

Neural control of 3-D gaze shifts in the primate

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Abstract: The neural mechanisms that specify target locations for gaze shifts and then convert these into desired patterns of coordinated eye and head movements are complex. Much of this complexity is only revealed when one takes a realistic three-dimensional (3-D) view of these processes, where fundamental computational problems such as kinematic redundancy, reference-frame transformations, and non-commutativity emerge. Here we review the underlying mechanisms and solutions for these problems, starting with a consideration of the kinematics of 3-D gaze shifts in human and non-human primates. We then consider the neural mechanisms, including cortical representation of gaze targets, the nature of the gaze motor command used by the superior colliculus, and how these gaze commands are decomposed into brainstem motor commands for the eyes and head. A general conclusion is that fairly simple coding mechanisms may be used to represent gaze at the cortical and collicular level, but this then necessitates complexity for the spatial updating of these representations and in the brainstem sensorimotor transformations that convert these signals into eye and head movements.

The problem of 3-D gaze shifts

The term 'gaze' is loosely used in common language to denote the direction in which one is looking. We can define this more rigorously as the visual axis (i.e., the line passing from the fovea through the optical focal point toward the object of current regard). By this definition, gaze is determined by the orientation of the eye in space, which in turn will be influenced by the orientation of the eye in the head, the head on the body, and the body with respect to

the earth. Of course, when the head is immobilized, as is often the case in the laboratory, gaze control becomes synonymous with oculomotor control. At the opposite extreme, in real life situations, where very large shifts in gaze are often required, the body also contributes. But here we will consider gaze control in the manner most commonly implied in the current literature, i.e., gaze movements produced by coordinated movements of the eyes and head.

Most studies of gaze control take a 1-D or 2-D approach. From this perspective, certain fundamental findings arise, among them, that gaze shifts generally start with a rapid eye movement (saccade) toward the desired visual target, followed closely by a slightly less rapid head movement in the same general direction (Morasso et al., 1973; Guitton and Volle, 1987; Freedman et al., 1996). When gaze first reaches the target, either at the end of the saccade or through

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a combination of the eye and head movement, the system locks gaze onto the target by engaging the vestibulo-ocular reflex (VOR). The VOR then stabilizes the gaze line by counter-rotating the eye against the movement of the head, which generally continues until the eyes are somewhat centered within the orbit (Fuller, 1996; Tweed, 1997). Most studies on the neurophysiological mechanisms for gaze control have thus focused on the mechanisms that coordinate the timing of these various stages.

However, if one is interested in the spatial aspects of gaze control, then one must seriously consider the 3-D geometry that pertains to eye movement, head movement, and their relation to the location of the visual target. The eyes and head both rotate *and* translate with respect to visual targets, where each of these types of motion have three degrees of freedom (Tweed and Vilis, 1987; Angelaki et al., 2000; Medendorp et al., 2002). Here we will mainly consider rotations and their effect on orientations of the eyes and head. These structures obviously rotate in the horizontal and vertical dimension. The third dimension is called torsion, which roughly refers to the tilting of the eyes or head about the gaze line (more rigorous definitions will be provided in the next section).

As we shall see, both the eyes and head have the musculature necessary to rotate in all three of these degrees of freedom (Simpson and Graf, 1981; Suzuki et al., 1999). So when one moves from a 2-D to a 3-D perspective, the first and most obvious question to ask is, what does torsion do, and how is it controlled? But this is only the beginning, because in 3-D (i.e., in the real world) a number of computational problems arise that are either not present or are obscure from a more abstract 2-D perspective. First, there is the degrees of freedom problem (Bernstein, 1967). Since gaze direction is inherently a 2-D variable, the eyes and head, each with their three degrees of freedom, have an infinite number of ways to contribute to the same gaze direction. For example, one could fixate a visual target and spin the eyes torsionally about the line of sight without changing gaze. Obviously we do not do this normally, but scientists in this field are interested in which choices of orientation the system actually makes, how it implements these choices and what this says about the neural mechanisms involved (Helmholtz, 1867; Nakayama, 1975; Tweed

and Vilis, 1990; Straumann et al., 1991; Hepp, 1994; Crawford and Vilis, 1995).

Another computational problem that presents itself in 3-D is the non-commutativity of rotations (Westheimer, 1957; Tweed et al., 1999). When rotations are not constrained to occur about a single fixed axis — as they never are for the eyes and head — then the order of rotation has a strong effect on the final orientation. For example, a 30° upward rotation followed by a 30° leftward rotation results in a different final orientation than the same two rotations in the reverse order. This has a number of implications for the motor control of gaze, which have been reviewed and argued to considerable extent elsewhere (Tweed and Vilis, 1987; Schnabolk and Raphan, 1994; Quaia and Optican, 1998).

Finally, the question of neural ‘reference frames’ and ‘coordinate systems’ often only becomes clearly delineated in 3-D (Soechting and Flanders, 1992). These terms are frequently used in the gaze control literature, very often inappropriately. When we define some spatial variable, we must do so with respect to some fixed reference frame. For a physiological example, the initial visual stimulus is defined in an ocular frame, where the activity of ganglion cells specifies the direction of a given target with respect to the fovea, all within a 2-D retinal map that is fixed to the eye. In comparison, the eyes move relative to the head so the eye muscles are organized in a head-centered frame, and similarly the neck muscles are organized with respect to a trunk-fixed frame.

