The neural basis of smooth pursuit eye movements in the rhesus monkey brain

Uwe J. Ilg*, Peter Thier

University of Tuebingen, Department of Cognitive Neurology, Hertie-Institute for Clinical Brain Research, Ofried-Muller-Strasse 27, D-72076 Tuebingen, Germany

ARTICLE INFO

Article history:
Accepted 26 August 2008
Available online xxx

Keywords:
Area MT
Area MST
Frontal eye field
Cerebellum

ABSTRACT

Smooth pursuit eye movements are performed in order to prevent retinal image blur of a moving object. Rhesus monkeys are able to perform smooth pursuit eye movements quite similar as humans, even if the pursuit target does not consist in a simple moving dot. Therefore, the study of the neuronal responses as well as the consequences of micro-stimulation and lesions in trained monkeys performing smooth pursuit is a powerful approach to understand the human pursuit system. The processing of visual motion is achieved in the primary visual cortex and the middle temporal area. Further processing including the combination of retinal image motion signals with extra-retinal signals such as the ongoing eye and head movement occurs in subsequent cortical areas as the medial superior temporal area, the ventral intraparietal area and the frontal and supplementary eye field. The frontal eye field especially contributes anticipatory signals which have a substantial influence on the execution of smooth pursuit. All these cortical areas send information to the pontine nuclei, which in turn provide the input to the cerebellum. The cerebellum contains two pursuit representations: in the paraflocculus/flocculus region and in the posterior vermis. While the first representation is most likely involved in the coordination of pursuit and the vestibular-ocular reflex, the latter is involved in the precise adjustments of the eye movements such as adaptation of pursuit initiation. The output of the cerebellum is directed to the moto-neurons of the extraocular muscles in the brainstem.

© 2008 Elsevier Inc. All rights reserved.

1. Properties of smooth pursuit eye movements

The primate visual system is characterized by a large binocular visual field and a high spatial resolution restricted to the central visual field called fovea (see glossary). Since the number of axons in the optic nerve (see glossary) is limited, it is impossible to achieve a high spatial resolution throughout the entire visual field. However, this restriction imperatively demands for very precise movements of the eye. This demand is satisfied by two different forms of eye movements, saccades and smooth pursuit. Saccades are high velocity gaze shifts that allow us to bring the image of an object of interest into the fovea, followed by visual fixation, an active process, rather than just the absence of an eye movement. However, in many cases objects move relative to the beholder. This is where smooth pursuit eye movements come into play. They stabilize the image of the moving object on the fovea, once saccades have placed it there, thereby allowing the continuous high acuity scrutiny of the object at stake (Bridgeman, Deubel, & Haarmeier, 1999; Haarmeier & Thier, 1999). Both saccades and smooth pursuit eye movements may be complemented by head movements expanding their range. While serving a common purpose, the deployment of foveal vision, saccades and pursuit have very different phylogenies and, moreover, are determined by different functional constraints. In order to understand the phylogenies of saccades and pursuit, it is useful to imagine a hypothetical common vertebrate ancestor with lateral eyes, but in common with us with six extra-ocular muscles and three semicircular canals. This prototypical vertebrate is able to perform stabilisatory eye movements such as the vestibular ocular reflex (VOR) and the optokinetic reflex (OKR) (see glossary). The quick phases occurring in these eye movements represent the future phylogenetic representative of saccades. This assumption is supported by the finding that quick phases and saccades in human share identical dynamic properties (Ron, Robinson, & Skavenski, 1972). The slow phases might represent the origin of the development of the smooth pursuit eye movements. This is indicated by the finding that neurons in the primate nucleus of the optic tract are activated during the execution of optokinetic reflex as well as during pursuit (Ilg & Hoffmann, 1996). Hence it is not surprising that the brain networks underlying saccades and smooth pursuit have been conceived as being largely disparate. However, obviously, saccades and smooth pursuit have to be linked and recent advances in their study have begun to tell us how their coordination may be accomplished by the brain Krauzlis (2005). In this review, we will try to enlighten the pursuit system with special emphasis on the neuronal...
responses recorded from various areas of the rhesus brain during the execution of smooth pursuit (see Fig. 1). Similar aspects of the human pursuit system revealed by imaging studies are given by the chapter of Lencer and Trillenberg “in this special issue”. The chapter by Sharpe emphasizes the effects of lesions while the chapter written by Barnes presents details of cognitive processing underlying the execution of pursuit.

