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The neural basis of smooth-pursuit eye movements

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Smooth-pursuit eye movements are used to stabilize the image of a moving object of interest on the fovea, thus guaranteeing its high-acuity scrutiny. Such movements are based on a phylogenetically recent cerebro-ponto-cerebellar pathway that has evolved in parallel with foveal vision. Recent work has shown that a network of several cerebrocortical areas directs attention to objects of interest moving in three dimensions and reconstructs the trajectory of the target in extrapersonal space, thereby integrating various sources of multimodal sensory and efference copy information, as well as cognitive influences such as prediction. This cortical network is the starting point of a set of parallel cerebrofugal projections that use different parts of the dorsal pontine nuclei and the neighboring rostral nucleus reticularis tegmenti pontis as intermediate stations to feed two areas of the cerebellum, the flocculus-paraflocculus and the posterior vermis, which make mainly complementary contributions to the control of smooth pursuit.

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Introduction

The primate visual system is characterized by binocular visual fields and a high-resolution fovea that offers considerable advantages for the detailed analysis of visual objects. Two forms of eye movements — saccades and smooth pursuit — enable us to make use of this specialization. Saccades are high-velocity gaze shifts, which enable us to bring the image of an object of interest onto the fovea, that are followed by visual fixation, which is an active process rather than the absence of an eye movement. In many situations, however, objects move relative to the beholder, and this is where smooth-pursuit eye movements come into play. These movements stabilize the image of the moving object on the fovea once saccades have placed it there, thereby facilitating continuous high-acuity scrutiny of the object in question [1,2].

Both saccades and smooth-pursuit eye movements can be complemented by head movements that expand their range. Although they serve a common purpose — namely, the deployment of foveal vision — saccades and smooth pursuit have distinct phylogenies and, moreover, are determined by different functional constraints. Thus, it is not surprising that the brain networks that underlie these two forms of eye movement have been considered to be largely disparate. However, it is obvious that saccades and smooth pursuit must be linked, and recent advances in their study have begun to tell us how their coordination might be accomplished by the brain [3•]. In this review, we summarize our recent view of the pathways that mediate smooth-pursuit eye movements, emphasizing the important role of the exchange of information between cerebral cortex and the cerebellum.

The functional properties of smooth-pursuit eye movements

Smooth-pursuit eye movements can be modeled successfully as a closed-loop system that tries to stabilize the target on the fovea by continuously translating signals and converting deviations from the ideal trajectory into compensatory eye movements [4]. Behavioral studies have shown that, in addition to retinal velocity of the target image, image acceleration [5] and position relative to the fovea [6•] are used as visual error signals that drive the pursuit controller. In an alternative group of ‘nonretinal’ models, the pursuit controller is envisaged to work on error signals resulting from a comparison of gaze movement with target movement in extrapersonal space [7]. Gaze is given as the sum of eye and head movements, whereas target movement in space has to be reconstructed by adding retinal image movement, eye and head movements [8]. Although they are not necessarily needed to account for the eye movement behavior of head-fixed subjects who are probed with moving visual targets, models that assume world-centered representations of target movement allow a parsimonious description of smooth-pursuit behavior under more natural conditions [9,10].

Rather than pursuing elementary visual targets, as occurs in the typical laboratory situation, human subjects pursue under natural conditions multimodal representations of behaviorally relevant objects that are built on different sensory modalities, each ruled by a specific sensory frame of reference. The perceptual valence of this multimodal representation is modified by experience, expectations and other forms of top-down information [11]. In other words, encoding a unified object under natural conditions requires the integration of information in a common

frame of reference. This preference for a specific, common, nonsensory frame of reference — namely, extrapersonal space — facilitates both the integration of head movements into smooth-pursuit behavior and the coordination of perception and action [12**].

