CHAPTER 5

Control of saccadic eye movements and combined eye/head gaze shifts by the medio-posterior cerebellum

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Abstract: The cerebellar areas involved in the control of saccades have recently been identified in the medio-posterior cerebellum (MPC). Unit activity recordings, experimental lesions and electrical microstimulation of this region in cats and monkeys have provided a considerable amount of data and allowed the development of new computational models. In this paper, we review these data and concepts about cerebellar function, discuss their importance and limitations and suggest future directions for research. The anatomical data indicate that the MPC has more than one site of action in the visuo-oculomotor system. In contrast, most models emphasize the role of cerebellar connections with immediate pre-oculomotor circuits in the reticular formation, and only one recent model also incorporates the ascending projections of the MPC to the superior colliculus. A major challenge for future studies, in continuation with this initial attempt, is to determine whether the various cerebellar output pathways correspond to distinct contributions to the control of saccadic eye movements. Also, a series of recent studies in the cat have indicated a more general role of the MPC in the control of orienting movements in space, calling for an increasing effort to the study of the MPC in the production of head-unrestrained saccadic gaze shifts.

Introduction

There has been a long-standing tradition of studying the role of the cerebellum in motor functions. This interest originates in the 19th century with the first detailed description of the cerebellar syndrome (Flourens, 1824) and with the pioneering anatomical description of the cerebellar architecture (Cajal, 1888) and was later renewed by the use of computers to simulate the processing performed by the cerebellar cortex (Marr, 1969; Albus, 1971). More recently, the use of neurophysiological and functional imaging techniques has contributed to the establishment of several cerebellar theories in motor control and in other cognitive functions (see reviews in: Ito, 1984; Thach et al., 1992; Schmahmann, 1996). The present paper focuses on motor aspects and specifically reviews the recently emerging effort allocated to the study of the cerebellar role in the production of quick orienting movements (saccades) of the line of sight.

Saccadic shifts of the line of sight (gaze) towards a visual target represent a good model for studying the role of the cerebellum in the control of goal-directed action (Robinson and Fuchs, 2001). Indeed, saccadic eye movements are relatively simple motor responses and our knowledge about their dynamical and metrical properties as well as their underlying neural control is much more advanced than for any other motor response involving the squeletomotor system (see Guitton et al., 2003, this volume; Lünneburger et al., 2003, this volume; Sparks and Gandhi, 2003, this volume; Guettion et al., 2003, this volume; Lünneberger et al., 2003, this volume; Sparks and Gandhi, 2003, this volume).
2003, this volume). In addition, the understanding of the physiopathological bases of saccade dysmetria will help in alleviating the disastrous consequences of cerebellar damage in patients.

In this paper, we review experimental data and theoretical studies addressing the role of the cerebellum in the control of orienting gaze shifts. We will first review anatomical and functional data and then confront these data to the predictions of recent models of saccadic control that incorporate the cerebellum. The cerebellar adaptive control will be treated in this paper only when providing complementary information as to the neural processes and pathways underlying the control of saccades. Neurophysiological data have been provided mostly by studies performed in the monkey, and in the cat especially in relation to head-unrestrained gaze shifts.

**Cerebellar territories involved in saccadic control**

According to the functional organization of the cerebellum into parasagittal zones, the vermis and underlying fastigial nucleus are involved in the control of eye movements, reflexive postural adjustments and autonomic function. Early studies led to the notion that the cerebellar vermis of the posterior lobe is specifically involved in oculomotor control. In particular, stimulation studies (Cohen et al., 1965; Ron and Robinson, 1973; Llinas and Wolfe, 1977; Gauthier and Stark, 1979) disclosed a widespread territory from which saccadic eye movements can be elicited with a preferential locus at the level of the posterior vermis. Lesion studies (Optican and Robinson, 1980; Optican et al., 1986) revealed that two distinct cerebellar territories are involved in the control of saccade: the vermis participates in generating the pulse of activity required to overcome the viscoelastic forces of the oculomotor plant and the flocculus contributes to the sustained activity required for holding the eye against passive elastic forces.

Using anatomical, electrophysiological and pharmacological approaches, Noda and colleagues (Noda, 1991) delineated within the medio-posterior cerebellum (MPC) the cerebellar territories involved in the control of saccade metrics (amplitude and direction). This ‘oculomotor cerebellum’ comprises the lobules Vlc and VII of the cerebellar vermis and their output target neurons in the caudal portion of the fastigial nucleus (cat: Courville and Diakiw, 1976; Hirai et al., 1982; monkey: Noda et al., 1990). This caudal part of the fastigial nucleus (cFN) thus constitutes the exclusive output of the MPC and has been named fastigial oculomotor region (FOR) by Noda. Together with the flocculus, the MPC is also involved in the control of smooth pursuit eye movements (Suzuki and Keller, 1988a,b; Pierrot-Desilligny et al., 1990; Büttnner et al., 1991; Kurzan et al., 1993; Fuchs et al., 1994; Robinson et al., 1997; Krauzlis and Miles, 1998; Takagi et al., 2000). Another functional zone of the fastigial nucleus, rostrally located (rFN), responds to optokinetic or vestibular stimulation (Büttnner et al., 1991, 1999; Gruart and Delgado-Garcia, 1994; Siebold et al., 1997) and would be involved in the control of the somatic musculature (Büttnner et al., 1991). The rFN will be discussed for comparison with the cFN in the light of its recently demonstrated involvement in the control of head-unrestrained gaze shifts.

Other cerebellar zones have saccade-related activity and project to oculomotor centers but there are no data showing a direct involvement in saccadic control (Takikawa et al., 1998; Robinson, 2000). More recently, the ventral zone of the interposed nucleus was proposed to be involved in the control of the vertical component of saccadic eye movements (Robinson, 2000).

**Input/output relationship of the MPC**

Anatomical data show a wide network with the cerebellum situated in parallel with respect to major motor and sensory pathways (Fig. 1). Afferent projections to the MPC contact both the vermis and the cFN, and many vermal projecting neurons produce a collateral to the cFN (Noda et al., 1990). (Noda et al., 1990). MPC input, like other cerebellar afferents, can be segregated into mossy fiber input and climbing fiber input.