The properties of the pursuit system of man and monkeys share many similarities. In both species, pursuit is dominated by the perceptual rather than the retinal stimulus (Freyberg & Ilg, 2007; Ilg & Thier, 1999; Steinbach, 1976). It is possible to record single-unit activity (see glossary) from various brain areas while highly trained monkeys perform smooth pursuit. In addition, the consequences of micro-stimulation and lesions can be examined. Finally, neuro-anatomical studies inform about the connectivity within specific brain areas. The combination of the results of all these different approaches yields a clear picture of the neuronal substrate of the pursuit system, the subject of this review.

The smooth pursuit eye movements can be modeled successfully as a closed loop control system whose drive is the retinal image movements of the target. Slight deviations of eye velocity from target velocity produce retinal slip signals which correct these deviations (Krauzlis & Lisberger, 1989). Behavioral studies have shown that in addition to retinal image velocity, also retinal image acceleration (Lisberger, Morris, & Tychsen, 1987) and retinal position of the target relative to the fovea (Blohm, Missal, & Lefevre, 2005) serve as input signals driving the pursuit controller. In an alternative group of “non-retinal” models, the controller is envisaged to work on error signals resulting from a comparison of gaze movement with target movement in space (Robinson, Gordon, & Gordon, 1986). 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 (Thier & Erickson, 1992). In principle, the eye movement behavior of head-fixed subjects tracking a moving visual target can be accounted by retinal models. However, models assuming world-centered representations of target movement allow a parsimonious description of pursuit behavior under more natural conditions (Dicie & Thier, 1999; Furman & Gur, 2003). Rather than pursuing elementary visual targets as in the typical laboratory situation, under natural conditions, we pursue multimodal representations of behaviorally relevant objects build 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 (Steinbach, 1976). In other words, encoding a unified object, under natural conditions, requires the integration of information in a common frame of reference. Preferring a specific common non-sensory frame of reference, namely extra-personal space, facilitates the integration of head movements into pursuit behavior and the coordination of perception and action (Ilg, Schumann, & Thier, 2004). Pursuit onset lags the onset of unexpected target movement by some 100 ms, largely due to the delays caused by the visual system. Later, during maintained smooth pursuit, the eye movement lag can be reduced and even nulled, if the future target trajectory can be predicted. The delay of pursuit initiation (see glossary) may be reduced or even turned into a lead if target movement can be anticipated (Jarrett & Barnes, 2002). Surprisingly, there are only marginal differences in the ability to perform anticipatory smooth pursuit between men and monkey (Freyberg & Ilg, 2007).

Because of the delay of eye movements prompted by unpredictable target movements, the first 100 ms of smooth pursuit may be conceived as an open-loop response based on prior target movement not yet affected by the eye movements itself (see Box 1). However, rather than being fixed, the response to this initial open-loop target movement can be modified in an appropriate manner by the experience of later changes in the speed of the target (“pursuit adaptation”, see Fig. 2 for an example. (Chou & Lisberger, 2004).
Box 1. Rashbass paradigm

If a target starts to move unexpectedly, pursuit initiation consists of a pre-saccadic initiation followed by an initial saccade. This saccade compensates the lag in the eye position responses due to the latency of the pursuit system. Since saccades reach peak eye velocities much higher as during smooth pursuit, the analysis of the initial acceleration of the eye can be substantially disturbed by the initial saccade. In the Rashbass paradigm, the target first steps in the opposite direction of its future movement direction. The size of the step is calculated by the latency times target velocity. As a consequence, the eye position approaches gradually target position without a saccade (see Fig. 2a).

Smooth pursuit stabilizes the object image on the fovea at the cost of retinal movement of the background image, according to the speed of the eye movement. The effects of the self-induced retinal image motion signals on the executed smooth pursuit eye movements are marginal since the sensitivity for global motion in the direction of self-induced retinal image motion is substantially decreased during execution of pursuit (Lindner & Ilg, 2006; Lindner, Schwarz, & Ilg, 2001; Schwarz & Ilg, 1999). Nevertheless, the background is perceived as stationary, because its perception is based on a comparison of the raw visual motion signals with an expectation of the visual consequences of the pursuit eye movement. This expectation is continuously updated in order to guarantee spatial stability despite the ever changing environmental conditions (Haarmeier, Bunjes, Lindner, Berret, & Thier, 2001; Lindner, Thier, Kircher, Haarmeier, & Leube, 2005). However, our perceptual stability is not perfect, small deviations in the percept of a stationary background are known as Filehne illusion (Filehne, 1922) (see glossary). For more details see the chapter by Barnes.