The onset of pursuit lags behind the onset of unexpected target movement by approximately 100 ms, mainly because of delays caused by the visual system. Subsequently, during maintained smooth pursuit, the lag in eye movement can be reduced or even abolished if the future target trajectory can be predicted. In addition, the delay in the initiation of pursuit can be reduced or even turned into a lead if target movement can be anticipated [13]. Owing to the delay in eye movements prompted by unpredictable target movements, the first 100 ms of pursuit can be considered as an open-loop response based on target movement that is not yet affected by compensatory eye movements. The response to this initial open-loop target movement is not fixed, however, but can be modified in an ecologically appropriate manner by the experience of later changes in the speed of the target (termed ‘pursuit adaptation’) [14*]. Smooth pursuit stabilizes the object image on the fovea at the cost of retinal motion of the background image, which is shifted on the retina according to the speed of the eye movement. The background is perceived as stationary, however, because its perception is based on a comparison of the raw visual motion signal with an expectation of the visual consequences of the smooth-pursuit eye movement. This expectation is updated continuously to guarantee spatial stability despite the ever-changing environmental conditions (Figure 1; [15,16*]).

The cerebro-ponto-cerebellar pathway in smooth pursuit

Smooth pursuit is mediated by a cerebro-ponto-cerebellar pathway, which largely bypasses the phylogenetically older centers for saccades in the brainstem tegmentum.

Cerebral cortex

Cerebral cortex contains several frontal and parietooccipital areas that have distinct roles in generating smooth-pursuit eye movements. For example, visual area middle temporal (MT) serves as a generic visual motion processor that contributes to smooth pursuit by extracting retinal motion of the target — one of the key inputs that drives smooth-pursuit eye movements. Correspondingly, lesions of selected parts of area MT render monkeys unable to pursue targets moving in the confines of the motion scotoma [17]. In area MT, object motion is represented relative to the retina.

By contrast, the lateral part of the neighboring middle superior temporal area (MSTl) seems to contain the explicit representation of object motion in world-centered coordinates [12**] foreseen by the ‘nonretinal’

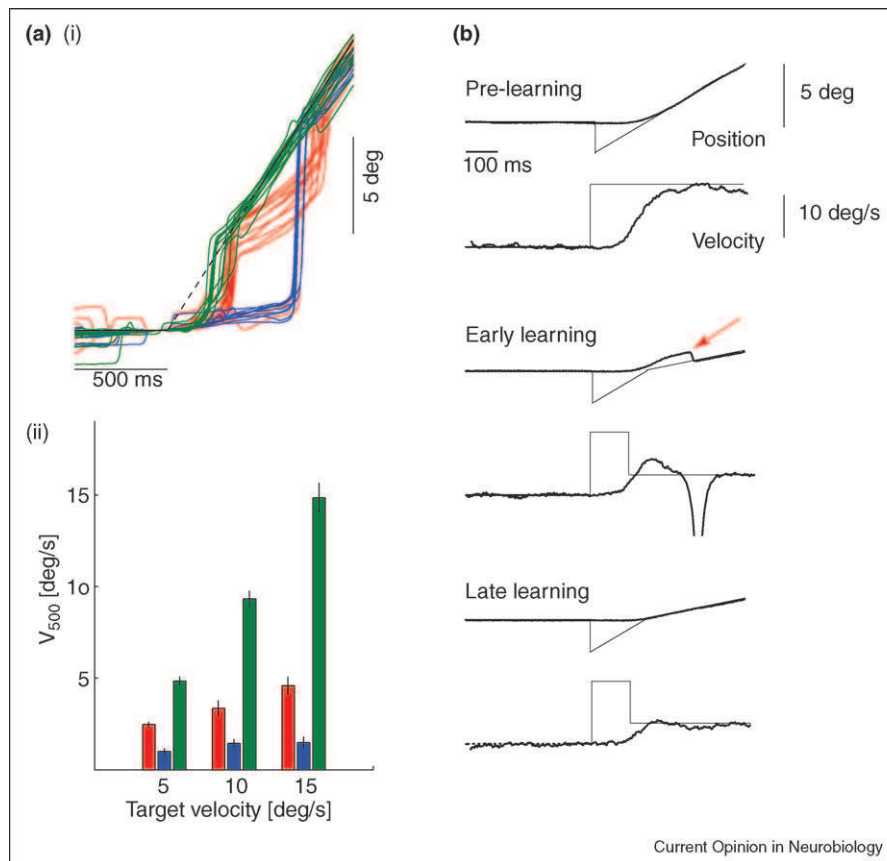
models of smooth pursuit [7,9]. This is suggested by the existence of MSTl visual tracking (VT) neurons — multimodal neurons that are sensitive to retinal image slip, to slow eye movements, and to slow head movements with identical preferred directions [8]. The notion that these three inputs might be used to reconstruct the movement of an object in world coordinates is supported by the observation that their discharge persists when movement of the object is compensated for by eye and/or head movements that stabilize the object image on the retina. This world-centered representation of object motion might be advantageous for several functions beyond the programming of smooth pursuit; however, its role in smooth pursuit is clearly demonstrated by the fact that lesions of MSTl cause an ipsiversive smooth-pursuit deficit. This deficit can be replicated by ‘lesioning’ a VT-neuron-like layer in a model that generates combined smooth-pursuit eye and head movements (Figure 2; [9]).