This is separate from the concept of a coordinate system, which provides a set of axes (or more correctly basis vectors) which are useful to describe the components of a variable within some frame (Soechting and Flanders, 1992). The choice of coordinate systems is arbitrary, as long as it ‘spans’ the degrees of freedom of the space, but as a default most people prefer orthonormal coordinate systems. We do this all the time do describe our data, but sticking to physiology, the retina does not have a coordinate system, whereas the eye muscles and vestibular canals do specify natural coordinates in a head frame (if we imply a certain coupling between the opponent pairs of these structures) (Simpson and Graf, 1985). The question of whether the neural control system itself employs such coordinate systems

is more controversial (Robinson, 1992; Crawford, 1994).

Once one has specified the reference frame and the coordinate system, one is then prepared to define a number of kinematic variables. But these are separate from the coordinate systems in which they operate. For example, one can use a given head-fixed coordinate system to define eye orientation, the angular velocity of the eye, eye rotations, displacements in eye orientation, and a number of other variables, each with a different meaning (Hepp, 1994; Crawford and Guitton, 1997). Thus, terms like ‘gaze coordinates’ or ‘velocity coordinates’ are not meaningful. In designing or understanding a control system, one must specify the frame of reference, the coordinates within this frame, and the variable being measured.

A very frequent error in the gaze control literature is to equate displacements with retinal coordinates and gaze positions with space coordinates. Or, to think that displacements are frame-free. It is true that displacements are defined with regard to a reference position, whereas positions, orientations, etc. must be defined with respect to single common zero point (i.e., a reference position). However, displacements are not frame-free (Hepp et al., 1993; Crawford and Guitton, 1997). Consider Sperry’s famous experiment of surgically rotating a frog’s eye by 180° (Sperry, 1943). When the frog then saw a fly displaced leftward in retinal coordinates, it flung its tongue rightward in frog head coordinates. So, the frame of reference for a displacement must be specified. This is very relevant here because many think that gaze is controlled largely through a series of internal displacement-like commands beginning with the visual target defined in the retinal frame and ending with the motor displacements of the eyes with respect to the head and the head with respect to the body (Becker and Jurgens, 1979; Van Opstal et al., 1991; Colby and Goldberg, 1999; Klier et al., 2001).

Moreover, the reference frame problem that we saw with the frog does not only occur for torsional eye orientations. We have shown that because of the geometry resulting from the way that light projects onto the retina and how this in turn depends on eye orientation, even moving the eyes up or down (left or right), changes the correspondence between the visual code and motor codes for target displacement

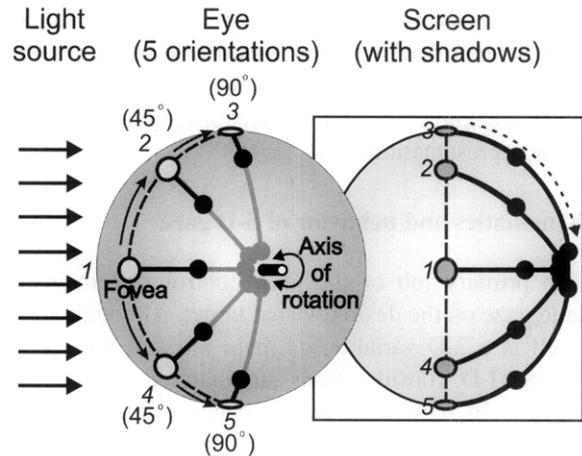


Fig. 1. Orientation-dependent geometry alters correspondence of visual and motor codes. A semi-transparent ‘eye’ is viewed from a behind-right perspective, where the eye is back-lit so that the shadows project onto a frontal screen. This projection system is not arbitrary, because it mirrors the geometry of the raw 2-D eye-coil signals used to measure gaze in physiological studies. At position 1, the eye is looking straight ahead, with the fovea (open disk) oriented at the back of the eye. Two sites of retinal stimulation (dot) are represented as ‘retinal error’ vectors emanating rightward from the fovea; one 40° right (black line) and one 80° right (gray line). These correspond to 40° and 80° rightward visual targets (dispensing with the optical inversion), as shown by the shadows projected on the screen (dot). This is the trivial situation in which a point of horizontal stimulation on the retina calls for a purely horizontal eye movement to acquire the target. But what if the eye rotates up or down about its horizontal axis by 45° or 90° (initial static eye orientations 2–5)? The stimulus vectors remain fixed anatomically on the same horizontal retinal meridian (so that from our space-fixed perspective they now appear rotated to non-horizontal lines). How do these same retinal displacements correspond to target displacements in visual space? The screen view indicates that these horizontal displacements (in retinal coordinates) now correspond to non-horizontal displacement vectors in space, the latter becoming more and more oblique as a function of the length of retinal vector and the amount of eye rotation. For example, at position 3, the 80° rightward retinal target would call for an eye movement qualitatively like the one indicated by the dashed arrow on the screen. (Adapted from Klier et al., 2001.)

in space (Fig. 1) (Crawford and Guitton, 1997; Klier et al., 2001).

The purpose of this chapter is to consider how the primate brain deals with the problems of excess degrees of freedom in gaze control and how it performs the visual–motor reference frame transformations alluded to above. We will deal first with the kinematic aspects of the behavior, followed by a

consideration of what variables are encoded in which frames/coordinate systems at various points within the gaze control system, and end by considering what we know about the transformations between these representations.