In the following, we explicate that the cerebral cortex contains several parieto-occipital and frontal areas with distinct roles in the generation of these components of smooth pursuit eye movements.

2. Middle temporal area (MT or V5)

Most prominently, the visual middle temporal area MT located in the posterior bank of the superior temporal sulcus serves as a generic visual motion processor. This area was firstly described in rhesus monkeys (Dubner & Zeki, 1971) and owl monkeys (Allman & Kaas, 1971). It contributes to smooth pursuit by extracting retinal motion signals of the target image, one of the key inputs driving the pursuit eye movement. There are five key arguments why area MT acts as a major hub with respect to visual motion processing underlying the execution of smooth pursuit eye movements. First, the time course and speed sensitivity of single units recorded from MT are very similar to those of smooth pursuit eye movements (Lisberger & Movshon, 1989). Second, lesions of selected parts of area MT render monkeys unable to pursue targets moving within the confines of the motion scotoma (Durstele & Wurtz, 1988). It is important to note that this deficit is directional, only if the target moves towards the le-
tion yields to acceleration if ipsiversive pursuit is executed. Independent of the strict representation of the contralateral visual field in each hemisphere, each hemisphere seems to code mainly for target movements directed towards it. Fourth, the initial response of single-units recorded from area MT elicits by tilted contours reveals a consistent directional error. If a bar is tilted -45° clockwise from the vertical and moves to the left, the initial response is directed approx. 45° up and to the left, i.e. perpendicular to the bar orientation. After a delay of about 150 ms, the population response is tuned to the real direction of the contour movement. Interestingly, a similar directional error is observed in the initiation of smooth pursuit response of monkeys and humans elicited by tilted moving contours (Born, Pack, Ponce, & Yi, 2006; Pack & Born, 2001; Wallace, Stone, & Masson, 2005). Fig. 3 shows an initial vertical eye velocity for tilted bars although the bars are moving exclusively horizontally. The misdirection of the population response as well as the initial pursuit response can be explained by the property of elementary motion detectors who are only able to code for movement perpendicular to a moving contour, also referred to as aperture problem. Only line-endings are able to indicate the true direction of motion as the famous barber pole illusion demonstrates (see Box 2).

**Box 2. Barber pole illusion**

If we watch a rotating barber pole consisting in a red and blue spiral, we do not see the rotation around a vertical axis. Instead, we perceive vertical movement only. This illusion documents that especially the terminators of a line element determine the direction of perceived motion.

(picture taken from wikipedia)
of directionally selective visual neurons. It is important to note that both sub-areas contain a complete representation of the contralateral visual field (Komatsu & Wurtz, 1988). First, the lateral part of neighboring area MST (=MSTl) located mainly in the fundus of the superior temporal sulcus seems to contain the explicit representation of object motion in world-centered coordinates (Ilg et al., 2004) foreseen by "non-retinal" models of smooth pursuit (Dicke & Thier, 1999; Robinson et al., 1986). World-centered coordinates allow the location of an object independent of the actual eye and head position of the observer (see Box 3). The same result was obtained from the analysis of brief global motion pulses during maintained pursuit: the responses recorded from MST reflected motion-in-space whereas responses recorded from MT reflected retinal image motion (Inaba, Shinomoto, Yamane, Takemura, & Kawano, 2007). The motion-in-space signals are carried by MST visual tracking (VT-) neurons which are multimodal neurons sensitive to retinal image slip, to slow eye movements as well as to slow head movements with identical preferred directions (Ilg & Thier, 2003; Thier & Erickson, 1992). 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 by eye and/or head movements, stabilizing the object image on the retina. This world-centered representation of object motion may be advantageous for a number of functions beyond the programming of smooth pursuit. However, its role in smooth pursuit is

**Fig. 3.** Mean horizontal and vertical eye velocity of a human subject. The subject was asked to track a leftward moving contour (length 20°) at three different orientations. Part a shows the horizontal velocity, b gives the vertical velocity. Note that in case of the vertical contour (0°), no vertical eye velocity was generated. However, if the contour is tilted clockwise (−45°), the eyes initially moved upward, in case of counterclockwise tilt (+45°), the eyes moved downward.
clearly demonstrated by the fact that lesions of MSTl cause an ipsiversive smooth pursuit deficit that can be replicated by “lesioning” a VT-neuron-like layer in a model generating smooth combined eye and head pursuit movements (Dicke & Thier, 1999).