Pursuit-related neurons are also found in the dorsal part of area MST (MSTd). The discharge of these neurons follows the onset of smooth pursuit by more than 50 ms [18]; this delay precludes the neurons from a role in pursuit initiation but is, in principle, compatible with a contribution to pursuit maintenance. The fact that these neurons are embedded in a visual network for the analysis of optic flow [19], however, might be more indicative of a role in eliminating eye-movement-induced flow components from the optic flow field, thereby facilitating the extraction of heading direction [19,20]. Neurons whose discharge starts after the onset of eye movements have also been reported in MSTl [21]. Unlike typical MSTl VT neurons, which lead pursuit onset by approximately 50 ms, however, this latter group is sensitive to eye position and not velocity [21].

Pursuit-related neurons have been reported in two other parietal areas: the lateral intraparietal (LIP) [22] and ventral intraparietal (VIP) areas [23,24]. Area LIP, probably corresponding to Ferrier’s parietal eye field, is the major saccade representation in posterior parietal cortex. If the occurrence of pursuit-related neurons in this region can be corroborated, area LIP will stand out as the only known example of a cortical area in which saccade and pursuit-related signals are not kept apart. This principle of anatomical segregation is best demonstrated by the frontal eye field (FEF).

In the FEF, saccades are represented in the anterior bank of the arcuate sulcus and the transition zone to neighboring superficial cortex [25]. By contrast, smooth pursuit is represented deeper in the posterior bank and the fundus of the arcuate sulcus, roughly at the level of the principle sulcus [26]. Microstimulation experiments indicate that the pursuit representation in the FEF is involved in setting the gain of the pursuit eye movement [27], and