Kinematics and behavior of 3-D gaze

The primary job of the gaze control system is to land gaze on the desired visual target. Although gaze itself is a 2-D variable, its main job still falls prey to the 3-D considerations summarized in the last section. In particular, the reference frame problem involved in converting a visual signal defined in the ocular frame into commands for movement relative to the head and body frames (Fig. 1). With the use of simulations, we have shown that a direct mapping of the components of the visual vector onto the components of a motor vector would produce accurate gaze shifts for small displacements, but progressively larger position-dependent errors for movements over 30° in amplitude (Crawford and Guitton, 1997; Klier and Crawford, 1998). One can appreciate this from Fig. 1 by considering what would happen if that one single horizontal retinal error were mapped onto the same horizontal gaze shift at all vertical positions, whereas the projection shows that the required gaze shift depends on initial positions. Conversely, the same simulations showed that in order to avoid these errors, the system has to take eye (and head) orientation into account. So does it?

We tested this by measuring saccades over a wide range of initial eye positions (including torsional eye positions induced by tilting the head) and found that saccades are more accurate than could be predicted by a simple displacement-to-displacement mapping (Klier and Crawford, 1998). Indeed, the predicted errors of this model become so huge within the range of head-free gaze control (up to 90°) that this hardly seems to deem further testing. Clearly, the neural control system performs a position-dependent reference frame transformation. Where and how this is done will be the subject of a later section.

Another, more extensively studied issue is the degrees of freedom problem. With the head immobilized, it is well known that the eye obeys Donders' law, i.e., for each gaze direction only one 3-D eye orientation is used (Donders, 1848). Listing's law

further specifies that the eye only assumes those orientations that can be reached by rotations about an axis in a head-fixed plane (Listing's plane) that is orthogonal to gaze at the special reference orientation called primary position (Helmholtz, 1867; Hepp, 1990; Tweed and Vilis, 1990). In other words, if we define these axes in a coordinate system where the vertical and horizontal axes are fixed in Listing's plane, and the orthogonal torsional axis is parallel to gaze at the primary position (Listing's coordinates), then Listing's law simply states that torsion is maintained at zero (Fig. 2A) (Westheimer, 1957). (Note that this is not the same as cyclotorsion about the line of sight, which shows so-called 'false torsion' at oblique eye orientations.)

Several studies in humans and monkeys have shown that a similar form of Donders' law also holds for the orientation of the eye-in-space when subjects make head-free gaze shifts (Straumann et al., 1991; Glenn and Vilis, 1992; Radau et al., 1994; Crawford et al., 1999; Ceylan et al., 2000). However, the constraint is not quite as stringent as Listing's law (i.e., the torsional standard deviations are 2–3 times higher). Moreover, instead of falling in a plane, the axes used to describe eye-in-space orientations form a twisted surface (Fig. 2B), when plotted in an orthogonal coordinate system where the forward-pointing torsional axis is fixed in space. This twist corresponds to the twist produced by rotating an object in Fick coordinates, where the vertical axis (for horizontal rotation) would be fixed in the body, the horizontal axis (for vertical rotation) would be fixed in the eye, and the third torsional axis would also be fixed in the eye and held at zero (Glenn and Vilis, 1992). (More accurately, the constraint is about half way between zero torsion in Fick and Listing's coordinates.) Orientations of the head show a similar Fick-like constraint, during gaze shifts (Fig. 2C). Obviously these are neural constraints since we can violate this rule by voluntarily rotating the head torsionally any time we want.

What about orientations of the eye relative to the head during these head-free gaze shifts? They need not show the same constraint as the eye-in-space, since the latter is the product of constraints in both the eye-in-head and head-in-space. It turns out that Listing's law is still obeyed by the eye-in-head, but only during fixations at the end of the gaze shift

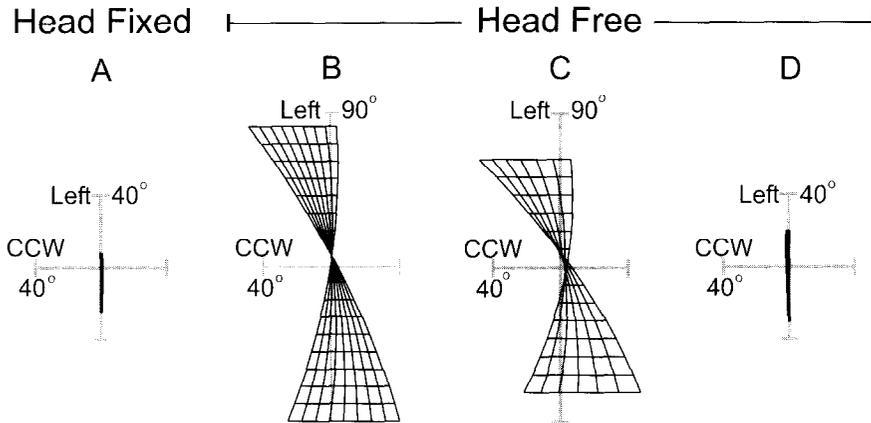


Fig. 2. Donders' law in head-fixed and head-free conditions. 2nd order surface fits were computed to fixation points (i.e., when the velocity of both the eye and head were $<10^\circ/\text{s}$) during random gaze shifts. Side views of the data are presented where torsion (i.e., clockwise and counterclockwise movements) fall along the abscissa. (A) In the head-fixed condition (where eye-in-space = eye-in-head), eye positions appear to lie in a flat plane viewed edge-on (i.e., Listing's plane). (B–D) In head-free condition, the eye-in-space (B) and head-in-space (C) positions look like flat planes twisted about the center (i.e., a Fick-like surface), while the eye-in-head (D) surface resembles the head-fixed condition.