**Afferent projections to the MPC**

According to the anatomical data in the monkey, the following structures provide the MPC with mossy fibers input, through mainly bilateral projections (Hoddevik et al., 1977; Batini et al., 1978; Gould, 1980; Carpenter and Batton, 1982; Dietrichs and Walberg, 1987; Gerrits and Voogd, 1987; Yamada
Fig. 1. This diagram shows the main anatomical connections of the medio-posterior cerebellum (MPC) with the centers involved in the production of orienting gaze shift toward a visual target. Inputs and outputs of the MPC are shown by open and filled arrows, respectively, indirect projections by dotted arrows, and inhibitory connections by a dash-terminated arrow.

and Noda, 1987; Blanks, 1988; Noda et al., 1990; Thielert and Thier, 1993). Dorsolateral pontine nuclei (DLPN) and nucleus reticularis tegmenti pontis (NRTP) provide the most numerous synaptic inputs, followed by the pontine paramedian reticular formation (PPRF), pontis raphe nucleus and the medullary reticular formation (MRF). The MPC also gets bilateral input, although less intense, from the vestibular complex (MVN, IVN, SVN) and NPH and directly from the vestibular apparatus (Kotchabhakdi and Walberg, 1978). Concerning the climbing fibers input, the exclusively crossed projections originate in the caudal portion of the medial accessory olive (MAO) (Hoddevik et al., 1977; Groenewegen and Voogd, 1977; Dietrichs and Walberg, 1985; Yamada and Noda, 1987; Noda et al., 1990).

Efferent projections of the MPC

The cFN constitutes the exclusive output of the MPC. It sends feedback projections to all structures afferenting it. Thus, the cFN projects to the brainstem reticular formation (Carpenter and Batton, 1982; McCrea and Baker, 1985; Noda et al., 1990; Homma et al., 1995), including the PPRF and the MRF where saccade related premotor neurons have been found, and vestibular complex (mostly MVN), the NRTP and DLPN nuclei, and the contralateral MAO (Dietrichs and Walberg, 1985). Whereas the NPH receives projections from the rFN (McCrea and Baker, 1985), it is debated whether this nucleus also gets input from the cFN (McCrea and Baker, 1985; Ohtsuka, 1988). The cFN is also contacting premotor neurons involved in the control of head movements, either through the vestibular complex and the reticulo-spinal neurons or directly by projections to the spinal cord cervical segments (Eccles et al., 1975; Matsushita and Hosoya, 1978). Other cerebellar influences over eye and head movements contributing to the saccadic shift of gaze in space also involve ascending projection of the cFN to the deep layers of the superior colliculus (SC). However, whether
and how the fastigial terminals in the SC motor map show a topographical organization is still a controversial issue, since the different studies suggest a preferential termination of fastigial fibers either in the rostral SC (Batton et al., 1977; May et al., 1990; Hirai et al., 1982), in the caudal SC (Roldan and Reinoso-Suarez, 1981) or do not show any clear topographical arrangement along the rostro-caudal axis of the SC (Kawamura et al., 1982; Sugimoto et al., 1982). Ascending projections towards the ventromedian thalamus (Nakano et al., 1980; Sugimoto et al., 1982; Jimenez-Castellanos and Reinoso-Suarez, 1985; Katoh and Deura, 1993) suggest a cerebellar influence upon areas of cerebral cortex (frontal and parietal lobe in the monkey: Sasaki et al., 1976; and in the cat: Kyuhou and Kawaguchi, 1987; Steriade, 1995). The contribution of these projections to the translation of sensory input into oculomotor commands is not known. Notably, these thalamic and collicular ascending projections originate exclusively from the caudal part of the FN, and not from its rostral portion.

In general, efferent neurons from the deep cerebellar nuclei are thought to exert an excitatory drive onto target neurons (see for example Ito et al., 1970, and Ohtsuka, 1988), the only known exception are inhibitory fastigial neurons projecting to the MAO (De Zeeuw et al., 1989; Ruigrok and Voogd, 1995). However, deep cerebellar nuclei neurons may contact different neuronal elements in the target structure, as demonstrated for cerebellar projections to the superior colliculus (Warton et al., 1983) and for fastigial projections to the thalamic nuclei (Kultas-Illinsky et al., 1980a,b). Thus, the fastigial projections may directly drive the output neurons of the targeted structure or the local interneurons.

Closed anatomical loops through the MPC

In agreement with the closed loop general organization of the cerebellum input/output channels (Allen and Tsukuhara, 1974; Middleton and Strick, 1998), the MPC can be involved in closed anatomical loops with most neural circuits of the brainstem involved in the control of saccadic eye movements and/or saccadic gaze shifts. This postulated closed loop arrangement may not be restricted to short brainstem–cerebellar interactions (MPC–reticular formation–MPC and MPC–vestibular complex–MPC loops) but could extend to longer loops including the superior colliculus (SC) (MPC–SC–NRTP–MPC), the spinal cord (MPC–spinal cord–lateral reticular nucleus–MPC) and the cerebral cortex (MPC–thalmus–FEF–DLPN–MPC loop in cat and monkey, MPC–thalmus–parietal lobe–DLPN–MPC loop in the cat). Thus, the MPC is ideally situated to influence the various sensorimotor transformation stages involved in the production of saccadic gaze shifts, including attentional mechanisms related to target selection and localization, specification of saccadic metrics, movement initiation, trajectory control and eye–head coordination. We address now the neurophysiological data that highlight which of these roles are achieved by the MPC, starting from the simplified situation where saccadic eye movements are performed without head movement.

Role of the MPC in saccadic control: head-restrained condition

Neuronal activity

The presence of saccade-related activity in the MPC has been reported by several studies (Llinas and Wolfe, 1977; Kase et al., 1980; Waterhouse and McElligott, 1980; McElligott and Keller, 1982; Suzuki and Keller, 1988a,b; Ohtsuka and Noda, 1990, 1991a,b; Ohtsuka and Noda, 1994; Helmchen et al., 1994; Helmchen and Büttner, 1995; Ohtsuka and Noda, 1995; Thier et al., 2000), in the vermal lobules VI/VII, in the caudal part of the fastigial nucleus, but not in its rostral part.