Figure 1

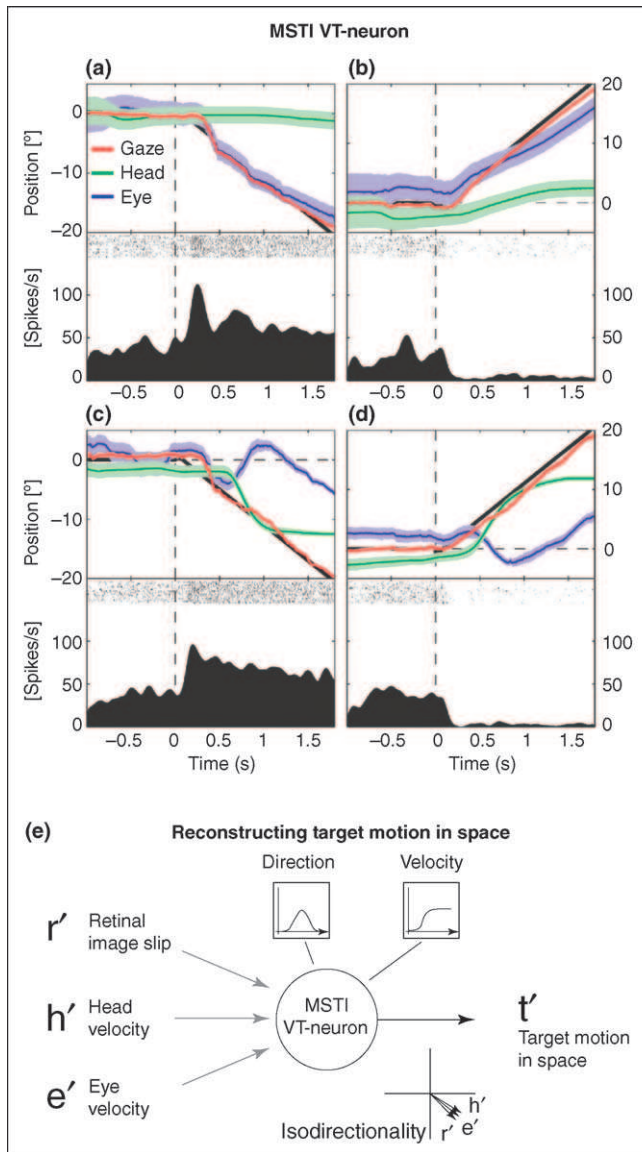


Influence of prediction and adaptation on smooth pursuit initiation. **(a)** Anticipatory smooth pursuit in a rhesus monkey, prompted by prior knowledge of the time and properties of the future ramp-like target movement. Each trial commenced with a constant period of fixation of a stationary spot in the center of the screen that was presented for 500 ms. At the same time that the fixation spot disappeared, the pursuit target started to move outwards from the center along the horizontal, starting from the position of the previous fixation spot but remaining invisible for the first 500 ms because it moved behind an occluder (the broken line represents the target trajectory behind the occluder). In 'movement-anticipation' trials (corresponding eye movements are shown in blue), the target moved either to the left or to the right at random. In 'direction-anticipation' trials, the target moved consistently to the right (corresponding eye movements are shown in red). In control trials, the target movement direction altered randomly between left and right (corresponding eye movements are shown in green) but, unlike in the direction-anticipation trials, the target was visible right from the start. **(i)** Individual trials of pursuit eye movements observed in the three conditions prompted by target movement at 15 °/s. **(ii)** Mean-eye velocity (V_{500}) and standard error of the eye velocity for the 100-ms bin just before the target became visible 500 ms after onset of its movement for three different target velocities. The monkey was able to generate anticipatory smooth pursuit specific for the velocity of target movement on both types of anticipation trial. **(b)** Example of smooth-pursuit adaptation in a rhesus monkey demonstrating that the early open-loop pursuit response can be modified in an ecologically useful manner. Smooth-pursuit eye movements were initiated by slow target movement to the right, after a small step to the left ('step-ramp sequence'). The purpose of this step was to bring the target image close to the fovea at the time of pursuit onset, thereby reducing the need for catch-up saccades. After a couple of trials in which the ramp velocity was kept constant at 15 °/s ('pre-learning'), the target velocity was dropped consistently from the initial 15 °/s to 5 °/s 100 ms after onset of the target movement in the following trials. Because the initial eye velocity, determined by the first (high-speed) part of the target ramp, exceeded the final target velocity in the first trials in which the target had changed velocity ('early learning'), the eyes of the monkey overshot the target, resulting in a substantial retinal error that had to be corrected by a leftward saccade (arrow). After several repetitions of this change in velocity ('late learning'), however, the initial eye velocity was reduced by an amount that enabled it to match the velocity of the target after the velocity change, thereby making corrective saccades unnecessary. Thin lines represent the position and velocity of the target, thick lines represent eye position and velocity, as indicated, in selected individual trials.

single-unit recordings suggest that this area is involved in predicting target trajectories [28] but it does not contribute to pursuit adaptation [14•]. Most FEF pursuit neurons encode pursuit trajectories along specific courses in three dimensions [29]; that is, they are not restricted to the two complementary reference frames of a vergence

(movement in depth) and a conjugate (movement in the frontoparallel plane) pursuit system, which dominates pursuit-related responses in the subcortical centers for pursuit and in area MST [30••]. Pursuit-related neurons with predictive discharge have been also observed in the supplementary eye field (SEF) [31]. As yet, the details of

