this sulcus and the adjacent portion of the precentral gyrus [8,9]. The specific role of this lateral locus remains to be determined, since it is activated both by single and combined eye and head movements [10•].

Pursuit eye movements

Interestingly, in two electrical stimulation studies of the human FEF, contralateral slow eye deviations were observed [11•,12•]. Such slow eye deviations could correspond to PEMs given their speed characteristics. The stimulation sites of these slow eye deviations were located in the precentral sulcus, more posterior than the stimulation sites for saccades [12•], a finding which is in accordance with fMRI data [4]. However, it should be noted that the human cerebral hemisphere, including the FEF, controls mainly ipsilateral PEMs, even though experimental data [5,6•] and human lesion studies [13] suggest that some degree of contralateral control by each area also exists. To explain this apparent discrepancy between this mainly ipsilateral hemispheric control of PEMs and the results of electrical stimulation studies, it may be assumed that stimulation, which was superficial in the FEF region in these studies, in fact involved only sites controlling contralateral PEMs. Indeed, such sites could be located, as in the monkey [14], more superficially than the ipsilateral PEM sites [12•]. Like lesion studies [13], fMRI studies suggest that the FEF also controls optokinetic nystagmus [15], with an activation existing in this area and in the other posterior hemispheric cerebral areas involved in PEM, but also with concomitant deactivation of the different cerebral areas involved in the vestibular control [16•]. Such results could be due to a reciprocal inhibitory visuo-vestibular interaction existing at the cortical level in order to

Figure 1. Main cortical areas and pathways involved in saccade control



SEF, supplementary eye field; sfs, superior frontal sulcus; CEF, cingulate eye field; cs, central sulcus; DLPFC, dorsolateral prefrontal cortex; pcs, precentral sulcus; FEF, frontal eye field; ips, intraparietal sulcus; ifs, inferior frontal sulcus; SMG, supramarginal gyrus; PCC, posterior cingulate cortex; SPL, superior parietal lobule; IPA, intraparietal areas; ls, lateral sulcus; AG, angular gyrus; PEF, posterior eye field; sts, superior temporal sulcus; pos, parieto-occipital sulcus; PHC, parahippocampal cortex; HF, hippocampal formation; SC, superior colliculus; RF, reticular formations.

maintain the perception of self-motion. Finally, in the monkey, it has been shown that the FEF neurons controlling PEMs are also involved in vergence, a result which suggests that PEMs are coded in three-dimensional space by the frontal cortex [17•].

Saccades

Antisaccades are intentional saccades which have to be made in the direction opposite to a suddenly appearing peripheral visual target. These saccades comprise two different mechanisms [2]: (1) inhibition of an unwanted reflexive misdirected saccade, triggered towards the visible target by the PEF when such inhibition – being under the control of the DLPFC (see below) – is no longer efficient; the percentage of these misdirected saccades (i.e. errors) reflects the inhibition function; and (2) concomitant triggering of an intentional correct antisaccade, made in the direction opposite to the target by the FEF. Pro-saccades (reflexive visually guided saccades) and antisaccades were studied using fMRI in two reports [18•,19••]. In both reports, activation was observed just before antisaccades in the FEF but not in the PEF, confirming that such intentional saccades require an early preparation by the former but not by the latter. However, contrary to a suggestion existing in another recent fMRI study [20], this does not mean that inhibition of misdirected reflexive pro-saccades is organized in the FEF. In fact, an activation of the right DLPFC was also noted just before antisaccades in one of these fMRI studies [19••], in accordance with the results of previous functional imaging studies [21,22]. Taken together, these fMRI studies confirm the results of lesion studies with specific damage to the DLPFC or the FEF that had previously clearly shown that inhibition of

misdirected reflexive pro-saccades depends upon the former and the triggering of correct antisaccades upon the latter (Fig. 1) [13,23,24•]. The inhibition of reflexive saccades by the DLPFC could be exerted directly on the superior colliculus, without involving other cortical areas [23], via a prefronto-collicular tract [25•]. In addition, it may be mentioned that an ipsilateral conjugate eye deviation with paresis of voluntary contralateral gaze was observed in a patient with a relatively small infarct affecting the FEF region [26•].

