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Cortical and sub-cortical control of saccades and clinical application

Contrôle cortical et sous-cortical des saccades et application clinique

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ABSTRACT

Saccades allow object of interest that are perceived by the peripheral retina to be displayed on the fovea, a small central retinal area of maximum visual accuracy. Saccades may be generated under a large variety of circumstances, from reflexive like saccades (e.g. towards a threatening visual cue) to highly volitional saccades (e.g. towards the memorized location of a no longer present visual cue). These different contexts correspond to different complexities of decision-making processes and, on a behavioral aspect, to saccades with different latencies, and to the involvement of different cortical areas. However, whatever their type, saccades need to be fast, in order to avoid any persaccadic visual blur, and accurate since the fovea represents less than 1° of visual angle. This combination of accuracy and velocity is achieved thanks to a collaboration of brainstem and cerebellar oculomotor structures. The basic neural structures involved in these processes are reviewed, a special emphasis being given to clinically relevant mechanisms.

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RÉSUMÉ

Les saccades permettent de disposer l’image d’un objet perçu en vision périphérique sur la fovéa, une petite région de la rétine centrale où l’acuité visuelle est maximale. Les saccades peuvent être produites dans des conditions très variées, allant des saccades très « reflexes » (dirigée par exemple vers un stimulus menaçant) aux saccades très volontaires (dirigée par exemple vers l’emplacement mémorisé d’un stimulus disparu). Ces différents contextes dans lesquels peuvent être déclenchées des saccades correspondent à des processus de décision différents, se traduisent sur un plan comportemental par des temps de reaction différents et à la mise en jeu d’aires cérébrales différentes. Cependant, quel que soit leur type, les saccades doivent être à la fois rapides, afin de limiter le flou visuel qui pourrait provenir du glissement rétinien de l’image, et précises car la fovea représente moins d’un degré d’angle visuel. Cette combinaison de vitesse et de précision est assurée par la collaboration de structures oculomotrices situées dans le cervelet et le tronc cérébral. Les bases neurales qui sous-tendent ces processus sont ici revues, en insistant davantage sur ceux qui présentent une pertinence clinique.

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While you are reading this article and taking notes, a small flying animal suddenly lands on the left side of the page. Its image, being perceived by your peripheral retina, is unclear. You are therefore unable to determine if it’s a fly or a mosquito. Two situations may then happen. If you are afraid of sticking insects, you will rapidly need to know. In order to provide a detailed analysis of the insect, you will have to display its image on the foveal area of your eyes, i.e. where visual accuracy is the best. You will hence orient your sight towards the animal. This eye movement, called a reactive (or reflexive) visually-guided saccade, will be triggered by the appearance of the insect and directed toward it. You may however be concentrated on your reading and about to write down some notes; although you did pay attention to the insect, you will nevertheless decide to pick up your red pen, on the other side of the page. You will therefore trigger a volitional saccade, i.e. a saccade triggered at your own pace and towards a selected object. Reactive and volitional saccades share similar properties, such as high velocity (up to 500° per second) and high accuracy (amplitude error below 10%). Indeed, both need to be fast, otherwise a visual blur resulting from the slipping of the image across your retina might occur, and need to be accurate, since their goal is to display the image of interest on the fovea, which represents only 1% of the surface of the retina. These properties are achieved mainly thanks to the cerebellum and the brainstem that contains the saccade generator. However, these two types of saccades, being triggered in different contexts and resulting from more or less elaborated decision processes, are controlled by partially different higher level cortical areas.

The aim of this review is to present the main cerebral structures and mechanisms involved in saccade control and illustrate the clinical consequences of their dysfunction. To this end, we will focus especially on physiological processings that have clear relevance in clinical practice.

1. Neural basis of saccade control

The oculomotor network is composed of visual afferent pathways and areas, cortical oculomotor areas involved the computation of saccadic commands and efferent oculomotor structures responsible for saccade execution (Fig. 1).

1.1. Afferent visual structures

The salient visual signal is perceived by the peripheral retina and carried towards the primary visual area through the geniculate body, in the posterior thalamus. Other accessory pathways, such as the direct retino-tectal pathway, are believed to play a minor role in saccade control in humans.