Box 3. Frame of references
In vision, the input is confined to a retinal frame of reference. The fovea represents the origin of this frame of reference. This frame might be important for the generation of eye movements. However, every eye movement produces an update of this coordinate system. Somatosensory information is coded with respect to the body surface. The localization of a sound source is performed within a head-centered frame of reference. In general, for the localization of an object in space—to serve as a target for a hand movement for instance—the actual input frame of reference has to be transformed to an external frame of reference. This transformation is achieved for instance by a combination of retinal information and information of eye and head position.

Similar to area MT, artificial activation of MSTI by means of intra-cortical micro-stimulation is able to modify ongoing smooth pursuit (Ilg & Schumann, 2007; Komatsu & Wurtz, 1989). If pursuit is directed in the preferred direction of the stimulated site in MST, stimulation elicits an acceleration of eye velocity, if pursuit is directed in the non-preferred direction eye velocity decelerates (Ilg & Schumann, 2007). Lesions in MST produce an ipsiversive deficit in steady-state pursuit (Dursteler & Wurtz, 1988; Dursteler, Wurtz, & Newsome, 1987; Ilg & Schumann, 2007; Yamasaki & Wurtz, 1991). Moreover, the effects of artificial manipulations of the neuronal activity in MST are not confined to smooth pursuit. The execution of goal-directed hand movements elicited by a moving target is also affected by these manipulations (Ilg & Schumann, 2007).

Second, pursuit-related responses can also be found in the dorsal part of area MST (=MSTd) located mainly in the anterior bank of the superior temporal sulcus. The discharge of these neurons follows smooth pursuit onset by more than 50 ms (Newsome, Wurtz, & Komatsu, 1988), precluding a major role in pursuit initiation, while in principle being compatible with a contribution to pursuit maintenance (see glossary). Some neurons display similar extra-retinal responses as observed in MSTI (Ono & Mustari, 2006). However, the fact that these neurons are embedded in a visual network for the analysis of optic flow (Duffy & Wurtz, 1991) may be more suggestive of a role in the elimination of eye movement induced flow components from the optic flow field, thereby facilitating the extraction of heading direction (Bradley, Maxwell, Andersen, Banks, & Shenoy, 1996; Duffy & Wurtz, 1991). In doing so, MSTd neurons seem to be able to compensate their focus tuning functions for different translational speeds (Lee, Pesaran, & Andersen, 2007). Neurons whose onset follows that of the eyes have also been reported in MSTI (Ilg & Thier, 2003). However, un-like typical MSTI VT-neurons, which lead pursuit onset by approximately 50 ms, this latter group is sensitive to eye position, rather than velocity (Ilg & Thier, 2003).

4. Frontal eye field (FEF)

The frontal eye field (FEF) (see glossary) is part of the cyto-architecturally defined Brodmann area 8 and contains a representation of saccades as well as of smooth pursuit. Saccades are represented in the anterior bank of the arcuate sulcus and the transition zone to neighboring superficial cortex (Bruce & Goldberg, 1985). On the other hand, smooth pursuit is represented deeper in the posterior bank and the fundus of the arcuate sulcus, roughly at the level of the principle sulcus (Gottlieb, MacAvoy, & Bruce, 1994). Here, we focus on the pursuit-related sub-area of FEF. Micro-stimulation experiments indicate that the pursuit representation in the FEF is involved in setting the gain (see glossary) of the pursuit eye movement (Tanaka & Lisberger, 2002) and single-unit recordings suggest that this area plays a role in predicting target trajectories (Fukushima, Yamanobe, Shinmei, & Fukushima, 2002a), while not contributing to pursuit adaptation (Chou & Lisberger, 2004). The analysis of the dynamic covariations of neural and pursuit responses in FEF revealed that a few FEF neurons are sufficient to drive pursuit (Schoppik, Nagel, & Lisberger, 2008). The majority of FEF pursuit neurons encode pursuit trajectories along specific trajectories in 3D (Fukushima et al., 2002b), i.e. they are not restricted to the two complementary reference frames of a vergence (movement in depth) and a conjugate pursuit system (movement in the frontoparallel plane), dominating pursuit-related responses in the sub-cortical centers for pursuit and in area MST (Akaou, Mustari, Fukushima, Kurkin, & Fukushima, 2005). However, when these neurons are tested during different static roll-tilt positions, the pursuit activity was not affected by this manipulation suggesting that these neurons use a head or trunk-centered frame of reference (Kurkin, Akaou, Fukushima, & Fukushima, 2007).