The supplementary eye field

The human SEF is located on the medial surface of the superior frontal gyrus, in the upper part of the paracentral sulcus (Fig. 1) [27]. The SEF is connected with all areas involved in eye movement control – the FEF, the DLPFC, the anterior cingulate cortex [28•] – and also the posterior parietal cortex. Lesion studies have shown that the SEF is involved in motor programmes comprising a saccade combined with a body movement or a sequence of several successive saccades [2]. In the case of a saccade sequence, TMS and fMRI studies have also shown that a more anterior region (i.e. the pre-SEF) is involved during the presentation of the visual stimulation sequence (motor learning), whereas the SEF proper is involved just before the execution of the motor sequence [2]. In an electrophysiological study in the monkey, using a saccade sequence, it was confirmed that the SEF neurons are involved in the coding of temporally ordered saccadic eye movements [29•]. In a recent TMS study, stimulation applied over the SEF resulted in a disruption of the saccade order in a double-step paradigm (comprising a sequence of two successive saccades) [30]. This result may therefore also have been due to the SEF control of saccade sequences. Furthermore, it should be pointed out that in a recent experimental study in the monkey, using an intentional visually guided saccade task in which a single saccade had to be performed, it was shown that a higher number of SEF neurons were active than FEF and PEF neurons and this activity was observed earlier [31]. Therefore, the SEF could prepare all motor programmes early, even when they are limited to a single saccade. This may also explain the SEF activation observed in fMRI studies in all single and sequence saccade paradigms [9], whatever the nature of the single saccade to be performed. Thus, this point illustrates how an area (i.e. the SEF) may be active using fMRI without being in fact crucial to the correct execution of a paradigm (e.g. a single memory-guided saccade), as suggested by lesion and TMS studies on the SEF [2].

The dorsolateral prefrontal cortex

The DLPFC is involved in saccade inhibition (see above), but also in short-term spatial memory and in decisional processes (Fig. 1) [2].

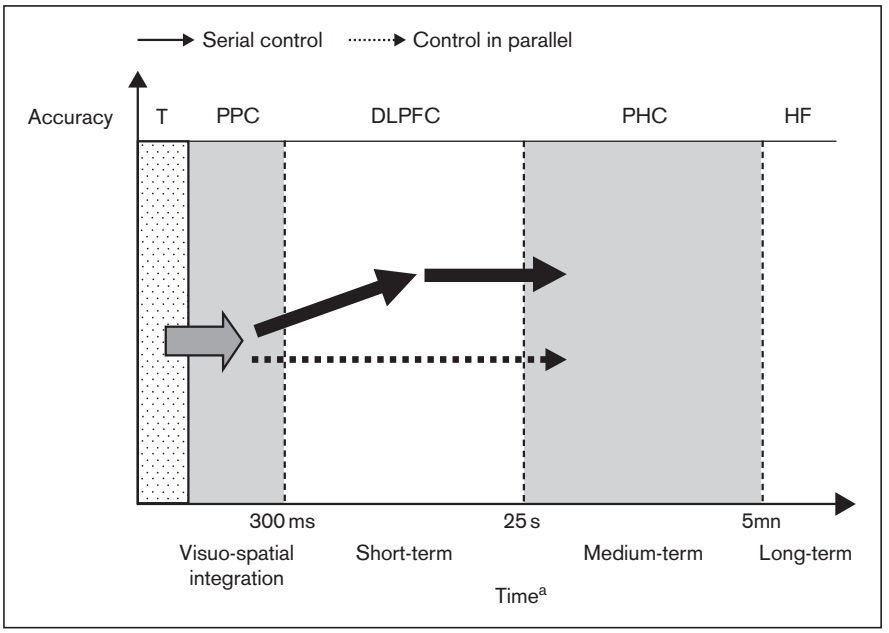
Spatial memory

The control of spatial memory in the human cerebral cortex was recently reviewed [32]. The memory-guided saccade paradigm is commonly used to study this function with eye movements. In this paradigm, the participant has to memorize the location of a target flashed in the peripheral visual field while fixating a central point, and then, after a delay of several seconds or more, make a memory-guided saccade to the remembered position of the flash. The amplitude of this saccade may be considered as a reflection of spatial memory. Lesion studies suggest that the DLPFC, and, more particularly, area 46 of Brodmann and the adjacent Brodmann area 9, both located in the middle frontal gyrus, are involved in the control of memory-guided saccades [24•,33]. In a TMS study, it was stated that DLPFC control of memory-guided saccades is exerted during the delay period, when spatial memory is involved [34]. FMRI studies have confirmed the involvement of Brodmann area 46 in spatial memory [35,36], with an activity in this area that can last at least 24 s [35]. In a psychophysical study in normal subjects, it was suggested that a spatial memory system other than that controlled by the DLPFC is involved for delays of over 20–25 s [37]. A lesion study has led us to assume that this other system, controlling medium-term spatial memory, could involve the para-hippocampal cortex (PHC) (Fig. 2) [38]. One of the questions raised by the existence of these two successive systems controlling spatial memory is that of whether their controls are exerted in series (i.e. with a memorized coding in the PHC completely built from the DLPFC information) or in parallel (i.e. with the PHC coding built independently of the DLPFC information).