To understand the functional significance of these saccade-related activities, several studies have tried to determine their specificity relative to the type of saccades (Ohtsuka and Noda, 1992; Helmchen et al., 1994; Helmchen and Büttner, 1995), their dependency relative to orbital eye position (McElligott and Keller, 1982; Ohtsuka and Noda, 1991a; Fuchs et al., 1993; Helmchen et al., 1994; Ohtsuka et al., 1994; Thier et al., 2000) and their tuning relative to the saccade direction (Hepp et al., 1982; Ohtsuka and Noda, 1991a; Fuchs et al., 1993; Ohtsuka and Noda, 1994; Ohtsuka et al., 1994; Thier et al., 2000). As a general cerebellar feature (see Mushiake and Strick, 1993), the motor discharges of MPC sac-
Saccadic neurons are in general stronger for visually triggered saccades than for spontaneous or internally triggered saccades (Ohtsuka and Noda, 1992; see also Mano et al., 1996 for saccadic neurons recorded from the cerebellar hemisphere). In addition, the burst discharge during spontaneous saccades is indistinguishable from the burst observed during quick phases of vestibular and optokinetic nystagmus, and is stronger when these fast eye movements are produced in the light than in darkness (Helmchen et al., 1994; Helmchen and Böttner, 1995). Concerning the initial eye position dependency, a few studies have directly investigated this influence and failed to reveal any consistent effect (Ohtsuka and Noda, 1991; Helmchen et al., 1994; Ohtsuka et al., 1994; Haas et al., 1999) or found a rather weak effect (Fuchs et al., 1993; but see McElligott and Keller, 1982). This tuning of MPC neurons discharge by eye position is rather weak and contrasts with the activity found in structures supplying a strong input to it such as the NRTP (Crandall and Keller, 1985). It also contrasts with the gain field modulation found in extracerebellar structures like the deep superior colliculus (Van Opstal et al., 1995) and the posterior parietal cortex (Andersen et al., 1990). At the level of the oculomotor vermis, Ohtsuka and Noda (1995) reported three types of saccade-related Purkinje cells according to their discharge pattern: phasic, pause and phasic-tonic. The phasic neurons were further classified as bi- and uni-directional, the majority of uni-directional neurons discharging for ipsiversive saccades (but see Helmchen and Böttner, 1995). At the level of the cFN, all studies have found that neurons generate a burst during the saccade irrespective of its direction and amplitude. For contraversive saccades, the burst duration generally increases with saccade duration (Ohtsuka and Noda, 1990, 1991a; Fuchs et al., 1993; Helmchen et al., 1994). Thus, for a given saccade amplitude, neither the frequency nor the duration of the burst can be used to extract any relevant information about saccade direction. Many fastigial neurons also show a pause in activity either before or after the burst, especially for large saccades. The clearest distinctive feature of the burst activity of cFN neurons in the context of directional coding appears to be the timing of the burst of activity relative to saccade onset. Indeed, the burst of cFN neurons tends to be timed to the onset of contraversive saccades with an average lead time of 20 ms (‘early burst’), while the burst of the same neurons occurs later during the course of ipsiversive movements (‘late burst’). From these observations and from lesion data, it was suggested that the cFN helps to accelerate contraversive saccades and to decelerate ipsiversive saccades. Given the inhibition exerted by the cerebellar vermis onto the deep nuclei, the fast decline and the fast rise of the burst activity produced by omnidirectional Purkinje cells in relation to ipsiversive and contraversive saccades, respectively, would contribute to the cessation of the cFN early burst and to the sudden onset of cFN late burst (Ohtsuka and Noda, 1992).

Although much less investigated, a strong sustained activity is also typical of neurons in the deep cerebellar nuclei and is classically reported also for neurons in the cerebellar vermis. This tonic activity is found for both saccade-related and non-saccade-related neurons. A weak relationship with eye position has been reported only for a minority of cFN tonic neurons in the cat (type I eye position: Gruart and Delgado-Garcia, 1994) and in the monkey (Fuchs et al., 1993). Although they do not report any spontaneous or gaze-evoked nystagmus, the lesion studies suggest a possible function of MPC tonic activity in maintaining tonic gaze direction (see below). Proprioceptive inputs from the extraocular and neck muscles (Fuchs and Kornhuber, 1969; Batti et al., 1974; Berthoz and Llinas, 1974; Schwartz and Tomlinson, 1977) could account for this activity. Responses related to slow eye movements (during vestibular or optokinetic stimulation or during smooth pursuit) have also been reported in the cerebellar vermis (Precht et al., 1977; Suzuki and Keller, 1988a,b) and in the fastigial nucleus (Furuya et al., 1975; Fuchs et al., 1994; Gruart and Delgado-Garcia, 1994). Finally, old studies have reported a number of non-motor activities in the MPC, including responses to visual (Koella, 1959; Freeman, 1970; Buchtel et al., 1972, Donaldson and Hawthorne, 1979; Kawamura et al., 1990) and auditory stimuli (Wolfe, 1972; Altman et al., 1976).

**Electrical microstimulation**

Several authors have found that saccadic eye movements can be evoked in the head-restrained animal.
by electrical microstimulation of the cerebellar posterior lobe and of the underlying fastigial nucleus (Cohen et al., 1965; Ron and Robinson, 1973; Linas and Wolfe, 1977; Gauthier and Stark, 1979; Keller et al., 1983; McElligott and Keller, 1984; ; Fujikado and Noda, 1987; Noda and Fujikado, 1987a,b; Ohtsuka et al., 1987; Noda et al., 1988, 1991; Murakami et al., 1991; Sato and Noda, 1992; Godschalk et al., 1994; Goffart et al., 1998c, 1999). The use of low-intensity (< 10 μA) high-frequency electrical stimulation in the monkey led to delineate the so-called ‘oculomotor vermis’ in the lobules VIc and VII and the fastigial oculomotor region (FOR) in the caudal part of the fastigial nucleus (Noda and Fujikado, 1987a,b; Noda et al., 1988). The metrics of the evoked saccades depend both on the stimulation locus and the stimulation parameters. Saccades evoked from the oculomotor vermis are directed toward the stimulation side and their vertical component varies in a topographically ordered manner. These saccades likely result from the activation of Purkinje cells since their occurrence is suppressed when Purkinje cells are lesioned by local injection of kainic acid or when Purkinje cells connections to cFN neurons are blocked by local injection of bicuculline (Noda and Fujikado, 1987a,b; Noda et al., 1988; Sato and Noda, 1992). When the electrical stimulation is applied to the fastigial nucleus, both ipsiversive and contraversive saccades can be elicited depending on the stimulated site and on the stimulation parameters. Ipsiversive saccades are produced by stimulation of the dorso-caudal part of the fastigial nucleus and disappear after local injection of bicuculline, suggesting that these saccades result from the recruitment of the Purkinje cells axons (Noda et al., 1988). Contraversive saccades are evoked from the rostro-ventral portion of the fastigial nucleus, seemingly by recruiting the axons of FOR neurons (Noda et al., 1988). In a more recent study, using electrical microstimulation with lower-frequency and longer-duration stimulation trains, contraversive saccades could also be evoked from the dorso-caudal part of the fastigial nucleus (Goffart et al., 1998c, 1999). Interestingly, these saccades are triggered by the offset of the stimulation train, suggesting that they resulted from a microstimulation-induced postsynaptic rebound in the firing of FOR neurons (Aizenman and Linden, 1999). Finally, electrical microstimulation of the fastigial nucleus in the head-unrestrained cat evokes a rapid head movement in addition to the saccadic eye movement, and the metrics of both eye and head movements vary as a function of microstimulation parameters (Goffart et al., 2001; Pélisson et al., 2002).

In sum, the short latency of saccades evoked from stimulating the MPC (15–20 ms), the low current threshold (about 10 μA) and the effect of stimulation temporal parameters on the duration and velocity of evoked saccades are consistent with the anatomical projections from the FN to the brainstem regions where the premotor saccade-related neurons are located. This conclusion is further supported by experiments where the electrical stimulation interferes with the production of a visually triggered saccade, as described in the following.