Similar to the pursuit-related activity recorded from MSTI, the pursuit-related responses from FEF not only reflect the processing of visual motion signals, but also contain extra-retinal signals related to the ongoing eye movements. As Fig. 4a documents, the population response recorded from 46 visual tracking neurons during the pursuit of a real target (hour glass of 20° height) are not different to those recorded during pursuit of an imaginary target (same hour glass with blanked center). Note that during pursuit of the imaginary target, there was no visual stimulation within the blanked central 12° of visual field. Therefore, the observed activity in this condition clearly indicates the presence of eye movement related signals.

The latency of the pursuit-related activity shown in Fig. 4a is in the range between 80 and 90 ms. This is very similar to the shortest values reported by others (Akaou, Saito, Fukushima, Kurkin, & Fukushima, 2007). The latencies of the neuronal responses are clearly shorter than the observed eye movement latencies. As Fig. 4b shows, the population responses to preferred and non-preferred pursuit direction are significantly different just from their onset. Interestingly, there is a slight increase in activity during the initial 500 ms fixation interval in each experimental condition. Since the direction of target movement in each trial was randomized, the monkeys could not anticipate in which direction the target would move, but they could anticipate that a moving target would appear. There are two indications of anticipation in the population responses shown in Fig. 4. First, there is a slight increase of firing rate during initial fixation which is independent of the direction and type of target movement. Second, the firing of the neurons became regular before target motion onset as the drop of the Fano factor (see glossary) shown in Fig. 4c shows.

In order to further examine the contributions of the FEF to anticipatory smooth pursuit, we tested these neurons in a paradigm that enables the monkey to predict the appearance of a moving target. As noted earlier, the lag of pursuit initiation can be avoided if the onset of target motion is predictable. Fig. 5 shows the initiation of visually-guided pursuit (Fig. 5a), in a condition in which the appearance of the moving target was predictable (Figs. 5c and d) and in a control condition without this possibility (Fig. 5b). The pursuit-related activity recorded from FEF reflects the amount of prediction. This response is selective for the predicted direction of target motion. If the monkey predicts movement in the non-preferred direction, the neuronal activity remains at spontaneous level.
Finally, the neuronal activity from FEF is not only important for the generation of smooth pursuit, but is also able to explain motion-induced errors in goal-directed behavior. If saccades have to be directed towards a moving target, the saccade amplitude is adapted to target velocity. The influence of motion signals on saccade amplitude can be mimicked by micro-stimulation in FEF in the absence of visual motion signals (Schafer & Moore, 2007).

Speaking more generally, the projections from FEF to other cortical areas may represent the substrate of shifting the spotlight of attention (Armstrong & Moore, 2007).

5. Supplementary eye field (SEF)

Similar to the FEF, the supplementary eye field (SEF) (see glossary) of the frontal lobe is primarily associated with the execution of saccades. As the results of recent studies imply, its most prominent function seems to be a monitor of saccade performance (Stuphorn & Schall, 2006; Stuphorn, Taylor, & Schall, 2000). However, pursuit-related neurons with predictive discharge have also been observed in the SEF (Missal & Heinen, 2004). In addition, the activity recorded from SEF is able to bridge occluded parts of the target trajectory. If the monkey performed an “*” task, the neuronal activity coded for the invisible target trajectory (Kim, Badler, & Heinen, 2005). As yet, the anatomical location of these very different responses within the entire SEF has not been worked out in detail.