Figure 2



MSTI VT-neuron encodes target motion in extrapersonal space. (a–d) Discharge of a typical visual-tracking (VT) neuron recorded from the lateral part of the middle superior temporal (MSTI) area during pursuit with only the eyes moving (smooth-pursuit eye and movement [SPEM]) (a,b) and during pursuit with both the head and the eyes moving (smooth-pursuit eye and head movement [SPEHM]) (c,d). In (a,c), target movement occurred in the preferred direction of the neuron; in (b,d), target movement occurred in the nonpreferred direction. Target position is shown in black, mean eye position in blue, mean head position in green and mean gaze position in red. The shaded bands accompanying the mean position curves reflect the standard errors. The discharge is characterized by raster plots and spike density functions ($\sigma = 40$ ms). Note that during SPEHM (c,d), the head movements were characterized by an overshoot in velocity prompting a compensatory eye-in-head movement in the opposite direction; however, the discharge rate in both the preferred and the nonpreferred direction did not change as a consequence of these eye movements. Moreover, the discharge rate depended significantly on the direction of target movement (two-way analysis of variance, $P < 0.0001$). By contrast, the influence of the type of tracking (i.e. SPEM versus SPEHM) was not significant

their anatomical location relative to that of saccade-related SEF neurons have not been elucidated. Moreover, it is not known whether, similar to neurons in the FEF, they encode movement in three dimensions.

Pontine nuclei and nucleus reticularis tegmenti pontis

The dorsal pontine nuclei (PN) are the principal recipients of efferents originating from the parietooccipital and frontal areas that contribute to smooth pursuit, as well as efferents from the regions of cerebral cortex involved in saccades [32–40]. A second, albeit less important in quantitative terms, source of oculomotor input to the dorsolateral pontine nucleus is the superior colliculus [41], the projections of which are largely confined to the dorsolateral pontine nucleus. Almost one-half of the neurons in the dorsal PN of monkeys show signals that are relevant to smooth pursuit or saccades in roughly equal numbers [42••]. In contrast to early reports that emphasized the specific role of the dorsolateral pontine nucleus in smooth pursuit, signals related to smooth pursuit have now been observed in the intermediate and medial parts of the dorsal PN. By the same token, saccade-related activity can be found throughout the whole dorsal PN [42••].

The causal role of pursuit-related neurons in the dorsolateral parts of the PN has been established by lesion experiments [43–45], which as yet are not available for the more medial parts of the dorsal PN. In general, the response features of oculomotor PN neurons are diverse and often reminiscent of the different types of pursuit or saccade-related neuron described in cerebral cortex. The anatomical organization of the corticopontine projection is characterized by divergence, with multiple and disparate patches of axon terminals labeled by injections of anterograde tracers into distinct cortical and subcortical locations. Moreover, patches labeled from disparate locations lack significant overlap [46]. Thus, one would expect that streams of oculomotor signals with distinct cerebrocortical and collicular sources would remain separated at the level of the PN. Contrary to this expectation, however, the existence of a considerable population of neurons that are sensitive to smooth pursuit as well as to saccades [42••], which is not found at the level of cerebral cortex, suggests that there is substantial functional convergence. The basis of this functional convergence remains unknown; nevertheless, it is likely that it underlies the shared sensitivities shown by many oculomotor Purkinje cells in the posterior vermis and the flocculus–paraflocculus [47,48], the principal recipients of projections from the dorsal PN.

($P = 0.182$). Modified, with permission, from [12••]. (e) The properties of MSTI VT neurons can be explained if one assumes that such a neuron adds three inputs — namely, retinal image motion, and eye and head motion — to reconstruct target motion in space. Modified, with permission, from [9].