(Fig. 2D) (Tweed et al., 1998; Crawford et al., 1999). In contrast, during the gaze shift, the eye-in-head violates all forms of Donders' law (Tweed et al., 1998; Crawford et al., 1999). This is not due to sloppiness, but rather because the VOR phase of the gaze shift cannot simultaneously obey Donders' law and stabilize the retinal image. So the VOR chooses to stabilize vision, producing real torsional eye-in-head rotations (Crawford and Vilis, 1991; Misslisch and Hess, 2000). In order to counteract these effects and end up with the eye in Listing's plane rather than with some willy-nilly level of torsion, the system has also developed a rather sophisticated mechanism, generating saccades with torsional components that anticipate (in an equal and opposite way) the torsion produced by the VOR (Crawford et al., 1991; Tweed et al., 1998; Crawford et al., 1999). These movements are much too rapid and precise to be explained as any kind of passive mechanism (Seidman and Leigh, 1989). Thus, with careful measurement, one observes a continuous pattern of the eyes shooting out of and then coming back into Listing's plane by the end of the gaze shift.

Spatial updating

Every time one generates a gaze shift, it changes the spatial correspondence between the retina and the visual world. This is not a big deal for objects that are

continuously in clear view, but it does pose a problem for the remembered locations of objects because a memory trace coded in a raw visual frame would no longer be valid at the new eye position. Clearly the system is not fooled by this since we are able to generate accurate saccades to remembered targets after intervening gaze shifts (Hallett and Lightstone, 1976; Herter and Guitton, 1998), including gaze shifts composed of both eye and head movement. Although a number of mechanisms have been proposed to account for this perceptual stability, the weight of the current evidence suggests that each time gaze is shifted, internal representations of retinal targets are counter-rotated within the internal eye-centered maps of the visuomotor system, such that their spatial correspondence remains correct (Goldberg and Bruce, 1990; Duhamel et al., 1992; Walker et al., 1995; Henriques et al., 1998; Batista and Andersen, 2001; Medendorp and Crawford, 2002).

In 2-D models of this process, this internal re-mapping is accomplished by subtracting a 2-D motor vector representing the gaze shift (presumably in the form of an efference copy) from the visual vector (Goldberg and Bruce, 1990; Quaia et al., 1998). However, in the real 3-D system this would not work for a couple of reasons. First, since the eyes and head (Donders' law notwithstanding) do sometimes rotate torsionally, and this also changes the spatial correspondence of the retina to the world, one would