6. Intra-parietal sulcus

Within the intra-parietal sulcus, two different areas might be involved in the generation of smooth pursuit. Firstly, the lateral intra-parietal area LIP, probably corresponding to Ferrier’s parietal eye field (Ferrier, 1876), which is the major saccade representation in posterior parietal cortex. However, pursuit-related activity was also observed in this area (Bremmer, Distler, & Hoffmann, 1997). Different to the pursuit-related activity recorded from the other cortical areas, this activity seems to code mainly for eye position, not for eye velocity. Much earlier, visual tracking neurons were recorded from the adjacent area 7, which is located anterior to LIP on the adjacent gyrus (Lynch, Mountcastle, Talbot, & Yin, 1977). Eye position responses were also recently reported from the medial part of area 7 (Raffi, Squatrito, & Maioli, 2007). These responses have quite long latencies in common with the eye position sensitive responses from MST. Long latencies make it impossible that these neurons contribute to the generation of smooth pursuit. Instead, these late responses might serve another purpose: the perceptual compensation of self-induced retinal motion signals. As explained earlier, stationary per-
ception despite eye movements can be explained by a comparison of the raw global motion signal with an expectation of the visual consequences of the eye movement (Haarmeier et al., 2001).

Secondly, pursuit related activity is also reported from the ventral part of the intra-parietal sulcus (VIP) (Colby, Duhamel, & Goldberg, 1993; Schlack, Hoffmann, & Bremmer, 2003). Since many neurons in this area are somatosensory responsive with facial receptive fields, area VIP is thought to represent the near space. As a consequence, these pursuit-related responses are tuned to rather high velocities (Schlack et al., 2003). The angular velocity of a target moving in the near space is higher as the angular velocity of a target moving in the distance.

After having presented all these different cortical areas most likely involved in the initiation and maintenance of smooth pursuit, the question appears how the information reaches the extra-ocular moto-neurons in the brainstem. The moto-neurons, which are responsible for the proper eye movement, are located in the three nuclei of the III IV and VI cranial nerves. It is important to note that saccades as well as smooth pursuit are achieved by the same motor units. The firing rate determines eye position and velocity. Most likely, the link of these cortical areas to the oculomotor system is the cortical projection to the pontine nuclei. As already mentioned, it seems less likely that only signals originating from MT are used to generated smooth pursuit eye movements. All the evidence presented above indicates that the execution of pursuit depends critically on additional cortical areas and not only on area MT.

7. Sub-cortical processing I: pretectum

The pretectum and the accessory optic system are important areas for the execution of the optokinetic reflex (OKR) in all vertebrates. This reflex is triggered by global motion of the entire environment and helps to stabilize the retinal image. Note that OKR is very different from smooth pursuit which is only executed if a small moving target is voluntarily tracked. Neurons recorded from the nucleus of the optic tract (NOT) are active during OKR and smooth pursuit (Ilg & Hoffmann, 1996; Mustari & Fuchs, 1989). In primates, the NOT receives mainly cortical input (Hoffmann, Distler, & Ilg, 1992; Ilg & Hoffmann, 1993). So although OKR and pursuit are very different types of eye movements, there is overlap with respect to the underlying neuronal substrate.