In two recent complementary TMS studies in normal participants, with stimulation of the DLPFC during either a short delay (3 s) or a long delay (30 s), abnormalities in the amplitude of memory-guided saccades were observed. These results suggest (1) a control of spatial memory by the DLPFC during the first seconds of the delay; and (2) a partial independence from the DLPFC state existing during these first seconds for the building of memorized information used in long delays [39•,40]. This confirms that, in long delays (30 s), medium-term spatial memory is controlled by another structure (probably the PHC), in which, however, memorized information could be built from both the DLPFC and another structure, probably the posterior parietal cortex (PPC). These results therefore suggest that the control of spatial memory by the DLPFC and then the PHC is exerted both serially between them, via the prefronto-temporal connections, and in parallel from the PPC, which is also connected with these two areas (Fig. 2). Finally, there is indirect evidence that long-term spatial memory (involved after a delay of a few minutes)

Figure 2. Hypothetical and schematic cortical control of spatial memory

T, target; PPC, posterior parietal cortex; DLPFC, dorsolateral prefrontal cortex; PHC, parahippocampal cortex; HF, hippocampal formation. [a] Time values are approximate.



is controlled by the hippocampal formation [32], but further studies are needed to confirm this. To conclude this review on the study of spatial memory using memory-guided saccades, it should be pointed out that this is a good example of how eye movements may be studied not simply *per se* but also used as a tool in neuropsychological or neuroscience research.

Decision

The DLPFC is also involved in the control of predictive saccades. In this paradigm, a visual target moves to locations and at times that are entirely predictable. Normal subjects soon start to make predictive saccades, anticipating the location to which the target is moving. After lesions limited to the DLPFC, the percentage of predictive saccades significantly decreases [24•]. These results in conjunction with those referred to above suggest that the DLPFC plays a crucial role in decisional processes governing eye movement behaviour, preparing intentional saccades by inhibiting unwanted reflexive saccades (inhibition), maintaining memorized information for forthcoming intentional saccades (short-term spatial memorization) or facilitating intentional anticipatory saccades (prediction), depending upon current external environmental and internal circumstances [24•]. In support of this decisional role, it may be mentioned that in an fMRI study in normal subjects, self-selecting the direction of the forthcoming saccade, the DLPFC was strongly activated during the selection period (Milea *et al.*, in preparation). This decisional role, which is important in guiding or inhibiting future responses, could be exerted through inhibitory interactions between neurons in the DLPFC, controlling the timing of neuronal activities during cognitive operations and thereby shaping the temporal flow of information [41].

Parietal lobe

In the parietal lobe, the location and function of the different areas involved in eye movements and attention are not well known.

Anatomy

The parietal lobe and more particularly its posterior part, the PPC, are involved in the control of saccades and attention. The PPC includes the intraparietal sulcus (IPS) extending from the post-central sulcus anteriorly to the parieto-occipital sulcus posteriorly (Fig. 1). The IPS is slightly oblique along the antero-posterior axis, and so is more lateral anteriorly and more medial posteriorly. The IPS, which is a deep sulcus, separates the superior parietal lobule (SPL) located medially (i.e. Brodmann area 7) from the inferior parietal lobule, located laterally. The latter comprises Brodmann area 40 (i.e. the supramarginal gyrus), lying anteriorly around the extremity of the lateral sulcus, and Brodmann area 39 (i.e. the angular gyrus), lying posteriorly around the extremity of the superior temporal sulcus (Fig. 1). Thus, the anatomy of the IPS is not simple, being relatively variable from one subject to another. Furthermore, in fMRI studies, it is difficult to differentiate activation related to saccades from that related to attention,

because a saccade always includes a shift of attention and a pure shift of visual attention usually activates saccade areas (e.g. the FEF) [2]. Consequently, the precise locations within the PPC of regions specifically controlling saccades or attention remain relatively uncertain.

