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The cortex is in overall control of 'voluntary' eye movement

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Abstract

The neural circuits that control eye movements are complex and distributed in brainstem, basal ganglia, cerebellum, and multiple areas of cortex. The anatomical function of the substrates implicated in eye movements has been studied for decades in numerous countries, laboratories, and clinics. The modest goal of this brief review is twofold. (1) To present a focused overview of the knowledge about the role of the cerebral cortex in voluntary control of eye movements. (2) To very briefly mention two findings showing that the accepted hierarchy between the frontal and the occipital sensory areas involved in sensory–motor transformation might not be so trivial to reconcile, and to interpret in the context of eye movement command. This presentation has been part of the 44th Cambridge Ophthalmological Symposium, on ocular motility, 3 September 2014 to 5 November 2014.
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Historically, in humans, the data describing the implications of cortical areas in controlling eye movement have been collected in patients with lesions or degenerative diseases, whereas in animal models, two ancient but still preferred tools, for the delineation of cortical regions, involved the two techniques of low-threshold current stimulation and the recording of extracellular activity.[1] More recently, ultrasonic[2] and transcranial magnetic stimulations,[3–5] as well as functional magnetic resonance imaging, provided complementary results to better understand with noninvasive techniques how eye movements are controlled by the brain.[6,7]

Within the frontal cortex, the cortical structures of the saccadic systems include; the frontal eye field (FEF) and its role in saccade and pursuit eye movement control, the supplementary eye field (SEF) and the dorsolateral prefrontal cortex (dlPFC). The SEF and the dlPFC are both involved in the decisional processes that is governing ocular motor behavior, such as when and how they inhibit an unwanted reflexive saccade. The SEF and the dlPFC are also having a role in making eye movement at a memorized location, as well as producing sequences eye movements. In the temporoparietal regions, the activity of the posterior parietal cortex is less implicated in movement execution *per se* but more involved in visuospatial integration and attention. Lastly, the anterior cingulate cortex appears to be mainly and indirectly involved in the control of externally guided eye movements and attentional mechanisms.

As briefly introduced above, in the frontal lobe, three main areas are involved in eye movement control (Figure 1). The FEF is involved in the preparation and triggering of all saccades.[8] In particular, FEF is involved in saccades generation, which are internally triggered toward a target already present (visually guided saccade), not yet present (predictive saccade), and no longer visible (memory-guided saccade) or located in the opposite direction (antisaccade). Despite some noticeable activity recorded in nonhuman primates, FEF region is believed to be less involved in the triggering of purely reflexive, visually guided saccades, which are externally triggered toward a stimulus appearing at a peripheral location. A subregion of FEF also controls pursuit eye movements, along with the cortex, the posterior temporoparietal areas,[9,10] and cerebellum.[11] In humans, studies using fMRI have delimited the location of the FEF mainly to the intersection between the precentral sulcus and the superior frontal

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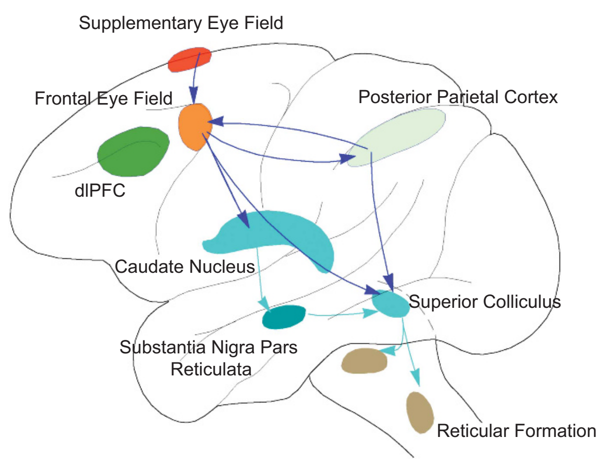

Figure 1 Supranuclear region implicated in the control of eye movements.

sulcus, whereas the pursuit-related area to a deeper region along the anterior wall, the fundus, and the deep part of the posterior wall.[10] In the precentral sulcus, aside 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.[12] The specific role of this lateral locus remains to be determined, as it is activated both by single and combined eye and head movements.[13]