8. Sub-cortical processing II: superior colliculus

Before discussing the role of the pontine nuclei, another sub-cortical structure with potential relevance for smooth pursuit has to be introduced. It is well established that the superior colliculus (see glossary) plays a major role in the generation of saccades (Sparks, 2002). Although the visual responses of neurons recorded from the SC do not express directionality, a hallmark of visual motion processing, this structure might also contribute to smooth pursuit. Recent work has shown that pursuit initiation is tightly connected to the programming of the initial saccade which removes the residual position error due to latency of visual motion processing. Both processes are dependent of the activity in the ros-
The dorsal pontine nuclei are the major recipients of efferent’s originating from the parieto-occipital and frontal areas contributing to smooth pursuit but also from those parts of the cerebral cortex involved in saccades (Boussaoud, Desimone, & Ungerleider, 1992; Fries, 1990; Giolli et al., 2001; Huerta, Krubitzer, & Kaas, 1986; Leichnetz, 2001; Leichnetz & Gonzalez-Ruiz, 1996; May & Andersen, 1986; Shook, Schlag-Rey, & Schlag, 1990; Stanton, Goldberg, & Bruce, 1988). A second, in quantitative terms less important source of oculomotor input to the dorsolateral pontine nucleus (DLPN) (see glossary) is the aforementioned superior colliculus (Harting, 1977), whose projections are largely confined to the dorsolateral pontine nucleus. Almost one half of the neurons in the dorsal pontine nuclei of monkey’s exhibit signals relevant for smooth pursuit or saccades in about equal numbers (Dicke, Barash, Ilg, & Thier, 2004). In contrast to early reports, which emphasized a specific role of the dorsolateral pontine nucleus in smooth pursuit, pursuit related signals have also been observed in the intermediate and medial parts of the dorsal pontine nuclei. By the same token, sac- cade-related activity can be found throughout the whole dorsal pontine nuclei (Dicke et al., 2004). The causal role of pursuit-re- lated neurons in the dorsolateral parts of the PN has been estab- lished by lesion experiments (Gaymard, Pierrot-Deseilly, Rivaud, & Velut, 1993; May, Keller, & Suzuki, 1988; Thier, Bachor, Faiss, Dichgans, & Koenig, 1991), as yet not available for the more medial parts of the dorsal PN. In general, the response features of oculomotor PN neurons are diverse, in many cases reminiscent of the different types of pursuit or saccade-related neurons described in cerebral cortex. The anatomical organization of the cortico-pon- tine projection is characterized by divergence, with multiple and disparate patches of axon terminals labelled from distinct cortical and sub-cortical locations. Moreover, patches labelled from dispa- rate locations lack significant overlap (Schwarz & Thier, 1999).

Hence, one would expect that streams of oculomotor signals hav- ing distinct cerebral-cortical and collicular sources should remain separated at the level of the PN. However, contrary to this expectation, the existence of a considerable population of neurons sensi- tive to smooth pursuit as well as to saccades (Dicke et al., 2004), not found at the level of cerebral cortex, suggests substantial func- tional convergence. The basis of this functional convergence re- mains unknown. In any case, it is likely that it underlies the shared sensitivities exhibited by many oculomotor Purkinje cells in the posterior vermis and the flocculus/paraflocculus (Leung, Suh, & Kettner, 2000; Suzuki & Keller, 1988), the major recipients of projections from the dorsal pontine nuclei. 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 exhibit a clear preference for the direction or velocity of the pursuit eye movement. Many more show sensitivity to eye velocity as well as to eye position with individually varying weights (Dicke et al., 2004; Ono, Das, Economides, & Mustari, 2005). An integration of position and velocity signals on the level of individual cells has also been observed in the flocculus/paraflocculus (Leung et al., 2000) and the posterior vermis (Haas, Dicke and Thier, unpublished observation). Finally, the earlier described ability to adapt pursuit initiation to constant changes in target velocity was impaired if DLPN was transiently lesioned by muscimol injections, at least not found at the level of cerebral cortex, suggesting substantial func- tionality. Pursuit-related neurons in the more rostral parts (rNRTP) (Ono, Das, & Mustari, 2004; Suzuki, Yamada, & Yee, 2003) and a prevalence 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) (Crandall & Keller, 1985; Gamlin & Clarke, 1995; Suzuki et al., 2003). A distinction between the oculomotor roles of the rostral and the caudal NRTDP is also supported by micro-stimulation stud- ies: stimulation of the rNRTDP evokes slow, pursuit-like eye move- ments, whereas stimulation of the cNRTDP elicits saccades (Yamada, Suzuki, & Yee, 1996). The fact that pursuit-related neu- rons in the rNRTDP show a strong influence of eye acceleration, not observed in the dorsal pontine nuclei, may point to a promi- nent role in pursuit-initiation (Ono et al., 2005).