The parietal eye field and attentional areas

The human PEF corresponds to the lateral intraparietal area of the monkey. The lateral intraparietal area is involved in the control of saccades [42], but also in attentional processes [43•,44••]. Furthermore, light stimulation of this area in the monkey results in a simple shift of visual attention (without eye movement), whereas stronger stimulation results in a saccade [45•]. These results emphasize the close links existing between saccades and attention, even in the same area. The PEF appears to be located along the IPS [46], within the sulcus, and, more precisely, after comparing the results of several more recent fMRI studies on saccades or visual attention [47–50,51•,52••], in its posterior half, adjacent laterally to the anterior part of the angular gyrus (Brodmann area 39) and medially to the posterior part of the SPL (Brodmann area 7). In this posterior IPS area and on the basis of the results of an fMRI study, using 4-tesla, the PEF could be located mainly in the medial wall of the IPS [53•]. The activation of the PEF is also modulated by head position [51•], a result which is probably related to the role of this area in visuo-spatial integration. Concerning this function, a recent TMS study [54] showed that the extraretinal signals required to determine the amplitude of the second saccade in the double-step paradigm reach the PPC, probably via the efferent-copy pathways, only 100 ms before the triggering of this saccade [54]. FMRI studies [53•,55•] have also shown that a spatial updating of visual information occurs in the human PPC (including the PEF region) after an eye movement.

There is now accumulative evidence, on the basis of fMRI studies, to suggest that the anterior part of the IPS (limited medially by the supramarginal gyrus, i.e. Brodmann area 40) is more involved in eye–hand coordination [47,49,56], and the posterior part of the SPL (close to the adjacent PEF) in attentional processes [48,49,52••,56,57•]. Furthermore, the supramarginal gyrus (Brodmann area 40), during saccades [58] or purely attention paradigms [48,49,57•,59], and the angular gyrus (Brodmann area 39), during reflexive saccades [60•], have more rarely been activated in fMRI studies. However, this also suggests a control of these areas in attention. These results may be related to the well-known visual neglect syndrome due to right PPC lesions affecting more particularly the angular gyrus [61].

The PEF projects to both the FEF and the superior colliculus (Fig. 1). In the monkey, these two projections appear to be qualitatively different, with a more visual involvement for the parieto-FEF projection and a more saccadic involvement for the parieto-superior colliculus projection [62]. The parieto-FEF projection could be mainly involved in visual fixation [13]. The results of a study in patients with lesions affecting the posterior part of the internal capsule [63•], damaging the direct parieto-collicular tract originating in the PEF, are in accordance with experimental results and confirm that the PEF is crucial for reflexive saccade generation [23] but not for intentional saccade generation. The latter depends mainly upon FEF control (see above).

Cingulate cortex

The cingulate cortex is divided into the anterior cingulate cortex (ACC) (Brodmann area 24) and the posterior cingulate cortex (PCC) (Brodmann area 23). The posterior part of the ACC is involved in saccade control [64], more precisely in intentional saccade control, but not in reflexive saccade control [65]. This 'cingulate eye field' (CEF), located at the limit between Brodmann areas 23 and 24, could, via an intentional motivation process, prepare all the frontal ocular motor areas involved in intentional saccade control to act in the forthcoming motor behaviour. The DLPFC is also under the control of the CEF, as suggested – after CEF lesions – by memory-guided saccade abnormalities [65] and by saccade inhibition impairment in the antisaccade paradigm [66•].

The role of the PCC is less well known, because in the monkey this area is influenced by saccade activity, but with a discharge occurring only after the saccade onset [67]. An fMRI study has shown that the PCC is active during reflexive saccades but not during intentional saccades [60•]. Thus, the PCC appears to be the equivalent, for reflexive saccade control, of the CEF (within the ACC) for intentional saccade control, namely by preparing the PEF to possibly act with a reflexive saccade when attentional processes become predominant. The PCC is also activated during PEM [68,69•]. Therefore, from an ocular motor point of view, the CEF (ACC) could prepare the forthcoming intentional eye movements, which are internally governed, whereas the PCC could control the other, externally-triggered eye movements: the reflexive saccades and smooth pursuit. PCC activity also appears to be related to attentional processes, though its precise role in this field is still unclear. Two fMRI studies, however, have suggested that the PCC is activated in purely attentional paradigms as soon as an informative cue indicates an imminent shift of visual attention [70,71•]. The PCC is connected to the IPS [71•], but further studies are needed to determine the precise role of this pathway.