1.2. Cortical oculomotor areas: target selection process and saccade decision making

After an initial processing in visual areas that is out of the scope of this review, the visual afferent signal is sent via the dorsal stream to the two main oculomotor areas, namely the parietal and the frontal eye fields (respectively PEF and FEF).

The FEF, located in the posterior part of the intraparietal sulcus, is mainly responsible for visuo-spatial attention and the transformation of the visual input into a motor command (Müri et al., 1996; Andersen et al., 1990; Gaymard et al., 1998). It is bilaterally and reciprocally connected with the FEF, located at the junction between the precentral sulcus and the superior frontal sulcus (Ferraina et al., 2002; Tian and Lynch, 1996; Amiez et al., 2006). The FEF is the main oculomotor area, being involved in target selection, saccade decision-making, visual to motor transformation and saccade initiation (Bruce and Goldberg, 1985; Thompson et al., 1997; Schall, 1997). In natural situations, saccades may be classified on a continuous gradient between quite “reflexive” saccades, e.g. triggered

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Fig. 1 – Main cerebral structures involved in saccade control. Only efferent pathways are schematically represented. The red color for dorsolateral prefrontal cortex (DLPFC) efferent tract denotes an inhibitory influence.
by the sudden onset of a threatening event (towards the insect), and highly volitional saccades, e.g. searching saccades in a stable environment (towards the red pencil). This gradient corresponds to the variable and relative contribution of bottom up and top down processes that regulate attentional shifts, and to the various complexities of decision-making processes (Hutton, 2008). On a behavioral aspect, these different contexts in which a saccade is triggered will be illustrated by variations of saccade reaction times. The minimum conduction time from the retina to the brainstem saccade generator via cortical areas is around 60 ms. Since saccade latencies are around 200 ms, the additional time is mainly related to decision processes. Indeed, express saccades, that result from an immediate visual to motor transformation with minimal decision-making, have very short latencies (80–130 ms), whereas remembered saccades that require high-level cognitive control, have latencies well above 200 ms. Both PEF and FEF would be simultaneously involved in saccade triggering, although a large body of evidence suggests the existence of a gradient between more reactive saccades, mainly generated by the PEF, and more volitional saccades, mainly generated by the FEF (Pierrot-Deseilligny et al., 1991a; Rivaud et al., 1994; Braun et al., 1992). In the present situation, the PEF will probably be more responsible for the reactive saccade towards the insect (bottom up shift of attention), with a shorter saccade latency, whereas the FEF will be more responsible for the voluntary saccade triggered towards the red pencil (top down control of attentional shift), with a longer latency.

In the second scenario, a reactive saccade towards the insect will first need to be canceled. Indeed, it is certainly useful to determine where to look, but it may also be useful to know where not to look. Another frontal area, the dorsolateral prefrontal cortex (DLPFC) will then interact with this cortical network and allow any unwanted reactive saccades to be canceled (Ploner et al., 2005; Condy et al., 2007). The DLPFC is not a true oculomotor area, since it does not contribute to saccade triggering per se. It should be noted that this same area is also responsible for spatial working memory, which allows the triggering of memory-guided saccades (saccades towards a remembered location) and predictive saccades (saccades towards an expected location) (Funahashi et al., 1993; Pierrot-Deseilligny et al., 2003). The maintenance of an internal representation during a short delay requires the internal signal to be protected against potential distractors.

Besides the FEF, the frontal lobe harbors a second oculomotor area, located on the medial wall near the paracentral sulcus, named the supplementary eye field (SEF) (Schlag and Schlag-Rey, 1987). This area, that has been more recently discovered, would be involved in especially higher order oculomotor control, such as conditional oculomotor associations (Chen and Wise, 1995), the chronological control of sequential saccades (Gaymard et al., 1993) and the modulation of the oculomotor system according to error monitoring (Emeric et al., 2010).