10. Cerebellum

The cerebellum (see glossary) deploys at least two areas for the processing of signals relevant for smooth pursuit, the flocculus/ paraflocculus complex and the posterior vermis, including lobuli VI and VII and adjoining parts of the caudal vermis. Rather than expressing redundancy, this multiplicity of cerebellar pursuit rep- resentations probably reflects the need to process pursuit related signals for different purposes and under different constraints. Purs- uit-related information in the flocculus/paraflocculus complex may be primarily required for the coordination of vestibular reflexes with pursuit behavior as during head unrestrained eye-head pursuit (Rambold, Churchland, Seelig, Jasmin, & Lisberger, 2002). Signals from the flocculus/paraflocculus complex access ocular moto-neurons via a direct projection to eye-head neurons in the vestibular nuclei (Roy & Cullen, 2003). Interestingly, there is a strong correlation between trial-by-trial variation of simple spike activity of floccular Purkinje cells and eye movement parameters (Medina & Lisberger, 2007). The observed eye position, velocity and acceleration values of individual trials are fed into a model generating a predicted firing rate on the base of the eye move- ments. These predicted firing rates correlate very well with the ob- served firing rates. On the other hand, the primary role of the second pursuit representation in vermal lobuli VI and VII (posterior vermis) seems to be the parametric adjustment of early open-loop smooth pursuit. It is important to note that the activity of some Purkinje cells in the posterior vermis is related to the execution of pursuit, not to the execution of saccades (Nitta, Akaor, Kurkin, & Fukushima, 2008). The involvement in the parametric adjustment is indicated by the deficits resulting from posterior vermal lesions which are considerably stronger for the open loop than for the later closed loop portion of pursuit. Moreover, they also involve an impairment of pursuit adaptation (Takagi, Zee, & Tamargo, 2000). The fact that the extent of the pursuit adaptation deficit par- allels that of a concomitant saccade adaptation deficit suggests a tight conjunction of the neuronal operations underlying these two forms of learning in the vermis, both possibly influenced by a common motor error signal. Most probably, the common neuro-
11. Conclusions and further research directions

The execution of smooth pursuit is tightly connected to the processing of visual motion. Early visual motion processing in primates is achieved by directionally selective neurons in area V1. Visual motion processing is condensed in area MT. Subsequently, the processing in areas MST, FEF, SEF, VIP, and LIP involves extra-retinal signals such as eye and head movement signals, predictive signals (see also chapter by Barnes) as well as movements of the spotlight of attention. All these cortical areas provide input, most likely a signal which describes target movement in an external frame of reference, to the pontine nuclei. The pons transmits the information to the cerebellum. The cerebellum is the site of motor learning such as the adaptation of pursuit initiation and the coordination of pursuit with eye movements elicited by head movements. Finally, the cerebellar output is directed towards the extra-ocular moto-neurons located in the III, IV, and VI cranial nuclei in the brainstem.

Due to numerous monkey studies presented in the review, the picture of the neuronal substrate underlying smooth pursuit is quite complete. Future research directions might focus on the following issues: First, the influence of cognitive signals on pursuit performance, especially the comparison between the human and monkey oculomotor behavior, is still not completely disclosed. Which areas in the primate brain process exclusively visual information, which areas are involved in the processing of cognitive signals? Second, we just begin to understand the overlap in the neuronal substrate underlying the execution of saccades and pursuit. Dorsal pontine nuclei and SC are brainstem structures which might contribute to the execution of both types of eye movements. Third, the analysis of trial-to-trial variability of the eye movements and the neuronal responses together with the analysis of the regularity of the elicited firing pattern will allow more detailed description of the specific contributions of a given area.

Acknowledgment

We thank Suryadeep Dash, Ulrich Biber, and Sylvana Freyberg for the data taken from their PhD projects.

References


Recent history of stimulus speeds affects the speed tuning of neurons in area MT. The Journal of Neuroscience, 27, 11009–11018.


Asymmetry in visual motion processing. Neuroreport, 10, 2477–2480.


Bypassing V1: A direct geniculate input to area MT. Nature Neuroscience, 7, 1123–1128.


Pursuing the perceptual rather than the retinal stimulus. Vision Research, 16, 1371–1376.

Executive control of countermoving saccades by the supplementary eye field. Nature Neuroscience, 9, 925–931.


Patterns of projections from the pontine nuclei and the nucleus reticularis tegmenti pontis to the posterior vermis in the rhesus monkey: A study using retrograde tracers. The Journal of Comparative Neurology, 337, 113–126.

Imperfect visual tracking eye movements due to an ischemic lesion of the basilar pons. Annals of Neurology, 29, 443–448.

Responses of visual-tracking neurons from cortical area MST-I to visual, eye and head motion. The European Journal of Neuroscience, 4, 539–553.