Conclusion

Figure 1 summarizes some of the cortical pathways and mechanisms involved in saccade control. Visual information originating in the occipital lobe becomes salient in the parietal lobe thanks to diverse attentional areas located in the posterior part of the SPL, the posterior part of the IPS, including the PEF, perhaps other intraparietal areas and probably also the IPL (supramarginal gyrus or angular gyrus). However, the specific roles of these different areas in attention control remain to be determined. These areas probably interact and interconnect with the PCC, influencing them upstream via an attentional motivation process. The PEF or a closed area also controls visuo-spatial integration. A reflexive saccade is triggered by the PEF if external circumstances require such a rapid response. This triggering is performed via the direct parieto-collicular tract passing through the posterior part of the internal capsule. In the event of a delayed response, visual information is transmitted from the PEF to the FEF for active fixation and from the intraparietal areas to the DLPFC for short-term spatial memorization (between 300 ms and 25 s). The DLPFC is involved in decisional processes governing ocular motor behaviour by inhibiting unwanted reflexive saccades (inhibition) controlled by the PEF or facilitating the triggering of anticipatory saccades (prediction) by the FEF. The inhibition of reflexive saccades originating in the DLPFC is probably exerted directly on the superior colliculus. When the response delays are longer, the PHC for medium-term spatial memory (between 25 s and a few minutes) and the hippocampal formation for long-term spatial memory (after a few minutes) store memorized information, reaching the medial temporal areas probably both serially from the DLPFC and in parallel from the PPC. The execution of intentional saccades is performed by the FEF, which is prepared to respond by the CEF (located in the ACC) influencing, via an intentional motivation process, all other frontal ocular motor areas. When motor programmes, comprising either a sequence of several successive saccades or single saccades combined with body movements, are planned, this involves the SEF just before the execution, after a probable learning in the pre-SEF. PEMs are controlled by the posterior hemispheric areas (not shown), located close to the angular gyrus at the temporo-parieto-occipital junction (medial superior temporal area and middle temporal area), but also by the FEF, the specific role of which in PEM generation is not yet really clear. Finally, the recent period has been rich in new information and interpretations concerning the cortical control of eye movements in humans, thanks to some lesion studies and especially to TMS and fMRI studies, which are currently in full development and can be expected to produce significant new advances in the near future.

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

1 Müri RM, Hess CW, Pierrot-Deseilligny C. Eye movements. In: Pascual-Leone A, Davey NJ, Rothwell J, *et al.* editors. Handbook of transcranial magnetic stimulation. London: Arnold; 2002. pp. 313–322.

2 Pierrot-Deseilligny C, Müri RM, Ploner CJ, *et al.* Cortical control of ocular saccades in humans: a model for motricity. Prog Brain Res 2003; 142:3–17.

3 Paus T. Location and function of the human frontal eye field: a selective review. Neuropsychologia 1996; 34:475–483.

4 Rosano C, Krisky CM, Welling JS, *et al.* Pursuit and saccadic eye movement subregions in human frontal eye field: a high-resolution fMRI investigation. Cereb Cortex 2002; 12:107–115.

5 Gottlieb JP, MacAvoy MG, Bruce CJ. Neural responses related to smooth-pursuit eye movements and their correspondence with electrically elicited smooth eye movements in the primate eye field. J Neurophysiol 1994; 72:1634–1653.

6 • Tanaka M, Lisberger SG. Role of arcuate frontal cortex of monkeys in smooth pursuit eye movements. I. Basic response properties to retinal image motion and position. J Neurophysiol 2002; 87:2684–2699.

The site related to pursuit eye movements is anatomically and functionally separate from the saccadic frontal eye field.

7 • Rosano C, Sweeney JA, Melchitzky DS, Lewis DA. The human precentral sulcus: chemoarchitecture of a region corresponding to the frontal eye fields. Brain Res 2003; 972:16–30.

This study provided evidence that the human FEF region identified in the precentral sulcus using fMRI is indeed characterized by a distinctive chemoarchitecture.

8 Lobel E, Kahane P, Leonards U. Localization of the human frontal eye fields: anatomical and functional findings from fMRI and intracerebral electrical stimulation. J Neurosurg 2001; 95:804–815.

9 Gagnon D, O'Driscoll GA, Petrides M, Pike GB. The effect of spatial and temporal information on saccades and neural activity in oculomotor structures. Brain 2002; 125:123–139.

10 • Petit L, Beauchamp M. Neural basis of visually guided head movements studied with fMRI. J Neurophysiol 2003; 89:2516–2527.

The role of the lateral part of the FEF, within the lateral portion of the precentral sulcus, is discussed.

11 • Milea D, Lobel E, Lehéricy S, *et al.* Intraoperative frontal eye field stimulation elicits ocular deviation and saccade suppression. Neuroreport 2002; 13:1359–1364.

Electrical stimulation of the frontal eye field may suppress self-paced saccades and elicit contralateral slow eye deviations.

12 • Blanke O, Seeck M. Direction of saccadic and smooth eye movements induced by electrical stimulation of the human frontal eye field: effect of orbital position. Exp Brain Res 2003; 150:174–183.