A first series of experiments used very brief stimulation trains during the on-going saccade to investigate how this would perturb the saccade. Such intra-saccadic stimulations have been applied in the monkey lobules V–VI (Keller et al., 1983), or over the oculomotor vermis through trans-cranial magnetic stimulation in human subjects (Hashimoto and Ohtsuka, 1995). A common observation of these two studies is the hypometria of contraversive saccades during the perturbed trials, with a perturbation latency estimated at 12 ms by Keller et al. (1983). However, whereas the local electrical stimulation failed to modify ipsiversive saccades, the trans-cranial magnetic stimulation increased the amplitude of ipsiversive saccades. This difference may be accounted for by the type of stimulation (electrical versus magnetic) or by the amount of tissue that was stimulated. Note that another study indicated that supra-threshold electrical stimulation of the cFN leads to similar perturbation of all on-going saccades, irrespective of their direction relative to the stimulated side (Noda et al., 1991). This study further demonstrated that monkeys did not compensate for the stimulation evoked saccade, since no secondary saccade was subsequently generated to bring the eyes back to the remembered location of the flashed target.

A second class of studies applied the short stimulation train prior to the onset of a visually triggered saccade to investigate how the electrically and visually elicited signals interact. Noda et al. (1991)
have applied a supra-threshold stimulation in the monkey fastigial nucleus in a paradigm similar to that originally designed by Mays and Sparks (1980). They reported that the stimulation-induced perturbation was not compensated during the subsequent saccade toward the remembered target location, i.e., the direction and amplitude of the saccade were the same as unperturbed saccades. This finding is reminiscent of the absence of compensation reported for some stimulated sites in the PPRF (Sparks et al., 1987) but contrasts with the compensation which is observed when supra reticular structures like the deep SC (Schiller and Sandell, 1983; Sparks and Mays, 1983; Pélisson et al., 1989; Schlag-Rey et al., 1989), the thalamic IML (Schlag and Schlag-Rey, 1987) and the FEF (Schiller and Sandell, 1983; Schlag and Schlag-Rey, 1987) are stimulated. However, another study from the same group (Ohtsuka and Noda, 1991b) suggests that correction saccades can be observed even in the case of a cerebellar microstimulation. This was observed when a sub-threshold stimulation, applied to the oculomotor vermis prior to saccade onset, reduces the amplitude of contraversive saccades. Recordings from cFN neurons further showed that the hypometria is associated with a truncation of the cFN presaccadic burst (Ohtsuka and Noda, 1991b). A tentative conclusion would be that a compensation is observed when a sub-threshold electrical microstimulation is applied to the oculomotor vermis level but not when a supra-threshold microstimulation is applied at the cFN level. However, given the recent observations reported by Goffart et al. (1999, see above), it is possible that the secondary saccades observed in the first case are not corrective but are simply due to a poststimulation rebound of FOR activity. Thus, further experiments are necessary to resolve the issue of the functional role of the oculomotor vermis and the cFN in the feedback control of saccade amplitude (Robinson, 1975). The other main outcome of these microstimulation studies provides a substrate for the MPC control of contraversive saccades and emphasizes the role of the cFN early burst. Indeed, they show that the amplitude of the contraversive saccade is correlated with the duration of the early cFN burst which is in turn controlled by the oculomotor vermis.

**Lesion/inactivation**

Several clinical studies and experimental studies in animals have contributed to the description of the oculomotor deficits induced by permanent or reversible lesions of the cerebellum (Aschoff and Cohen, 1971; Ritchie, 1976; Selhorst et al., 1976; Zee et al., 1976; Optican and Robinson, 1980; Vilis and Hore, 1981; Sato and Noda, 1992; Kurzan et al., 1993; Goldberg et al., 1993; Robinson et al., 1993; Ohtsuka et al., 1994; Vahedi et al., 1995; Goffart and Sparks, 1997; Takagi et al., 1998; Barash et al., 1999). When restricted to the MPC, the deficits concern the saccadic eye movements, eye fixation and spontaneous eye position. The vestibulo-ocular reflex remains normal when the cFN is inactivated (Kurzan et al., 1993) and the absence of spontaneous nystagmus indicates a normal vestibular balance and gaze holding (Goffart and Pélisson, 1998).

The most severe and consistent deficit of goal-directed saccades is the dysmetria, namely a disruption of the relationship between target eccentricity and saccade amplitude. Lesions restricted to the cerebellar vermis lead to hypometric horizontal saccades and asymmetric lesions or unilateral pharmacological decortications decrease the amplitude of ipsiversive saccade (Sato and Noda, 1992; Vahedi et al., 1995; Takagi et al., 1998; Barash et al., 1999). Conversely, lesions or inactivations restricted to the cFN lead to an opposite pattern. Following unilateral lesion, ipsiversive saccades become hypermetric and contraversive saccades hypometric, whereas following bilateral lesions a general saccade hypermetria is observed (Vilis and Hore, 1981; Goldberg et al., 1993; Kurzan et al., 1993; Robinson et al., 1993; Ohtsuka et al., 1994; Straube et al., 1995). The same pattern is observed after lesions involving both the vermis and cFN (Ritchie, 1976; Optican and Robinson, 1980). In general, lesions of the MPC alter the horizontal component of saccades performed in all directions, thereby modifying the amplitude of horizontal saccades, the amplitude and direction of oblique saccades and, in the case of unilateral lesions, the direction of vertical saccades (Robinson et al., 1993; Ohtsuka et al., 1994; Goffart et al., 1999). Although this pattern of errors corresponds to the ocular lateropulsion seen in different neurological patients (e.g. Straube et al., 1994), most
experimental studies have focused on the dysmetria of horizontal saccades.

An important issue is related to the type of error made by cerebellar subjects. Classically, saccade dysmetria has been described as a change in gain, i.e. in the ratio of the eye displacement to the target displacement. This type of analysis led to the notion that the MPC adjusts the gain of the transformation of retinal signals into saccadic motor commands, with different suggestions regarding the neural implementation of the postulated gain change (target position signal: Optican, 1982; eye position feedback signal: Keller, 1989; feedback comparator: Dean, 1995). More recently, following studies performed in the head-unrestrained cat (see below), the dysmetria of head-unrestrained gaze shifts in the cFN-inactivated monkey was described by plotting the relationship between the horizontal amplitude of the actual gaze displacement and that of the required gaze displacement (or target eccentricity or retinal error). A linear regression analysis disclosed that the slope of this relationship was systematically increased or reduced for ipsi- or contra-versive gaze saccades, respectively, consistent with the gain modifications reported earlier. However, the analysis also systematically reported changes in the intercept of the relationship. Thus the horizontal dysmetria can be decomposed in two errors, a proportional error that increases with horizontal target eccentricity and a constant error that, in contrast, is not sensitive to horizontal target eccentricity (Goffart et al., in preparation).