In clinical practice, lesions of a cortical eye field or its efferences mainly results in increased saccade reaction times. Depending on the affected area, saccade latencies will be increased in more or less selective contexts. In patients with cortico-basal degeneration for example, the parietal lobe is mainly affected by the degenerative process resulting in a typical increase of reactive saccade reaction times (Vidalihet et al., 1994). Conversely, a main oculomotor finding in patients with Huntington’s chorea is increased latencies of volitional saccades, reflecting an impaired FEF output (Klöppel et al., 2008). Saccade velocities are globally unaffected, and various degrees of inaccuracy, especially saccade hypometria, may be observed. In exceptional situations, both parietal and frontal eye fields may be damaged, resulting in extremely increased saccade reaction times, a clinical feature known as oculomotor apraxia (Pierrot-Deseilligny et al., 1988). A DLPFC lesion will induce a behavioral disorder known as increased distractibility, related to a weakened ability to cancel saccades to irrelevant environmental stimuli. This frontal lobe syndrome is at the origin of the antisaccade task, in which a subject is instructed to look in the direction opposite to suddenly presented peripheral stimuli. In patients with DLPFC disorders, such as patients with progressive supranuclear palsy (PSP), a markedly increased number of misdirected saccades (i.e. towards the target) is a key symptom (Pierrot-Deseilligny et al., 1991b). Although less commonly evaluated in clinical practice, a decreased accuracy of memory-guided saccades may also be observed (Ploner et al., 1999). Concerning the SEF, lesions of this area do not seem to affect basic saccade parameters (Gaymard et al., 1990; Stuphorn et al., 2010), but more works are definitely needed in order to determine a clear pattern with any clinical usefulness.

1.3. Sub-cortical structures: the basal ganglia and the superior colliculus

The superior colliculus (SC), located in the tectum of the upper brainstem, represents the main link between the retina and the brainstem saccade generator in lower vertebrates (Casagrande and Diamond, 1974). In more evolved species, it has become more and more under cortical influence. Indeed in primates, both PEF and FEF are directly connected with this key oculomotor structure. Whereas the parieto-tectal pathway is the unique route by which the FEF has access to the brainstem saccade generator (Lynch et al., 1985; Gaymard et al., 2003), the FEF has additional parallel tracts: an indirect tract towards the SC via relays in the basal ganglia, and direct tracts towards the brainstem (Huerta et al., 1986; Stanton et al., 1988).

The basal ganglia, namely the body of the caudate and the substantia nigra pars reticulata, being located on an FEF efferent pathway, belong therefore to the more volitional oculomotor network. Indeed, seminal experimental data have shown that they play a major role in higher order processings such as motivation, working memory and target selection processes (Hikosaka et al., 2000). The basal ganglia are thus involved in the control of higher order non-visually-guided saccades such as memory-guided or predictive saccades (Vermersch et al., 1999).

All major oculomotor efferent pathways project either directly or indirectly on the SC, one of the most investigated oculomotor areas. It is a multilayered structure, the most superficial of its seven layers being devoted to the processing of visual signals and its intermediate and deepest layers being mainly involved in the computation of the saccadic motor
command. These motor layers contain two types of saccade-related neurons: build-up neurons, whose activity rises progressively during the preparatory period and who is not necessarily linked to saccade triggering, and saccade burst neurons that discharge abruptly 20 ms before saccade onset. These neurons are organized along a rostro-caudal map that encodes saccade amplitudes, larger saccades being coded at more caudal sites of this map, the rostral pole being more concerned with fixation and microsaccades (Wurtz and Mohler, 1976; Munoz and Wurtz, 1993; Everling et al., 1998).

The SC would thus be under various degrees of cortical control, being involved in express saccade triggering, through a direct retino-parieto-tectal pathway, and in more volitional types of saccades, reflecting larger influence of the frontal lobe. The SC has a main ascending output towards the FEF via a thalamic relay (Sommer and Wurtz, 2004) and several descending outputs towards the brainstem (Wurtz and Albano, 1980). Direct pathways are sent towards the brainstem saccade generator, and an indirect pathway projects to the oculomotor cerebellum via pontine nuclei (Thier and Möck, 2006).