This provides an interesting discussion about the significance of contralateral slow eye deviations elicited by electrical stimulation.

13 Rivaud S, Müri RM, Gaymard B, *et al.* Eye movement disorders after frontal eye field lesions in humans. Exp Brain Res 1994; 102:110–120.

14 Gottlieb JP, Bruce CJ, MacAvoy MG. Smooth eye movement elicited by microstimulation in the primate frontal eye field. J Neurophysiol 1993; 69:786–799.

15 Dieterich M, Bucher SF, Seelos KC, Brandt T. Horizontal or vertical optokinetic stimulation activates visual motion-sensitive, ocular motor and vestibular cortex areas with right hemispheric dominance. A fMRI study. Brain 1998; 121:1479–1495.

16 • Dieterich M, Bense S, Stephan T, *et al.* FMRI signal increases and decreases in cortical areas during small-field optokinetic stimulation and central fixation. Exp Brain Res 2003; 148:117–127.

These authors describe an increase in activation in areas controlling optokinetic nystagmus, including the FEF, with concomitant decrease in the cortical areas involved in vestibular control, which could be related to a reciprocal visuo-vestibular inhibition existing at the cortical level for the perception of self-motion.

17 • Fukushima K, Yamanobe T, Shinmei Y, *et al.* Coding of smooth eye movements in three-dimensional space by the frontal cortex. Nature 2002; 419:157–162.

This reveals an important new finding on the FEF which is well summarized in the paper title.

18 Connolly JD, Goodale MA, Menon RS, Munoz DP. Human fMRI evidence for • the neural correlates of preparatory set. Nat Neurosci 2002; 5:1345–1352.
Antisaccades are prepared in the FEF, but this does not mean, according to the authors, that this area is involved in saccade inhibition.

19 De Souza JFX, Menon RS, Everling S. Preparatory set associated with pro-•• saccades and anti-saccades in humans investigated with event-related fMRI. J Neurophysiol 2003; 89:1016–1023.
In this study, an activation of the right DLPFC and of both FEF was observed just before antisaccades, showing that these two types of frontal areas are involved in the preparation of such saccades.

20 Cornelissen FW, Kimmig H, Shira M, *et al.* Event-related fMRI responses in the human frontal eye fields in a randomized pro- and antisaccade task. Exp Brain Res 2002; 145:270–274.

21 Sweeney JA, Mintun MA, Kwee S, *et al.* Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. J Neurophysiol 1996; 75:454–458.

22 Merriam EP, Colby CL, Thulborn KR, *et al.* Stimulus-response incompatibility activates cortex proximal to three eye fields. NeuroImage 2001; 13:794–800.

23 Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y. Cortical control of reflexive visually guided saccades. Brain 1991; 114:1473–1485.

24 Pierrot-Deseilligny C, Müri RM, Ploner CJ, *et al.* Decisional role of the • dorsolateral prefrontal cortex in ocular motor behaviour. Brain 2003; 126:1460–1473.
This was the first lesion study in humans with lesions limited to the DLPFC (area 46 of Brodmann), i.e. in the middle frontal gyrus, and report of the spectrum of abnormalities existing in all usual saccade paradigms, suggesting a decisional role of this area in ocular motor behaviour. In addition, the authors provide a useful comparison with abnormalities observed after pure FEF lesions.

25 Gaymard B, François C, Ploner CJ, *et al.* A direct prefrontotectal tract • against distractibility in the human brain. Ann Neurol 2003; 53:542–545.
This is a case report and anatomical study on the human prefronto-collicular pathway.

26 Tanaka H, Arai M, Kubo J, Hirata K. Conjugate eye deviation with head • version due to cortical infarction of the frontal eye field. Stroke 2002; 5:642–643.
A conjugate eye deviation may be observed after a small cortical infarction limited to the frontal eye field.

27 Grosbras MH, Lobel E, Van de Moortele PF, *et al.* An anatomical landmark for the supplementary eye fields in human revealed with functional magnetic resonance imaging. Cereb Cortex 1999; 9:705–711.

28 Luppino G, Rozzi S, Calzavara R, Matelli M. Prefrontal and agranular • cingulate projections to the dorsal premotor areas F2 and F7 in the macaque monkey. Eur J Neurosci 2003; 17:559–578.
This is a new contribution to the anatomical connections of the supplementary eye field.

29 Isoda M, Tanji J. Cellular activity in the supplementary eye field during • sequential performance of multiple saccades. J Neurophysiol 2002; 88:3541–3545.
The SEF neurons are involved in the coding of temporally ordered saccadic eye movements (sequences).