Another important question which must be solved to better understand the cerebellar deficits is whether the saccade dysmetria depends on eye position. Many investigators observed in the head-restrained cerebellar patient (Vahedi et al., 1995) or monkey (Ritchie, 1976; Optican and Robinson, 1980; Vilis and Hore, 1981; Sato and Noda, 1992; Robinson et al., 1993; Takagi et al., 1998) that the dysmetria does vary with initial orbital eye position such that centripetal saccades are more hypermetric than centrifugal ones (L. Goffart et al., unpublished data) or that centrifugal saccades are more hypometric than centripetal ones. From these studies it was concluded that the MPC takes into account the mechanical properties of the oculomotor apparatus by adding an orbital-dependent signal to the saccadic command in order to compensate for these peripheral nonlinearities. However, a major limitation of this hypothesis concerns the paucity of orbital-dependent modulation of neuronal activity recorded in the MPC (see above). In addition, under natural circumstances, shifting gaze involves a head movement together with the saccadic eye movement, and the mechanisms that compensate for initial eye position may be overestimated by artificially restraining the head.

Although less studied than the dysmetria of saccades, other oculomotor deficits have been reported after the lesion of the MPC, such as changes in the dynamics and latency of saccades, in fixing a visual target and in the spontaneous exploration of a visual scene. Modifications in saccade dynamics have been reported by different groups (Robinson et
al., 1993; Goffart et al., 2002), but not by others (see Selhorst et al., 1976; Zee et al., 1976; Ohtsuka et al., 1994). Takagi et al. (1998) reported that decorrelation could in some cases change the relationship between saccade amplitude and saccade duration or peak velocity (main sequence relationship) but further showed that the presence of a modification was not related to the size of the dysmetria. Similar observations were made in the head-unrestrained cat (Goffart et al., 1998a, see below). Concerning saccade latency, changes were not systematically examined. Modifications were found to various degrees between experimental subjects and studies (Robinson et al., 1993; Takagi et al., 1998). Systematic studies in the monkey revealed a slight but significant reduction in the latency of ipsiversonal saccades in the head-restrained monkey (Goffart et al., 2002). In the head-unrestrained cat, an additional increase in latency for contraversive saccades was observed (Goffart and Pélisson, 1997). A peculiar observation made during unilateral MPC inactivation is the presence of an error in fixation a visual target. On average this fixation offset is about 1–2 degrees in the trained monkey (Robinson et al., 1993), but values up to 7 degrees can be reached in some trials (Goffart et al., 2002; see also Ohtsuka et al., 1994). In the head-unrestrained cat, the fixation offset is larger, 5 degrees on average (Goffart and Pélisson, 1998). This type of error indicates either a difficulty in generating saccades with small amplitude or a bias in the processing of target-related signals or in the specification of the desired saccade amplitude. In either case, the fixation offset could be related to an imbalance in neuronal tonic activity between the two cFN. This fixation offset is reminiscent of that observed after lesions of other oculomotor structures such as the SC (Keating and Gooley, 1988) and the FEF (Dias and Segraves, 1999).

A final clue regarding saccade deficits following cerebellar dysfunction concerns the type and the timing of cerebellar signals which are required for generating accurate saccades and for appropriate visual fixation. Indeed, the studies reviewed above used an inactivation or lesion method that suppressed cerebellar output signals for a period which is very long relative to the time scale of events contributing to the production of a single saccade. A first attempt to specifically suppress the phasic saccade-related cFN activity was introduced by Noda and colleagues by electrical stimulation of the Purkinje cell afferents to the cFN (Ohtsuka and Noda, 1991b). By applying a sub-threshold electrical microstimulation prior to contraversive saccades, these authors could experimentally truncate the early burst of cFN neurons and then shorten the amplitude of the impending saccade. More recently, Goffart et al. (1999) used sub-threshold electrical microstimulation of the cFN afferents to study the various time windows during which the cerebellar control signals could influence the generation of saccades. The electrical microstimulation was too weak to evoke any immediate eye movement (instead, a delayed contraversive saccade timed with the offset of the stimulus was triggered, presumably reflecting a postinhibitory rebound phenomenon) but when applied in the period of a visually triggered saccade, saccades were strongly dysmetric in a way very similar to what is observed during local muscimol injection. The second major observation from this study is that the maximum dysmetria was obtained when the stimulation was applied during the on-going saccade, and not when restricted to the period prior to saccade onset. This result indicates that the critical time period for the influence of MPC output signals on saccade accuracy corresponds to the period when cFN neurons produce a saccade-related burst of action potential.

**Role of the MPC in saccadic control: head-unrestrained condition**

**Neuronal activity, electrical microstimulation**

Data describing the activity of MPC neurons in the head-unrestrained animal are not yet available. However, several studies have described neuronal responses to vestibular (Precht et al., 1977; Suzuki and Keller, 1982; Gruart and Delgado-Garcia, 1994) and neck-proprioceptive (Berthoz and Llinas, 1974) stimulation. During studies related to visual–vestibular interactions, neurons that respond in a synergistic manner to eye and head movements (gaze velocity neurons) and also to target retinal slip (target velocity neurons) were recorded in the vermal lobules VI–VII (Suzuki and Keller, 1988b) and in the cFN (Büttner et al., 1991). These data together indicate that the role of the MPC is not restricted to the
sole control of the eye displacement in the orbit, but extends to the control of head movements and gaze shifts.

Concerning electrical microstimulation, no study performed in the head-unrestrained condition has been published so far. We have recently explored the MPC in the cat to localize the areas from which saccades can be evoked at a low current intensity (threshold <30 μA). We then selected a few sites for a detailed analysis of head-restrained and head-unrestrained evoked responses. Although the histological verification is not yet available because the experiments are still going on, these sites are likely situated in the close vicinity of the cFN. All sites tested so far indicate the presence of a head movement that accompanies the evoked saccade. Depending on the stimulated site, the direction of the head movement can be similar or different from the direction of the concurrent gaze shift.

Very limited information about the role of the MPC in the control of gaze shifts in the head-unrestrained condition can be obtained from monkey studies (Ritchie, 1976) or clinical studies (Shimizu et al., 1981a,b). Using large lesions of the MPC in the monkey, Ritchie (1976) noted that the dysmetria of saccadic gaze shifts (eye in space) is largely independent of whether the animal can also move its head. This observation was also made in a first group of cerebellar patients by Shimizu et al. (1981b), but in a second group, only hypermetric patients and some hypometric patients showed the same tendency, whereas the gaze hypometria of the remaining subjects was reduced in the head-unrestrained condition as compared to the head-restrained condition. On the whole, these data are inconclusive because the data regarding head movements have not been systematically analyzed. Thus, it is not yet possible to determine whether the lesion affected the head movement and to which extent the head actually contributed to the dysmetria of gaze.