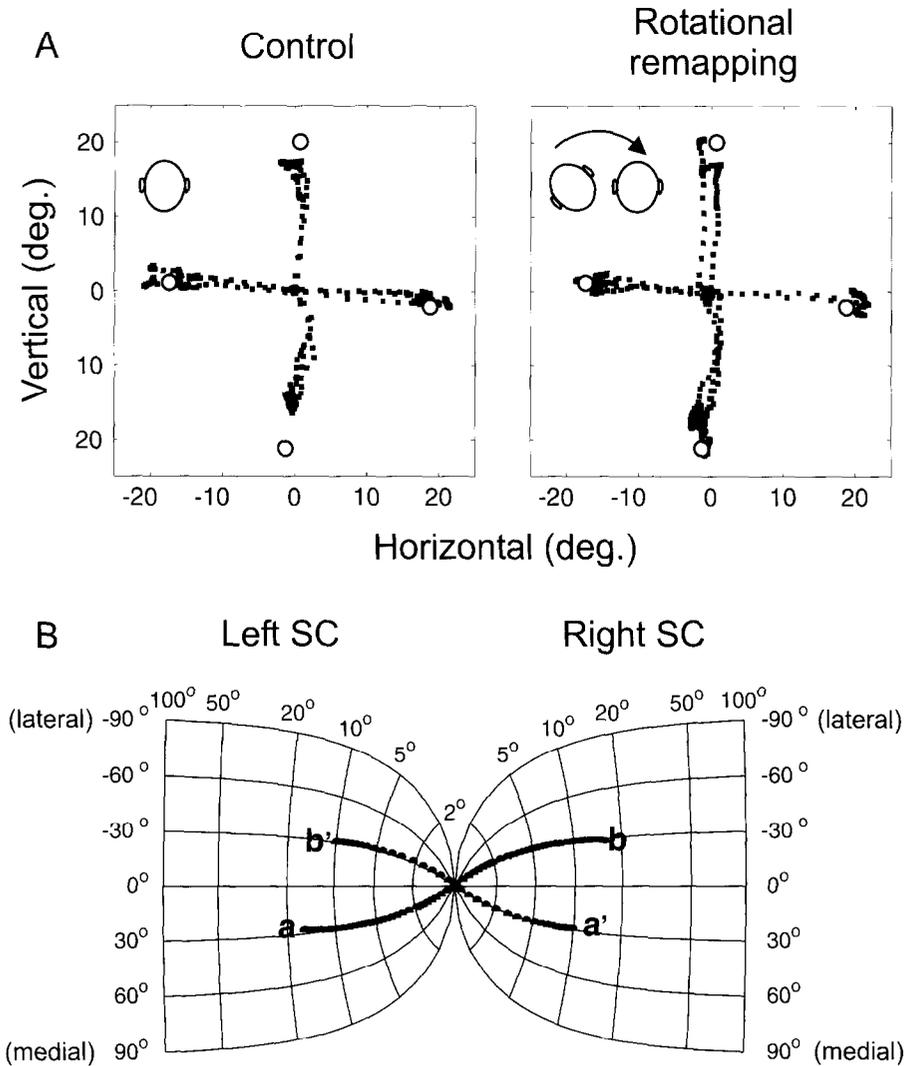


Fig. 3. Rotational remapping following intervening gaze shifts. (A) In the control condition (left panel) the subjects made no head movement before saccading to the remembered target (circle). In the 'rotational remapping' condition (right panel) the subjects perceived the target at a 45° rightward head tilt, rolled their heads upright, and subsequently made the saccade. One subject's performance to the four cardinal targets is shown. In both conditions, saccadic directions were accurate. (B) Rotational remapping on the superior colliculus map. A space-fixed target a (10° leftward and 30° upward) flashed when the eye is turned 45° counterclockwise, stimulates the left side of the retina. It is represented, therefore, on the left SC. But after the eye rotates upright, the remembered target is now to the right relative to the retina. In the collicular map its representation must cross the midline, from the left to the right SC (a'). At the same time, target b (10° rightward and 30° downward in space) should cross in the opposite direction, from the right SC to the left (b'). (Adapted from Medendorp et al., 2002.)

need a 3-D operator to provide optimal eye-centered re-mapping of the visual memory trace (Medendorp et al., 2002). Our recent experiment shows that the human system does indeed possess such an operator. Specifically, following torsional rotations of the eyes and head, subjects are still able to localize re-

membered visual targets using a saccade (Fig. 3A) (Medendorp et al., 2002).

Interestingly, this requires an internal 'rotational remapping', where the amount and direction of remapping depends both on the movement itself and initial location of the representation within the

internal eye-centered maps of the brain (e.g., in the superior colliculus) (Fig. 3B). Furthermore, the necessity of a 3-D feedback signal probably means that the efference copy is originating in the brainstem (and/or from vestibular feedback about head motion) before being fed back to higher visuomotor centers (Smith and Crawford, 2001a). Moreover, since such a remapping must be done as a rotation (i.e., a non-commutative process), this cannot be captured by a vector subtraction model. Our simulations further show that a non-commutative model is even required for saccades within Listing's plane, and the lack of errors observed when such saccades are tested again shows that the principles of non-commutativity are heeded in the internal re-mapping mechanism (Smith and Crawford, 2001a).

Another bit of interesting geometry that arises during head-free situations has more to do with translations. With the head free, the eye frequently translates through space as well as rotates (Medendorp et al., 1998). This again changes the correspondence between the internal eye-centered maps of space and the visual world, but this time in a way that depends on target depth (i.e., motion parallax) (Howard and Rogers, 1995). Our recent experiments show that during such translations, subjects are able to remember and saccade toward perceived target locations in a translation and depth-dependent manner (Medendorp et al., 2001). Again, this shows that the updating mechanism cannot rely on the efference feedback signal alone. Rather, the amount of internal 're-mapping' must also depend on local information content including the depth of the target.

Gaze target coding in the superior colliculus and frontal cortex

Over the last decade or two, there has been a general consensus that the superior colliculus (SC) encodes displacements in gaze, following a fairly orderly topographic map that begins with small displacements coded at the more anterior SC with subsequently larger displacements coded as one progresses toward the posterior SC (Straschill and Rieger, 1973; Guitton et al., 1980; Roucoux et al., 1980; Pare et al., 1994; see also Guitton et al., 2003, this volume). However, in light of the frame dependence of gaze displacements (Fig. 1), it is necessary to ask if these

are displacements in the ocular frame (i.e., retinal error), or displacements with respect to the body (i.e., motor error). Moreover, certain reports of gaze shifts evoked by stimulation of the posterior SC seemed to suggest that at least that portion of the structure might encode desired gaze directions (not displacement) relative to the body (Roucoux et al., 1980; Pare et al., 1994).

We tested between these options by stimulating different points of the SC in head-free monkeys and observing the position-dependencies in the evoked gaze shifts (Klier et al., 2001). Depending on the site, this produced a variety of different gaze shift sizes and directions, from small saccade-like movements, to very large gaze shifts involving both the eye and head (Fig. 4A–C). According to one model, this should have produced fixed-vector, position-independent gaze shifts, whereas at the opposite extreme one might predict movements that always converge to a common position for each site. An alternative explanation, according to the geometry illustrated in Fig. 1, holds that if the SC simply codes target direction relative to the eye (i.e., a retinal model), then this would tend to map onto relatively fixed-vector movements for smaller gaze shifts at more anterior sites, but progressively more convergent movements as one progresses more posteriorly, evoking larger movements (Klier et al., 2001).

Fig. 4D shows the results, plotting the level of position-dependence for gaze shifts evoked at each site as a function of the characteristic size of the gaze shifts evoked from that site. For reference the predictions of the three models are also shown. Clearly, the data followed the predictions of the retinal model. Moreover, this model explains why the anterior SC code seems to be more fixed-vector and the posterior SC more goal-directed. This pattern simply falls out of the geometry of projecting the eye-centered retinal code onto the required gaze shift from different initial gaze positions. Of course, if the SC is coding a simple target-in-retina signal, then this implies that something downstream must be implementing the position-dependencies required to map this signal onto the different gaze trajectories observed in our data, in other words, to implement the reference frame transformations required to activate eye and neck muscles which clearly are not organized in eye-fixed coordinates. This presumably