In clinical practice, the effect of basal ganglia dysfunction is mainly illustrated by the analysis of patients with degenerative disorders such as Parkinson’s disease. The resulting oculomotor impairments are however difficult to interpret, since compensatory mechanisms inevitably occur during the development of these slowly evolving processes. As a consequence, saccade deficits are quite discrete in patients with early Parkinson’s disease. Saccades may be hypometric, especially voluntary saccades performed in the absence of any visual target such as predictive or memory-guided saccades (Chan et al., 2005; Blekher et al., 2009; Matsumoto et al., 2011). These are then typically broken into multiple small successive saccades, the so-called multiple step saccades. Additional saccade impairments observed in patients with more evolved Parkinson’s disease or other parkinsonian syndromes most often result from the involvement of additional brain areas in the pathological process.

Selective lesions of the SC have been exceptionally reported in clinical practice. Their consequences affect every saccade parameter, as it would be expected from an area located at the interface between cortical and brainstem centers: saccades may be misdirected towards distractors, have reduced directional accuracy, longer reaction times and slower velocities (Dias et al., 1995; McPeek and Keller, 2004; Pierrot-Deseilligny et al., 1991a).

1.4 Brainstem and cerebellum

The brainstem saccade generator is located at two levels of the brainstem: in the pontine tegmentum, for the control of horizontal saccades, and in the pretectal area, for the control of vertical saccades (Leigh and Zee, 2006). The pontine generator contains two main populations of neurons: omnipause and burst neurons (Sparks, 2002). Omnipause neurons fire during fixation and are silent during saccades of any direction. They are controlled by collicular fixation neurons and exert a powerful inhibition on horizontal and vertical burst neurons (Sparks, 2002). Burst neurons are composed of excitatory burst neurons (EBN) that activate the agonist oculomotor neurons responsible for the desired saccade, and inhibitory burst neurons (IBN) that inhibit the contralateral saccade generator (Strassman et al., 1986a, 1986b).

Immediately before a saccade, omnipause neurons release burst neurons from inhibition, which results in a sudden discharge in burst neurons. EBNs ipsilateral to the saccade about to be triggered then receive an additional saccadic drive from the caudal SC and fire with a high frequency rate throughout the saccades. During saccade generation, the ipsilateral saccade generator is thus activated while the contralateral saccade generator is actively inhibited. EBNs are responsible for the initial saccade acceleration and encode saccade velocity. Near the end of the saccade, a brief activation of contralateral IBNs occurs, in order to rapidly inhibit the ipsilateral EBNs, thus providing a deceleration command that stops the saccade (Fuchs et al., 1993). This late activation of the contralateral IBNs is crucial for the control of saccade amplitude, and would be mainly under cerebellar control (Quiaux et al., 1999). Indeed, experimental studies have shown that the SC provides a directional saccadic drive with relative low amplitude accuracy and large trial to trial variability. Increased and fairly constant saccade accuracy would be achieved thanks to the colliculo-ponto-cerebellar network that ultimately drives the IBNs (Quiaux et al., 1999).

In the cerebellum, the main oculomotor structures involved in saccade control are the posterior vermis (lobules VI & VII) and the underlying caudal fastigial nucleus (Robinson et al., 1993; Girard and Berthoz, 2005; Glickstein et al., 2011). Recent findings support a role of additional lateral areas in the cerebellar hemisphere (Panouillères et al., 2012). The major role of these structures would be to ensure an on-line control of saccade amplitude through a feedback system (Kheradmand and Zee, 2011). Besides this quasi-instantaneous saccade control, the cerebellum is also responsible for long-term maintenance of saccade accuracy (Pélishon et al., 2010). This long-term control is reflected by the persistence of highly accurate saccades despite fatigue and in the elderly. It would rely on a colliculo-olivo-cerebellar network in which climbing fibers would convey systematic post-saccadic error signals in order to modify accordingly the cerebellar influence on saccade amplitude (Kojima et al., 2007; Soetedjo et al., 2009).