Lesion/inactivation

During the last decade we have used unilateral injections of muscimol to investigate in the head-unrestrained cat the role of the cFN in the control of visually triggered gaze shifts (Goffart and Pelisson, 1994, 1997, 1998; Goffart et al., 1998a,b). The main deficits found after cFN unilateral inactivation are spontaneous gaze deviation, fixation offset, dysmetria of the gaze displacements, marked modifications in the latency and moderate changes in the dynamics of gaze saccades. We present in the following these deficits and emphasize on the type of dysmetria and on the coordination between eye and head components.

Spontaneous gaze deviation and fixation offset

After unilateral cFN inactivations the spontaneous scanning of the lighted environment was mostly restricted to the ipsilesional visual hemifield. When a food target was presented to the animal, an offset ranging from 1 to 9.4 degrees toward the inactivated cFN (average value 4.9 degrees) was observed between the gaze and the target positions. The offset involved the head to a major extent, since the deviation of the eyes in the orbit was very small in these situations. When the head was restrained, the average deviation of the eyes in the orbit increased but with a smaller magnitude than the deviation of gaze observed in the head-unrestrained condition. These deviations of gaze in light with or without presentation of a visual target are reminiscent of the behavior of the head-restrained monkey, but in this last situation the reported ocular deviation was much smaller (1–2 degrees average fixation offset reported by Robinson et al., 1993, and Goffart et al., 2002; but see the 7-degrees fixation offset illustrated in the work of Ohtsuka et al., 1994). This quantitative difference of gaze deviation between the head-restrained and head-unrestrained studies could be due to the head mobility, to the constraints to make accurate fixation during both training and recording phases and/or to difference in visual system between the cat and the monkey. The deviation of the head is likely responsible for the gaze deviation since it is maintained when a food target is approached toward the animal’s yaw and when the animal tries to bite the food. Finally, when the animal is walking on the floor toward a food target located about 2 m in front, the locomotion path of the body is systematically curved toward the inactivated cFN (Guillaume et al.,
Such curved paths are predicted by a simple model assuming a systematic bias in the specification of the heading direction relative to the current target direction with a bias similar to the constant error of ipsiversive gaze shifts recorded before the locomotion tests (see below).

Gaze dysmetria

The amplitude of the primary saccadic gaze shift was strongly affected by inactivation of the cFN. Like the dysmetria observed in the head-restrained condition, gaze shifts were hypermetric or hypometric depending on their direction relative to the side of injection (ipsi- or contra-versive, respectively). Beyond this amplitude difference, a marked difference in the type of error emerged from our study: the contraversive hypometria could mainly be described by a slope decrease in the relationship between the horizontal amplitude of the gaze displacement response and the horizontal amplitude of the required gaze displacement (gain reduction), whereas the ipsiversive hypermetria was essentially related to an increase in the y-intercept. This relationship revealed the major contribution of a constant error (mean 10 degrees, ranging from 4 to 20 degrees) to the ipsilateral hypermetria with a rather limited change in gain. Several points which qualify the pattern of saccadic dysmetria are worth considering.

First, when the target was presented at the location of the actual gaze position, above or below it, the injected animals produced an inappropriate response bringing gaze away from the target toward the inactivated side, toward a position that corresponded approximately to the horizontal constant error value. Such responses reject the possibility that the change in y-intercept would be due to an erroneous extrapolation of the relationship between the horizontal amplitude of the gaze displacement and the horizontal amplitude of the required gaze displacement. Also, when the target was presented in the contralateral visual hemifield with an eccentricity smaller than the bias, the animal produced an ipsiversive gaze shift bringing again gaze away from the target. The horizontal constant error that characterizes the hypermetria of ipsiversive gaze shifts was interpreted as reflecting an impairment in the localization of the target or in the specification of the movement metrics prior to movement onset (Goffart and Pélisson, 1994, 1998). Qualitative observation of the straight trajectory of oblique ipsiversive gaze shifts toward a target presented on the horizontal azimuth and initiated from different vertical positions suggests that impairment is already acting at the gaze shift onset.

Second, for both the ipsiversive and contraversive gaze shifts, the dysmetria of gaze shifts is related to modifications in the amplitude of both eye and head components. These modifications of eye and head movements are such that their relative contributions to the amplitude of the gaze shift are barely changed relative to control gaze shifts with matched amplitudes. This result indicates that the injection of muscimol in the cFN does not interfere with mechanisms subtending the eye–head coordination and suggests an influence of cFN upon functional processes that are located centrally rather than peripherally along the visuomotor pathways involved in gaze shifts production.

Gaze latency

As suggested by the inappropriate gaze shifts, cFN inactivation also interfered in a consistent manner with mechanisms prior to gaze shift onset and more particularly with those involved in its initiation: the latency of ipsiversive movements of the eye and head decreased, whereas that of contraversive movements increased. Although the former effect was rather limited in amplitude because the latencies of control movements were already quite short in these food target paradigms, the maximum mean increase of contraversive responses latency reached 109% in these paradigms where both the direction and amplitude of the desired response were unpredictable. The modifications of latency were very similar in magnitude between the eye and the head movements such that the changes in eye/head delay were small (7.5 ms on average).

Gaze dynamics

The dynamics of dysmetric gaze shifts and of their eye and head components were first studied by plotting for each experiment the main sequence relationships. Qualitative examination of all these nonlinear relationships revealed a tendency for the velocity of
ipsiversive gaze shifts to be reduced after muscimol injection. The larger range of amplitudes after muscimol injection for ipsiversive gaze shifts facilitated the detection of a main sequence change for these gaze shifts as compared to contraversive ones. The quantitative comparison of normal and postinactivation peak gaze velocity for matched amplitude gaze shifts within a common range of 30 degrees revealed a consistent reduction in gaze velocity for both movement directions (55°/s on average). This slowing of gaze velocity resulted from combined modifications in the velocity of both eye and head components. In some experiments where the slowing of ipsiversive gaze shifts exceeded that of contraversive responses, the detailed analysis of the acceleration and the deceleration durations disclosed a predominant increase in the duration of the deceleration phase. Notably, in two experiments, a large reduction of gaze velocity has been observed during the postinactivation period without concomitant change in the size of gaze dysmetria, suggesting that modifications in the dynamics and metrics of gaze shifts following cFN inactivation are not related to each other but instead result from partly independent mechanisms.