As illustrated in Figure 2, the antisaccade paradigm permits to study intentional saccades that have to be made in the direction opposite to a suddenly appearing peripheral visual target.[14] To generate these movements at least two mechanisms are believed to be required: the inhibition of the unwanted reflexive saccade to the target; and the consecutive triggering of an intentional correct antisaccade made in the direction opposite to the target. Prosaccades and antisaccades have been intensively studied in humans (fMRI) and monkeys single unit (SU). In all reports, stronger activation has been observed just before antisaccades in the FEF than in prosaccade.[15,16] All these studies, confirm that such intentional saccades require an early preparation of FEF in antisaccades but not in prosaccades. However and although FEF is active in antisaccade preparation, these results do not demonstrate that inhibition or relocation of misdirected reflexive prosaccades are organized within the FEF *per se*. In fact, activation of the dlPFC and/or the SEF were also recorded just before antisaccades.[16] In that scenario, the inhibition of reflexive saccades by the dlPFC and/or SEF could be exerted via FEF or directly on the superior colliculus, without involving other cortical areas, via a prefrontocollicular tract.[17]

SEF is located on the medial surface of the superior frontal gyrus.[16] In humans, SEF is located in the upper part of the para-central sulcus (Figure 1). Anatomically

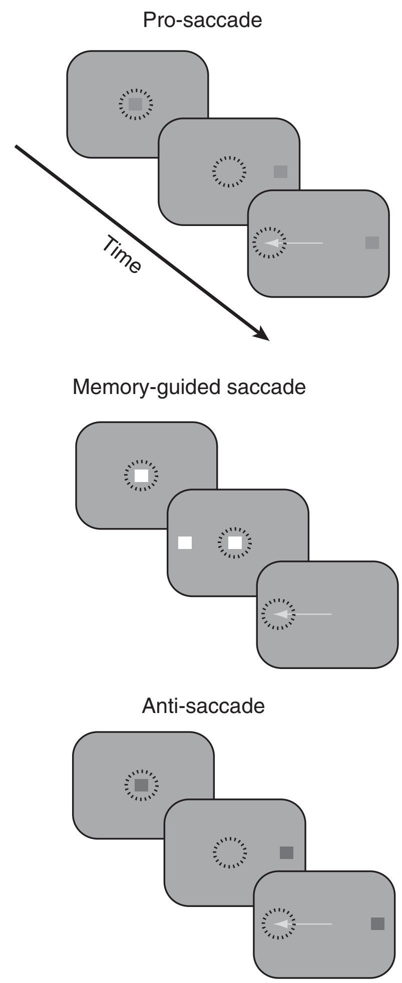

Figure 2 Saccade and saccadic paradigms.

SEF appears to be a critical node in the oculomotor circuit. SEF is connected with all areas involved in eye movement control—the FEF, the dlPFC, the anterior cingulate cortex (ACC), most of the parietal cortex, and also deep oculomotor structures in the brainstem. Electrical stimulation in monkey and lesion studies in humans have demonstrated that SEF is involved in motor program comprising a saccade combined with a body movement.[18] In SU-recording studies in monkey, using a saccade sequence, it was demonstrated that the SEF neurons are also involved in the coding of temporally ordered saccadic eye movements.[19] In the same vein, a recent TMS study in humans has shown that 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). Altogether, these results validate that the SEF control and have an important role in motor preparation rather than motor program by itself, even when they are limited to a single saccade.[8]

Slightly more rostral and lateral than the SEF (dlPFC Figure 1), the dlPFC is involved in saccade inhibition,[20] but see,[21] as well as, short-term spatial memory and in decision processes.[22] Human and nonhuman primates studies have demonstrated 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.[23] Aside its role in memory-guided saccades the dlPFC is also involved in the control of predictive saccades.[24] These results in conjunction with those referred to above suggest that the dlPFC has a crucial role in decisional processes governing eye movement behavior, 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.