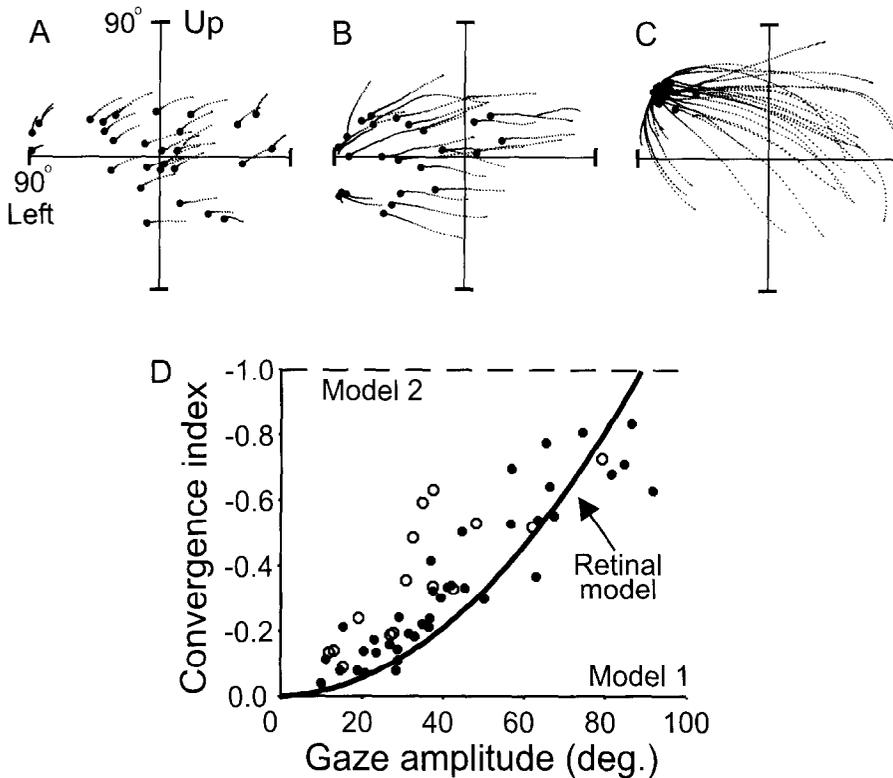


Fig. 4. Gaze target coding in the superior colliculus. (A–C) Trajectories evoked by stimulating three SC sites. Gaze plots are shown for a relatively anterior site ($\sim 30^\circ$ gaze shifts) (A), an intermediate site ($\sim 60^\circ$ gaze shifts) (B), and an extremely posterior site ($\sim 90^\circ$ gaze shifts) (C). Data are plotted in space coordinates and the final end-points of each movement are shown (dots). (D) A convergence index determines the most suitable model of SC coding. Gaze convergence indices from two monkeys (circle, dot) are plotted against the characteristic gaze amplitude for each stimulation site. One model (Model 1) predicts a fixed convergence index of 0 (slope along the abscissa) indicating fixed-vector, position-independent gaze shifts. Another model (Model 2) predicts a fixed convergence index of -1 (dashed line) indicating goal-directed, position-dependent gaze shifts. The retinal model requires that convergence indices be small for small gaze amplitudes, but then increase non-linearly for larger gaze amplitudes (continuous line). The data favor the retinal model and follow its predictions very closely. (Adapted from Klier et al., 2001.)

frees the job of the SC to deal with earlier aspects of gaze coding such as target selection and timing of the movement, within a relatively simple spatial frame. Consistent with this, the SC shows evidence of the eye-centered remapping across eye movements described in the previous section (Walker et al., 1995).

But what of the other, higher-level gaze-coding structures in the cortex? Recently, we have performed a similar series of experiments involving stimulation of the supplementary eye fields (SEF) of the frontal cortex. Again, this is a structure for which there is considerable controversy about whether it codes fixed-vector movements or goal-directed gaze shifts (or even more complex object-centered codes)

(Russo and Bruce, 1993; Tehovnik et al., 1998; Olson and Gettner, 1999). Our hypothesis was that, if a wide enough range of head-free gaze shifts could be evoked, they might be shown to follow the predictions of the retinal model. However, the results have not been as straightforward as those for the SC (Martinez-Trujillo et al., 2002). With the head free to move, stimulation of the SEF did produce gaze shifts with considerable head movement from many sites. And this did substantially change the apparent coding in these structures as compared to head-fixed controls. However, when the data were plotted as in Fig. 4D, we found sites that fit into the predictions of all three models. Thus, the SEF may be a center

for integrating and providing signals for gaze shifts in a variety of different frames, but like with the SC, it very likely does not concern itself with computing the detailed kinematics of the gaze shift.

Role of the superior colliculus in 3-D eye-head coordination

As mentioned in the previous section, stimulation of the SC produces gaze shifts involving movement of both the eyes and the head. But does this mean that the SC codes separate, parallel commands for the eyes and head, or that the SC simply codes a shift in gaze, with coordination of the eye and head organized downstream? The weight of opinion and evidence from microstimulation and single-unit recording studies currently falls toward the latter option (Munoz and Guitton, 1991; Freedman et al., 1996; Freedman and Sparks, 1997; Klier et al., 2001). Consistent with this, we have recently trained monkeys to alter their patterns of eye-head coordination in a context-dependent fashion, and have found that at least some of this context-dependent behavior is retained when the SC is stimulated, as if some state-dependent coordination variable were retained downstream from the SC (Constantin et al., 2001).