**Specificity of deficits: comparison between cFN and rFN inactivation**

In another study we made similar muscimol injections in the rostral part of the fastigial nucleus (rFN) and compared in the same animals the resulting deficits to those induced by injections in the caudal part (Pélisson et al., 1998). Since the cFN and rFN have both common and specific outputs, this comparison allowed to test the link between gaze dysmetria and the inactivated fastigial efferences. Some deficits induced by cFN inactivation could also be observed when the injection was made in the rFN. For example, ipsiversive gaze shifts were hypermetric and their latency reduced, whereas contraversive gaze shifts were hypometric and their latency increased during rFN and cFN inactivations. A moderate decrease in gaze velocity was also observed in both conditions. Modifications of eye–head coordination were quite limited, and were significantly smaller after inactivation of the cFN than after inactivation of the rFN. Other deficits induced by rFN inactivation differed from those induced by cFN inactivation. Indeed, in the head-unrestrained condition, the eyes were severely deviated in the orbit in the former case and barely in the latter. After muscimol injection in the rFN, the dysmetria was characterized by a rather small change in y-intercept of the relationship between the horizontal target eccentricity and the horizontal amplitude of the subsequent gaze shift. Finally, a strong postural deficit was found exclusively after muscimol injection in the rFN, but not when the cFN was inactivated. Three conclusions can be drawn from these data. First, a previously unknown contribution of the rFN to the control of head-unrestrained gaze shifts is demonstrated. Second, the modified pattern of deficits according to the inactivation locus in the fastigial nucleus underlines the specificity of our inactivation methods. Third, this pattern defining a functional distinction between rFN and cFN can be used to relate some deficits to different fastigial output pathways: the ipsiversive bias of gaze shifts and fixation offset could be related to ascending fastigial projections to the thalamus and SC which arise specifically from the cFN, whereas the deviation of the eyes in the orbit could be due to the descending projections from the rFN to the nucleus prepositus hypoglossi (McCrea and Baker, 1985).

**cFN inactivation and SC stimulation**

To better understand the functional nature of gaze dysmetria during cFN inactivation and get further insight into the neural processes controlled by the MPC, we combined in the head-unrestrained cat unilateral inactivation of the cFN with electrical microstimulation of the deep superior colliculus (dSC). Gaze shifts have been evoked by dSC microstimulation with two objectives: first, to modify the position of gaze prior to its launch toward a previously presented visual target and to test whether cFN inactivation impaired the feedback mechanisms that compensate for such gaze perturbation (Mays and Sparks, 1980; Pélisson et al., 1995), and second, to elicit gaze shifts from various dSC loci and to test whether the SC motor map is impaired by cFN inactivation.

The first study was motivated by the hypothesis that the MPC would be part of the local feedback loop controlling the on-going trajectory of saccades.
(Vilis and Hore, 1981; Keller, 1989). Assuming that the compensatory mechanisms are part of this local feedback loop, this hypothesis predicts that the animal’s capability to compensate for an unexpected saccade perturbation should be altered during dysfunction of the MPC. Since the dynamic feedback concept has been extended to the control of head-unrestrained gaze shifts (Laurutis and Robinson, 1986; Pélisson et al., 1988; Munoz et al., 1991; Guitteny, 1992; Lefèvre and Galiana, 1992; Pélisson et al., 1995; Phillips et al., 1995), we tested the involvement of the MPC in the feedback mechanisms controlling combined eye-head gaze shifts (Goffart et al., 1998a). A previous study has indicated that in a similar experimental situation with the head unrestrained, normal cats do produce an accurate compensation to a gaze perturbation induced by SC stimulation during the reaction time period (Pélisson et al., 1995). In cFN-inactivated animals, perturbations were again followed by compensations which brought gaze to the same location as gaze shifts during unperturbed trials. This is true for both ipsiversive and contraversive perturbations, indicating that irrespective of the dysmetria induced by cFN inactivation, the encoding of gaze (or separate eye and head) feedback signals are still operating normally in the cFN-inactivated animals. In agreement with the limited modification of gaze dynamics reported above, these results suggest that the dysmetria of gaze shifts are not related to an impaired feedback control.

The second study addressed the question of the state of the SC motor map during cFN inactivation (Guillaume and Pélisson, 2001). To this aim, we studied the effect of cFN inactivation on the properties of head-unrestrained gaze shifts evoked by SC microstimulation. Focussing on near-horizontal gaze shifts, we varied the location of the stimulated sites along the SC rostro-caudal axis and for each site \( n = 18 \) in two cats we tested various stimulation currents. The analysis of the metrics and latency of evoked gaze shifts indicated that the cFN inactivation resulted in a strong distortion of the SC motor map coding for ipsiversive responses (SC contralateral to inactivated cFN) and for a moderate reduction of the amplitude coding in the opposite SC. Indeed, the amplitude of ipsiversive gaze shifts was modified — relative to responses elicited before cFN inactivation — in a manner that depended on the position of the stimulated SC site: it increased for sites located in the rostral 2/3 of the SC, but decreased for the remaining caudal zone, with one site in the transition zone providing gaze shifts with an unchanged amplitude. In contrast, contraversive gaze shifts elicited from the opposite SC all had a moderately reduced amplitude, except for the most caudal site (no change). Based on these results, Guillaume and Pélisson (2001) proposed that the MPC influences both the SC and downstream centers through parallel fastigial output pathways.

**Role of the MPC in saccadic control: models**

Models of saccadic and gaze control systems that include the medio-posterior cerebellum and make predictions about saccade dysmetria can be distinguished into system theory models (Optican, 1982; Keller, 1989) based on the local feedback loop structure of the original model of Robinson (1975) and neurophysiologically oriented models which additionally attempt to incorporate detailed neurophysiological data (Dean, 1995; Quaia et al., 1999). In the former category, the models suggest that the medio-posterior cerebellum is located upstream from the feedback control of saccades (Optican, 1982) or is part of the feedback loop (Keller, 1989). These formal models do not simulate the actual neural activity and do not consider the connectivity of cerebellar neurons but provide formal predictions regarding the saccade metrics and dynamics following cerebellar dysfunction. Although they both predict saccade dysmetria, their predictions differ when one considers the dynamics of saccades, since only the feedback model predicts changes in saccade dynamics. Note that in this latter case, the predicted changes associated with hypometric and hypermetric saccades are opposite to each other. These predictions are not consistent with the lesion data since changes in the main sequence relationships, when they occur, always correspond to a reduction of saccade velocity. The second category of models (Dean, 1995; Quaia et al., 1999) has recently been developed to incorporate the accumulating neurophysiological data in the monkey. These models follow the concept, initially proposed by Noda (1991) and supported by data from Fuchs’ laboratory (Fuchs et al., 1993).
that the cFN helps accelerate contraversive saccades and decelerate ipsiversive saccades by sending to the pre-oculomotor burst neurons an early and a late burst of activity, respectively. Thus, contrary to the above formal models, the postulated influence of the cFN on the saccadic circuitry is non-linear, i.e. do not act as a simple gain control. Whereas the model published by Dean (1995) focuses on these fastigio-reticular projections (see also the models by Schweighofer et al., 1996, and Gancarz and Grossberg, 1999, regarding the adaptive control of saccades), the model proposed later by Optican and colleagues (Quaia et al., 1999) also attributes a role to fastigial efferences toward the SC. Dean proposed a way to combine neurophysiological data in a Robinson type model (Van Gisbergen et al., 1981) by suggesting that the cFN adds temporally coded signals at the level of the feedback comparator. Specifically, in the model, the early burst of the contralateral cFN and the late burst of the ipsilateral cFN (‘braking signal’) are respectively added and subtracted from the EBNs saccade-related activity at a postsynaptic level. This model accurately simulates the generalized hypermetria of saccades following bilateral cFN inactivation as well as the metrics of saccades following unilateral cFN inactivation in the head-unrestrained monkey. The limitation of this model rests on its structure which excludes any other MPC outputs, particularly ascending fastigial projections to the thalamus and SC. Besides a conceptual schema proposed by Houk et al. (1992), the model published by Optican’s group (Quaia et al., 1999) is the first to present a synergetic contribution of the cerebellar output pathways to the brainstem reticular formation and SC. It is suggested that (1) the SC provides the brainstem pulse generator with an initial directional drive, (2) the medio-posterior cerebellum, which is located inside the local feedback loop, monitors on-line saccadic motor error and is responsible for terminating the saccade by turning off (‘choke signal’) the motoneurons drive through a projection from the cFN to the contralateral IBNs, and (3) the cerebellum also modulates SC activity.