All these decisional rules that are important in guiding or inhibiting future responses are believed to be exerted through inhibitory interactions between neurons in the dlPFC, FEF, SEF, and parietal regions. In particular, the control of the timing during cognitive operations might be thereby shaped by the temporal flow of information between FEF, SEF, and dlPFC.[25]

In the parietal lobe, the location and function of subregions involved in eye movements and attention have been studied intensively, but are still not so well known.[26,27] The parietal lobe and more particularly its posterior part, the PPC, are involved in the control of saccades and attention. In humans and nonhuman primates, the PPC includes the intraparietal sulcus (IPS) extending from the post-central sulcus anteriorly to the parieto-occipital sulcus posteriorly (Figure 1). The anatomy of the IPS is not trivial to compare across subjects and species, being relatively variable from one subject to another.[28] The human parietal-eye-field (PEF) corresponds to the lateral intraparietal area of the monkey. The lateral intraparietal area is involved in the control of saccades, but also in attentional processes. Furthermore, low threshold of electrical stimulation of this area in the monkey or human results in a simple shift of visual attention (without eye movement), whereas stronger stimulation results in a saccade.[29–31] These results emphasize in PPC but also in other brain regions, the close but distinct circuits existing between saccades and attention, even in the same area.[32–34] The PEF appears to be located along the IPS, within the sulcus, 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).

As it has been noticed in SEF, the activation of the PEF is also modulated by head position. The PEF projects to both the FEF and the superior colliculus (Figure 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 parietosuperior colliculus projection. The parieto-FEF projection is believed to be mainly involved in visual processing, whereas the parietocolliculus projection is more involved in express saccades.[32] The results of studies in patients with lesions affecting the posterior part of the internal capsule, damaging the direct parietocollicular tract originating in the PEF, are in accordance with the experimental results and confirm that the PEF is crucial for reflexive saccade generation, but not for intentional saccade generation. The latter depends mainly upon FEF, SEF, and dlPFC activities.[25]

Finally, the cingulate cortex, which is not *per se* an oculomotor area, has also been found to have an important role in the control of voluntary saccades. In particular, the rostral part of the cingulate cortex is involved in intentional saccade control, but not in reflexive saccade control. The dorsal bank of the ACC is involved, via direct connections to SEF, in preparing all the frontal ocular motor areas involved in intentional saccade control to act in the forthcoming motor behavior. The dlPFC is also connected to ACC.[35,36]

Discussion

In the illustrated classical view of this brief document, it is argued that the signal sufficient to elicit reflexive saccades are largely generated by the short loop, through the posterior part of the internal capsule, between the parietal and the superior colliculus, whereas voluntary eye movements required the additive and active signal from frontomedian regions including FEF, dlPFC, SEF, and ACC. However, some findings suggest that saccades might be generated in a much more intermixed activities than previously thought.

In 1991, Felleman and Van Essen[37] have proposed a hierarchical model of visual processing that is largely accepted. In this model, visual information reaches the frontal cortex and FEF in particular, at a very high level (which could be functionally transcript by a delayed visual response in these frontal areas). Although, these conceptions did account for psychophysiological models and hypotheses, important functional contradictions have been reported but rarely highlighted in particular in the oculomotor literature. First, recent experiments have demonstrated that the neuronal activities in monkeys, but also in humans, can reach the frontal part of the cortex and FEF in particular only after 60 ms (latencies comparable to early response in visual cortex).[38–40] Second and rarely accounted for in the literature of express saccades, some anatomical findings provide evidence that part of the activity in the frontal cortex mainly drive, via connections to extrastriate visual areas, feedforward signals and not, as often reported, feedback signals.[32,41]

Conclusion

All the accumulated studies in humans and nonhuman primates have been extremely important to describe the cortical control of eye movements. At the present day, in the frontal cortex, FEF is believed to be involved for the execution of intentional saccades. The neuronal responses present in FEF are prepared by the activities in SEF, ACC, and dlPFC, whereas in the parietal lobe, short loops, through the posterior part of the internal capsule, between the parietal and the superior colliculus, are believed to be sufficient to elicit reflexive saccades. However, to mention only two findings that are going against the grain in the literature of eye movements control: (1) the hierarchy between the frontal, the parietal, and the sensory areas might have been too simplified; (2) the antomicofunctional constrains present for the sensory–motor transformation might not be so trivial to reconcile with the current hierarchy of visual areas. Despite tremendous efforts and many successful findings, future researches are still required to causally disentangle the roles and hierarchies of the cortical and subcortical areas responsible for the control of voluntary eye movements.

Conflict of interest

The author declares no conflict of interest.

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