So then, what happens downstream from the SC? We have already mentioned that a reference frame transformation must occur downstream, but in the current context, it is also important to consider the role of the SC in the 3-D aspects of eye-head coordination. As described in an earlier section, both the eye and head obey Donders' law, at least during fixations, and this involves a precise coordinating mechanism between torsion produced during the saccade and VOR stages of the eye-in-head movement. If the SC encodes an early 'gaze relative to eye' signal, then one would expect these neural constraints and coordination mechanisms to also be implemented downstream from the SC. In other words, one would expect that stimulation of the would produce fully formed gaze shifts (in the 3-D sense), including movements that obey Donders' law and show anticipatory torsion in the saccades. This indeed is what we found (Crawford et al., 2000), as shown in Fig. 5. Most interestingly, stimulation of one site in the SC could produce saccades with zero torsion with the

head fixed, or with various amounts of torsion that correctly anticipated the oncoming VOR phase when the head was free. Since the VOR can only be predicted by knowing the intended head movement, this again suggests that a very sophisticated mechanism for coordinating the eye to-the-head is located in the neural transformations downstream from the SC.

Intrinsic coordinate systems for oculomotor control

To better understand the signal output by the SC, it is necessary to know how these signals must finally be 'read' by the downstream motor control centers for the eye (and head). In the case of the eye, it is well documented that the motor command for saccades takes the form of a velocity-like signal, whose horizontal components are largely organized in the paramedian pontine reticular formation (PPRF) (Luschei and Fuchs, 1972; Hepp and Henn, 1983), and whose vertical and torsional signals are organized in the midbrain rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) (King and Fuchs, 1979; Buttner-Ennever et al., 1982; Henn et al., 1989). It is also accepted that these velocity-like commands are then neurally integrated (in the mathematical sense) to produce the tonic signal that holds the eye in place at the end of the movement. Again, there is an anatomic division between the horizontal and vertical/torsional components, with the former organized in the region of the medial vestibular nucleus (MVN) (Cannon and Robinson, 1987; Cheron and Godaux, 1987), and the latter organized in the midbrain interstitial nucleus of Cajal (INC) (Crawford et al., 1991; Fukushima, 1991).

Interestingly, the arrangement of these signals suggests a coordinate system very similar to that observed in the vestibular canals and the extra-ocular muscles. Specifically, the PPRF/MVN corresponding to the horizontal canals/recti, and the riMLF/INC possessing neurons with tuning resembling the directions controlled by the vertical canals/muscles (Fukushima et al., 1987). In particular, the midbrain seems to separate neurons into populations encoding up/clockwise or down/clockwise directions on the right side (subjects point of view) and up/counterclockwise or down/counterclockwise directions on the left side (Crawford et al., 1991).

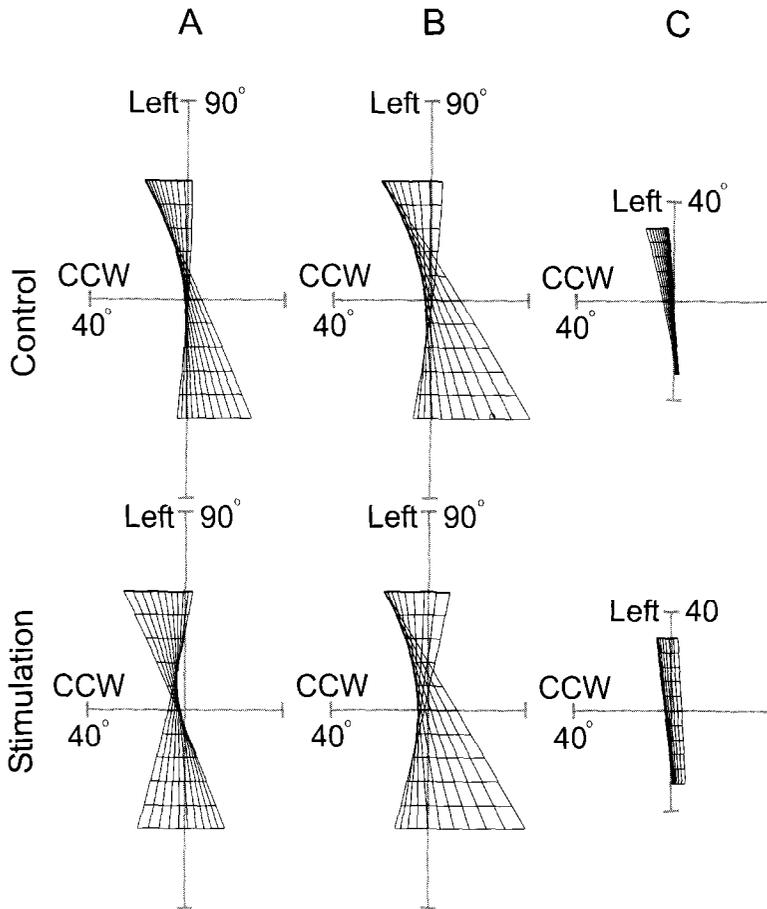


Fig. 5. 3-D eye-head coordination is implemented downstream from the SC. Best-fit surfaces for the eye-in-space (A), head-in-space (B) and eye-in-head (C) from control (top row) and SC stimulation-induced (bottom row) trials. The six variables describing 2nd order best-fit surfaces to the endpoints of control (top row) and SC stimulation-induced (bottom row) data were averaged across all random files (control data) and all sites tested (SC stimulation data). The six averaged variables produced 2nd order surfaces which are shown from a side view (torsion along the abscissa). Statistical analysis showed that the corresponding surfaces were not significantly different from one another.