This model is a valuable effort to incorporate the contribution of many oculomotor structures (parietal and frontal cortices, SC, cerebellum, brainstem reticular formation) in a functionally tractable scheme compatible with the main features of SC and cerebellar contribution to saccade production. However, this model fails to predict the well established hypometria of saccades directed away from a lesioned cFN. Also, the hypothesized topographically coded wave of activity between the two cFN assumes a recruitment of cFN neurons that depends on the saccade size, which is not consistent with the evidence of cFN neurons discharging in relation to all saccades, regardless of their amplitude. In addition, predictions regarding electrically evoked saccades and compensatory responses to stimulation-induced perturbations have not been found experimentally, and instead, the electrical SC stimulation can still produce staircase saccades during cFN inactivation (Guillaume and Pelisson, 2001) and the capability to compensate for such collicular-evoked saccades is preserved (Goffart et al., 1998a). Finally, both Dean’s and Quaia’s models predict that the pre-oculomotor burst neurons (EBN, IBN) should demonstrate a late burst of activity during OFF-directed saccades, a possibility which is debated given the controversial empirical data (Van Gisbergen et al., 1981; Cullen and Guitton, 1997).

In summary, models of the MPC need to incorporate the results reviewed above. In addition, given the evidence that the role of the MPC is not restricted to the movement of the eyes in the orbit, future modelling studies should specify how the cerebellum controls saccadic gaze shifts and eye–head coordination processes when these two platforms are synergistically involved.

**Concluding remarks and perspectives**

Beyond the precise delineation of the various cerebellar zones involved in saccadic eye movements, the spectacular explosion of empirical data observed during the last decade in cerebellar saccadic neurophysiology has led to the elaboration of the first testable models incorporating both neurophysiological and functional information. An immense hope shared by researchers and clinicians is that, due to its relatively circumscribed structure and known neurophysiology, the saccadic system offers a valuable model to study the cerebellar role in sensorimotor transformations.

While current models focus on the production of horizontal saccadic eye movements (with the excep-
tion of the model of Quaia et al., 1999, which deals with both horizontal and vertical saccadic components), shifting gaze in space under natural conditions rarely corresponds to such a simplified case, but instead involves 3-D movements of the eyes in the orbit, the coupling between versional and vergence ocular responses as well as between eye, head and sometimes torso movements (see Takagi et al., 2003, this volume, and Klier et al., 2003, this volume). As recent data already suggest, addressing these various aspects in more detail will tell us that the role of the cerebellum in gaze shifts is more general than just controlling the motion of the eyes in the orbit. These new studies will also provide fruitful information on the neural signals influenced by cerebellar activity and will have to differentiate whether: (1) the cerebellum controls desired displacement signals, feedback signals or downstream motor commands; (2) signals related to eye, head and body axis are influenced by parallel cerebellar output pathways or a gaze- (or target-) related signal is directly under cerebellar control; (3) version and vergence signals are controlled separately or the desired displacement of gaze in space is directly modulated by cerebellar activity; (4) the cerebellum is involved in the computation necessary for the kinematic control of eye, head and gaze movements to account for the neural implementation of Donders’ law and Listing’s law.

Evidently, the answers to these functionally oriented questions will bring new information about the functional input–output relationships of the cerebellum with other oculomotor structures. For example, the demonstration of an involvement of the MPC in controlling desired gaze displacement will advocate for a significant involvement of fastigio-tectal reciprocal projections, given the strongly suggested involvement of the SC in the encoding of a gaze displacement command (Munoz et al., 1991; Freedman and Sparks, 1991; Guillon et al., 2003, this volume; Sparks and Gandhi, 2003, this volume). Given all these possible modes and levels of control, what then can we expect from these future studies? There are at least three reasons why we believe that the MPC influences the saccadic orienting gaze behavior through multiple levels of actions. The first is related to the cerebellar connectivity which is organized in closed loops with multiple neural centers situated at different levels along the sensorimotor pathways, the second reason comes from our recent study of gaze shifts evoked electrically from the SC in the head-unrestrained cat. Indeed, the pattern of modifications of gaze amplitude and latency following cFN inactivation is consistent with a dual role of the MPC, through parallel fastigial projections toward the SC and toward downstream centers (Guillaume and Pélisson, 2001). The third reason is more indirect and is related to the neural substrate of saccadic adaptation. Although the whole network of structures involved in saccadic adaptation remains to be elucidated, it is clear from lesion and activation studies that the MPC is critically involved (Goldberg et al., 1993; Desmurget et al., 1998, 2000; Takagi et al., 1998; Barash et al., 1999). Interestingly, saccadic adaptation has been shown in human subjects to be highly specific to the type of saccade tested. For example, adaptation of reflexive visual saccades does not transfer to internally generated visual or memory saccades (Deubel, 1995). Given that the neural substrates of these different saccade types are partly separated (for review see Pierrot-Deseilligny et al., 1995, 2003, this volume), the cerebellar-dependent mechanisms underlying the adaptation of different saccade types supposedly occur at different sensorimotor levels.

To conclude, further investigations of the role of the cerebellum should progressively release the various degrees of freedom which are typically involved in the production of saccadic gaze shifts in the natural world. Although difficult, this task will benefit from recent developments of gaze control models and will prove necessary for a comprehensive understanding of the cerebellar role in motor control.

**Abbreviations**

- **MPC** - medio-posterior cerebellum
- **FN** - fastigial nucleus
- **rFN** - rostral fastigial nucleus
- **cFN** - caudal fastigial nucleus
- **FOR** - fastigial oculomotor region
- **DLPN** - dorsolateral pontine nucleus
- **NRTP** - nucleus reticularis tegmenti pontis
- **MAO** - medial accessory olive
- **PPRF** - paramedian pontine reticular formation
- **MRF** - mesencephalic reticular formation
- **EBN** - excitatory burst neuron
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