30 Tobler PN, Müri RM. Role of human frontal and supplementary eye fields in double step saccades. NeuroReport 2002; 13:253–255.

31 Coe B, Tomihara K, Matsusawa M, Hikosaka O. Visual and anticipatory bias in three cortical eye fields of the monkey during an adaptive decision-making task. J Neurosci 2002; 22:5081–5090.

32 Pierrot-Deseilligny C, Müri RM, Rivaud-Péchoux S, *et al.* Cortical control of spatial memory in humans: the visuo-oculomotor model. Ann Neurol 2002; 52:10–19.

33 Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y. Cortical control of memory-guided saccades in man. Exp Brain Res 1991; 83:607–617.

34 Müri RM, Vermersch AI, Rivaud S, *et al.* Effects of single-pulse transcranial magnetic stimulation over the prefrontal and posterior parietal cortices during memory-guided saccades in humans. J Neurophysiol 1996; 76:2102–2106.

35 Leung HC, Gore JC, Goldman-Rakic PS. Sustained mnemonic response in the middle human frontal gyrus during on-line storage of spatial memoranda. J Cogn Neurosci 2002; 14:659–671.

36 Sakai K, Rowe JB, Passingham RE. Active maintenance in prefrontal area 46 creates distractor-resistant memory. Nat Neurosci 2002; 5:479–483.

37 Ploner CJ, Gaymard B, Rivaud S, *et al.* Temporal limits of spatial working memory in humans. Eur J Neurosci 1998; 10:794–797.

38 Ploner CJ, Gaymard B, Rivaud-Péchoux S, *et al.* Lesions affecting the parahippocampal cortex yield spatial memory deficits in humans. Cereb Cortex 2000; 10:1211–1216.

39 Nyffeler T, Pierrot-Deseilligny C, Felblinger J, *et al.* Time-dependent • hierarchical organization of spatial working memory: a transcranial magnetic stimulation study. Eur J Neurosci 2002; 16:1823–1827.
This is an interesting contribution to the study of spatial memory in the human dorsolateral prefrontal cortex.

40 Nyffeler T, Pierrot-Deseilligny C, Hess CW, Müri RM. Parallel and serial processing components in memory-guided saccades. Exp Brain Res 2004; 154:109–112.

41 Constantinidis C, Williams GV, Goldman-Rakic P. A role for inhibition in shaping the temporal flow of information in prefrontal cortex. Nat Neurosci 2002; 5:175–180.

42 Leigh RJ, Zee DS. The neurology of eye movements. 3rd ed. Oxford: Oxford University Press; 1999.

43 Wardak C, Olivier E, Duhamel JR. Saccadic target selection deficits after • lateral intraparietal area inactivation in monkeys. J Neurosci 2002; 22:9877–9884.
This study on the monkey PEF showed that the area is important for selecting visual targets.

44 Bilsey JW, Goldberg ME. Neuronal activity in the lateral intraparietal area and •• spatial attention. Science 2003; 299:81–86.
The lateral intraparietal area (PEF) is also clearly involved in attentional processes.

45 Cutrell EB, Marrocco RT. Electrical stimulation of primate posterior parietal • cortex initiates orienting and alerting components of covert attention. Exp Brain Res 2002; 144:103–113.
Depending upon the stimulation intensity, a simple shift of attention or a saccade is elicited by PPC stimulation.

46 Müri RM, Iba-Zizen MT, Derosier C, *et al.* Location of the human posterior eye field with functional magnetic resonance imaging. J Neurol Neurosurg Psychiatry 1996; 60:445–448.

47 Kawashima R, Naitoh E, Matsumara M, *et al.* Topographic representation in human intraparietal sulcus of reaching and saccade. NeuroReport 1996; 7:1253–1256.

48 Büchel C, Josephs O, Rees G, *et al.* The functional anatomy of attention to visual motion. Brain 1998; 121:1281–1294.

49 Simon O, Mangin JF, Cohen L, *et al.* Topographical layout of hand, eye, calculation and language-related areas in the human parietal lobe. Neuron 2002; 33:475–487.

50 Culham JC, Kanwisher NG. Neuroimaging of cognitive functions in human parietal cortex. Curr Opin Neurobiol 2001; 11:157–163.

51 Brotchie PR, Lee MB, Chen DY, *et al.* Head position modulates activity in the • human parietal eye fields. NeuroImage 2003; 18: 178-184.
The human PEF is located in the posterior part of the intraparietal sulcus and its activity is modulated by head position.