In clinical practice, lesions of the oculomotor cerebellum markedly affect saccade accuracy with less alteration of saccade velocities and latencies (Takagi et al., 1998, Vahedi et al., 1995). The most typical aspect observed in cerebellar patient is the highly variability of saccade amplitude. Different patterns of hypo and hypermetria may be observed depending on the side of the lesion and on the affected structure (vermis or fastigial nucleus) (Kheradmand and Zee, 2011) (Fig. 2). Whereas saccade hypometria may be observed after extracebellar lesions, saccade hypermetria strongly suggests a cerebellar syndrome. Damage to the brainstem saccade generator results in a major and highly specific impairment: saccade slowing (Pierrot-Deseilligny et al., 1982). Whereas subtle alterations of saccade velocities may be caused by extra-brainstem lesions, a clear decreased saccade velocity is highly indicative of a lesion involving the saccade generator. A selective slowing of horizontal saccades results from a lesion affecting the pontine saccade generator (Fig. 2) and a selective slowing of vertical saccades results from a lesion affecting the
mesencephalic saccade generator (Pierrot-Deseilligny, 1985). Conversely, a dysfunction of omnipause neurons, connected with both pontine and mesencephalic burst neurons, results in a homogeneous slowing of both horizontal and vertical saccades (Kaneko, 1996).

2. Clinical examination of saccade parameters

Useful information may be obtained by the clinical examination of saccades. The examiner must be placed in front of the patient that is informed to keep the head straight. The examiner’s finger or a colored object is then placed laterally, either right or left at eye level, and the subject is asked to look successively at the examiners eyes then at the peripheral object. During the initial fixation period, any abnormal eye movement or position of the eyes must be noted. During horizontal saccades, both eyes must be carefully observed. Do the eyes move in synchrony or is there any, even subtle, loss of conjugacy? Do both eyes move with normal velocity? During a normal saccade, it is typically impossible for the examiner to follow the subject’s eyes, otherwise a decreased velocity is likely. Are saccades accurate? In healthy subjects, a physiological dysmetria may be perceived clinically as a small undershoot, the initial saccade landing close to the target: a short corrective saccade in the same direction as the initial saccade is needed in order to reach the target. A large corrective saccade in the same direction as the initial saccade denotes an excessive undershoot. The triggering of a backward corrective saccade (in the opposite direction to the initial saccade) denotes an overshoot, i.e. saccade hypermetria. Persistent saccade hypermetria is highly suggestive of a cerebellar disorder. In case of discrete cerebellar syndrome, saccade hypermetria may be restricted to centripetal saccades. The eyes should be maintained a few seconds in the lateral position in order to detect any abnormal eye movement (e.g. gaze evoked or downbeat nystagmus). A similar procedure is done along the vertical axis, but it should be reminded that upward saccades are uncomfortable in older subjects, and are therefore often of restricted amplitude, probably because of mechanical factors. In such cases however, saccade velocity is normal.

A more detailed and quantitative examination requires the use of a recording device. Video-bases eye trackers are now widely used, this method being totally non invasive. It allows the recording and analysis of horizontal and vertical eye movements with reasonable accuracy, provided it has an adequate sampling rate (250 Hz or above). Importantly, each oculomotor lab should establish its own normal values obtained from the analysis of a large number of healthy subjects performing the same tasks in the same conditions as patients (luminance, timing, instruction etc.).

Different saccade tasks may then be analyzed, for example reactive saccades, memory-guided saccades or antisaccades (saccades performed in the direction opposite to the target). The analysis is usually done off-line with softwares able to detect saccades onset and offset, and provide saccade latencies, mean and maximum velocities and amplitudes.

Fig. 2 – Examples of horizontal saccade recordings. A. Normal saccade. B. Slow saccade. C. Hypometric saccade. D. Hypermetric saccade. Vertical arrow heads represent target onset. The horizontal dotted lines represent lateral target location. Scale: in A, the horizontal bar represents 200 ms, the vertical bar 5°.
A manual control of each saccade is however systematically needed after the automatic analysis.

Disclosure of interest

The author declares that he has no conflict of interest concerning this article.

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