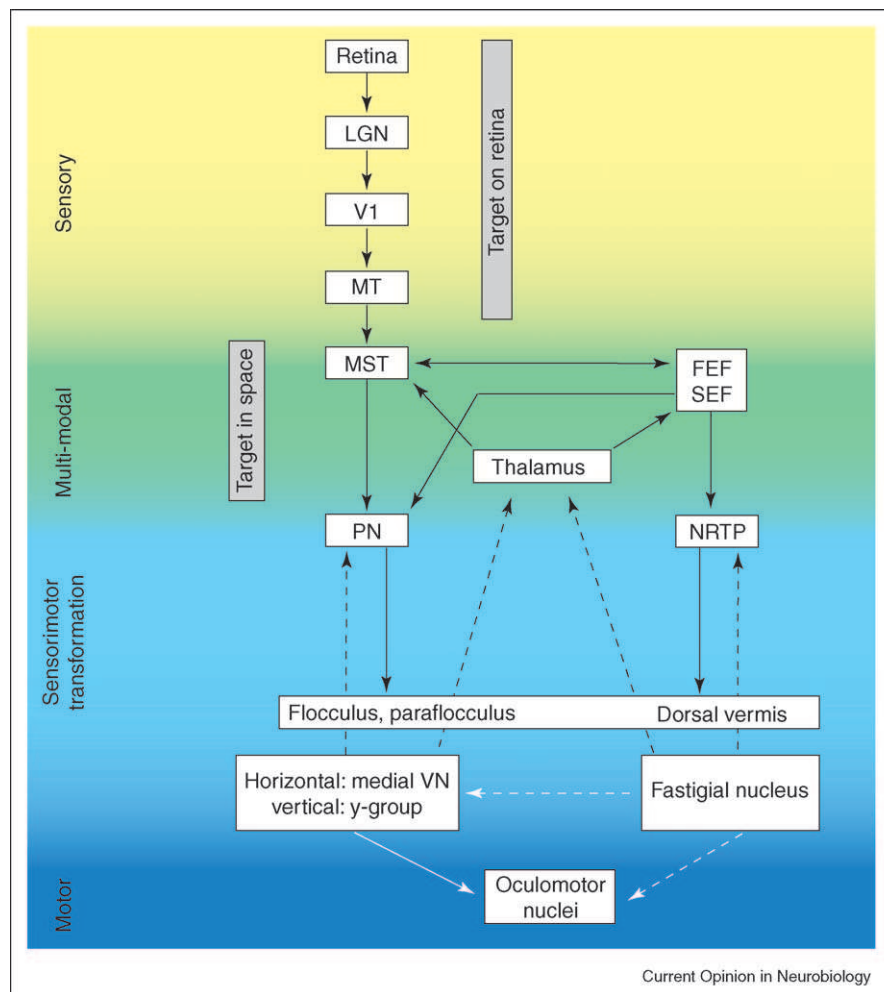
Another feature that distinguishes neurons in the dorsal PN from those of their input in cerebral cortex is the fact that only a minority of them show a clear preference for the direction or velocity of the pursuit eye movement. Many more show sensitivity to both eye velocity and eye position with individually varying weights [42,49]. An integration of position and velocity signals on the level of individual cells has been also observed in the flocculus–paraflocculus [48] and the posterior vermis (R Haas, PW Dicke, P Thier, unpublished).

Another source of pursuit-related information for the cerebellum is the nucleus reticularis tegmenti pontis (NRTP), which is located in the pontine brain stem close to the midline and dorsal to the PN. Although in general it

is less dominated by cerebrocortical input, the NRTP receives fibers from both the lateral (FEF) and the dorsomedial eye field (SEF) [32,34,36,38,50], in addition to receiving a substantial input from the superior colliculus. By contrast, input from the parietal centers of smooth pursuit seems to be very weak at best [39,50].

The NRTP projects to several cerebellar regions involved in eye movements, among them the two chief representations of smooth-pursuit eye movements: the flocculus–paraflocculus complex and the posterior vermis [51–53]. In general, visual and oculomotor activity seems to be concentrated in the more medial region of the NRTP with a preponderance of pursuit-related neurons in the more rostral parts (rNRTP) [54,55], and a preva-

Figure 3



The major substrates of smooth-pursuit eye movements and their connections. Broken lines indicate connections that are still hypothetical or have not been elucidated in sufficient detail. The scheme considers observations, not discussed in the main text, that suggest that signals for horizontal and vertical smooth pursuit are dealt with by different parts of the vestibular complex: namely, horizontal smooth pursuit by medial vestibular nuclei; and vertical smooth pursuit by the y-group — a small cell group that caps the inferior cerebellar peduncle and that, similar to vestibular complex neurons, receives primary vestibular afferents. Abbreviations: FEF, frontal eye field; LGN, lateral geniculate nucleus; MST, middle superior temporal; MT, middle temporal; NRTP, nucleus reticularis tegmenti pontis; PN, pontine nuclei; SEF, supplementary eye field; V1, primary visual cortex; VN, vestibular nuclei.