52 Macaluso E, Driver J, Frith CD. Multimodal spatial representations engaged •• in human parietal cortex during both saccadic and manual spatial orienting. Curr Biol 2003; 13:990–999.
In this interesting study, clever paradigms and a conjunction analysis suggested that the posterior part of the superior parietal lobule and the anterior part of the intraparietal sulcus are involved in attentional processes but not in motor (saccade) execution.

53 Medendorp WP, Goltz HC, Vilis T, Crawford JD. Gaze-centered updating of • visual space in human parietal cortex. J Neurosci 2003; 23:6209–6214.
This fMRI study showed that the human PPC dynamically updates the spatial goals for action in a gaze-centred frame.

54 Van Donkelaar P, Müri RM. Craniotopic updating of visual space across saccades in the human posterior parietal cortex. Proc R Soc Lond 2002; 269:735–739.

55 Merriam EP, Genovese CR, Colby CL. Spatial updating in human parietal • cortex. Neuron 2003; 39:361–373.
This fMRI study showed that after an eye movement a spatial updating of visual information occurs in the human parietal cortex.

56 De Souza JFX, Dukelow SP, Gati JS, *et al.* Eye position signal modulates a human parietal pointing region during memory-guided movements. J Neurosci 2000; 20:5835–5840.

57 Yantis S, Schwarzbach J, Serences JT, *et al.* Transient neural activity in • human parietal cortex during spatial attention shifts. Nat Neurosci 2002; 5:995–1002.
This interesting fMRI study used a purely attentional paradigm, in which activation was found in the posterior part of the superior parietal lobule and the anterior part of the inferior parietal lobule (possibly the supramarginal gyrus).

58 Perry RJ, Zeki S. The neurology of saccades and covert shifts in spatial attention. Brain 2000; 123:2273–2288.

59 Corbetta M, Kincade JM, Shulman GL. Neural systems for visual orienting and their relationships to spatial working memory. J Cogn Neurosci 2002; 14:508–523.

60 • Mort DJ, Perry RJ, Mannan SK, *et al*. Differential cortical activation during voluntary and reflexive saccades in man. NeuroImage 2003; 18:231–246.
Activation of the posterior cingulate cortex during reflexive visually guided saccades.

61 Mort DJ, Malhotra P, Mannan SK, *et al*. The anatomy of visual neglect. Brain 2003; 126:1986–1997.

62 Ferraina S, Paré M, Wurtz RH. Comparison of cortico-cortical and cortico-collicular signals for the generation of saccadic eye movements. J Neurophysiol 2002; 87:845–858.

63 • Gaymard B, Lynch J, Ploner CJ, *et al*. The parieto-collicular pathway: anatomical location and contribution to saccade generation. Eur J Neurosci 2003; 17:1518–1526.
This anatomical and lesional study confirmed that the PEF, via its direct projection to the superior colliculus passing through the posterior part of the internal capsule, is involved in reflexive saccade generation but not in intentional saccade generation.

64 Paus T, Petrides M, Evans AC, Meyer E. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. J Neurophysiol 1993; 70:453–469.

65 Gaymard B, Rivaud S, Cassarini JF, *et al*. Effects of anterior cingulate cortex lesions on ocular saccades in humans. Exp Brain Res 1998; 120:173–183.

66 • Milea D, Lehéricy S, Rivaud-Péchoux S, *et al*. Antisaccade deficit after anterior cingulate cortex resection. NeuroReport 2003; 14:283–287.
The anterior cingulate cortex could also control inhibition in the antisaccade paradigm.

67 Olson CR, Musil SY, Goldberg ME. Single neurons in posterior cingulate cortex of behaving macaque: eye movement signals. J Neurophysiol 1996; 76:3285–3300.

68 Berman RA, Colby CL, Genovese CR, *et al*. Cortical networks subversing pursuit and saccadic eye movements in humans: an fMRI study. Hum Brain Mapping 1999; 8:209–225.

69 • Tanabe J, Tregellas J, Miller D, *et al*. Brain activation during smooth-pursuit eye movements. NeuroImage 2002; 17: 1315-1324.
The authors describe activation of the posterior cingulate cortex during pursuit eye movements.

70 Hopfinger JB, Buonocore MH, Mangun GR. The neural mechanisms of top-down attentional control. Nat Neurosci 2000; 3:284–291.

71 • Small DM, Gitelman DR, Gregory MD, *et al*. The posterior cingulate and medial prefrontal cortex mediate the anticipatory allocation of spatial attention. NeuroImage 2003; 633–641.
This important fMRI study suggested that the posterior cingulate cortex is involved in the preparation of on-going attentional mechanisms via a motivation process.