lence of saccade-related and eye-position-related neurons, as well as neurons related to vergence and ocular accommodation, in its more caudal and dorsal segment (cNRTP) [54,56,57]. A distinction between the oculomotor roles of the rNRTP and the cNRTP is also supported by microstimulation studies: stimulation of the rNRTP evokes slow, pursuit-like eye movements, whereas stimulation of the cNRTP elicits saccades [58]. The fact that pursuit-related neurons in the rNRTP show a strong influence of eye acceleration, which is not observed in the dorsal PN, might indicate that the rNRTP has a prominent role in pursuit initiation [49].

Cerebellum

The cerebellum uses at least two areas for processing signals relevant to smooth pursuit: the flocculus–paraflocculus complex; and the posterior vermis, which includes lobuli VI and VII and adjoining parts of the caudal vermis. Rather than expressing redundancy, this multiplicity of cerebellar pursuit representations probably reflects the need to process pursuit-related signals for different purposes and under different constraints.

Pursuit-related information in the flocculus–paraflocculus complex might be primarily required for the coordination of vestibular reflexes with pursuit behavior, which is needed, for example, during head-unrestrained eye–head pursuit [59]. Signals from the flocculus–paraflocculus complex access ocular motoneurons via a direct projection to eye–head neurons in the vestibular nuclei [60]. By contrast, the primary role of the second pursuit representation in vermal lobuli VI and VII (the posterior vermis) seems to be the parametric adjustment of early open-loop smooth pursuit. Such a role is indicated by posterior vermal lesions, which result in deficits that are considerably stronger for the open-loop portion than for the later closed-loop portion of pursuit. Moreover, these lesions also impair pursuit adaptation [61]. The fact that the extent of the pursuit adaptation deficit parallels that of a concomitant deficit in saccade adaptation suggests that there is a tight conjunction of the neuronal operations underlying these two forms of learning in the vermis, which are both possibly influenced by a common motor error signal. Purkinje cells (P-cells) are probably the common neural substrate because they exhibit responses to both saccades and smooth pursuit. These P-cells are intermingled with saccade- and pursuit-only P cells ([47]; and R Haas, PW Dicke, P Thier, unpublished). Pursuit-related information reaches the brainstem tegmentum via the caudal fastigial nucleus [62,63]. Whether this pursuit pathway influences motoneurons via the vestibular nuclei, which is known to receive input from different parts of the fastigial nuclei [64], remains to be shown (Figure 3).

Conclusions

We have begun to understand the function of the dorsal PN and the NRTP as intermediary stations in a

distributed transformation of sensory and higher-order representations of target movement provided by cerebral cortex into signals that are suitable to control the extraocular motoneurons at the level of the cerebellum. Meanwhile, the study of the other branch of what seems to be a closed loop — the projection back from the cerebellum to cortex — has also started. Recent experiments addressing the role of the cerebello-recipient thalamus [65**] suggest that an important role of this pathway back to cortex might be to provide an efference copy of the pursuit eye movement command, among other functions needed for the coordinate transformations that lead to a representation of target movement in nonretinal coordinates. To understand the role of this cerebello-thalamo-cerebral pathway in full, it will be essential to elucidate the details of its anatomy and to describe the signal transformations at each stage. Then again, we still need a much clearer view of the respective roles of the various pursuit representations in the basilar pons and the cerebellum.

The immediate benefit of the work to be done will be a better understanding of the neuronal basis of smooth pursuit and possibly an answer to why smooth pursuit is the sole kind of motor behavior that is not only impaired but actually completely abolished after loss of the cerebellum [66]. Beyond furthering our view of the cerebro-ponto-cerebellar basis of smooth pursuit, the future results promise important lessons for other types of goal-directed behavior.

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