This has given rise to speculation about whether these apparent intrinsic neural coordinates correspond best to those of the canals or muscles (Robinson and Zee, 1981; Robinson, 1985; Simpson and Graf, 1985; Crawford et al., 1991; Crawford and Vilis, 1992).

However, a third possibility is that, although their organization may be influenced by and optimized in similar ways to both of these, they may in fact align best with something else, i.e., Listing's plane (Crawford and Vilis, 1992; Crawford, 1994). If the oculomotor system used a canal/muscle-like coordinate system that aligned with Listing's plane,

then this would provide the advantage that symmetric bilateral activation would cancel out torsion in Listing's coordinates, specifying movements and positions in Listing's plane. Conversely, torsional movements away from Listing's plane would then require an activation pattern that was asymmetric across the two sides of the brain, either preferentially activating more 'clockwise' neurons on the right side or 'counterclockwise' neurons on the left. Observation of the eye rotations produced by stimulating the riMLF and INC, and the patterns of eye rotation or eye position holding retained after reversibly inactivating these structures are consistent with this

scheme, suggesting that these structures code head-fixed coordinate axes aligned with and symmetric about Listing's plane (Crawford and Vilis, 1992; Crawford, 1994).

Intrinsic coordinates for head control

Compared to the oculomotor system, less is known about the brainstem circuits for control of head movement, and how they are driven by higher-level circuits in the SC and cortex. Structures implicated in head control include the vestibular nuclei (Banovetz et al., 1995; Roy and Cullen, 2001), the PPRF (Robinson et al., 1994; Sparks et al., 2001), inhibitory oculomotor burst neurons (Cullen and Guitton, 1997), the central mesencephalic reticular formation (cMRF) (Waitzman, 2001), and the INC (Fukushima et al., 1987). Although evidence is sketchy, it seems that the circuits for head movement control might be organized along similar lines as those for oculomotor control, perhaps even sharing common neural signals (Grantyn and Berthoz, 1987; Guitton, 1992). In particular, it could be that the horizontal and vertical components of the head control signals are similarly partitioned between the pons and midbrain, and that velocity signals derived from gaze commands might be integrated to represent and control final head posture.

To test the latter idea, we recently explored the INC in the head-free monkey, with the use of microstimulation and injection of muscimol, a GABA_A agonist which reversibly suppresses the activity in local populations of cell bodies. In these experiments (Klier et al., 2002), we confirmed that stimulation of the right/left produced clockwise/counterclockwise head rotations (from the subject's perspective) (Hasler and Hess, 1954), much like the oculomotor results (Crawford et al., 1991). These head rotations also showed signs of holding their final position (until corrected), as if the signal had been neurally integrated. Moreover, injection of muscimol into the same sites produced a pattern of head drift consistent with the idea that the INC was the neural integrator for torsional and vertical head postures. Complimenting the stimulation data, this drift finally settled with the head deviated in torsionally orientations (Fig. 6), i.e., clockwise for left injections and counterclockwise for right injections. (Note, this is

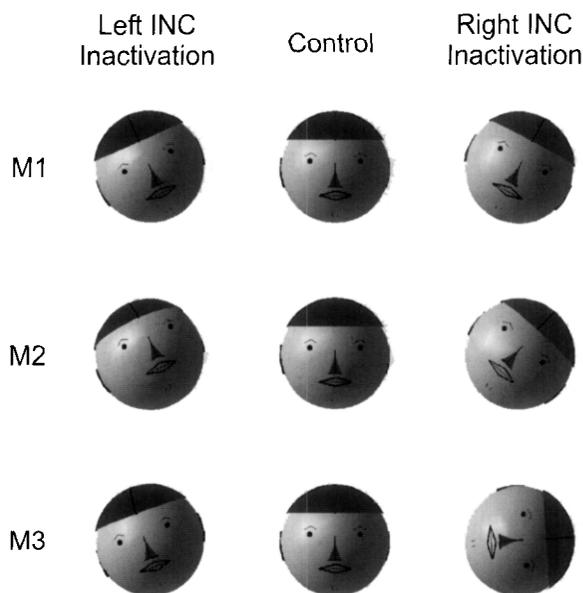


Fig. 6. Unilateral INC inactivation produces torticollis-like head postures. In controls (center column) the head is upright and points directly straight ahead (i.e., torsion component = vertical component = horizontal component = 0). After left INC inactivation (left column) the head assumes unnatural CW head orientations, whereas after right INC inactivation (right column) the head assumes unnatural CCW head orientations. Data are shown from three monkeys (M1, M2 and M3). (Adapted from Klier et al., 2002.)

opposite to the directions elicited by stimulating the same sites.) These findings suggest that the INC is also a neural integrator for torsional/vertical head posture, and further implicate it in the etiology of torticollis (Sano et al., 1972), a clinical disorder that results in head postures similar to those observed in Fig. 6.

These data clearly implicate the INC in the 3-D aspects of head control, but to understand this as a control system, more detailed questions arise. For example, supposing the basic scheme mentioned in the preceding paragraphs is right, is there a specific coordinate system that best describes the organization of vertical, torsional, and horizontal head control signals in the brainstem? To follow the oculomotor example, our head movement results suggest a coordinate system consistent with a canal-like coordinate system (Klier et al., 1999). But whereas in the oculomotor system it made sense to align that coordinate system with Listing's plane, here it would make

sense to align the coordinates more with the Fick strategy observed in natural behavior (i.e., so that the amount of torsion in or out of the Fick-like Donders' constraint could be determined through the bilateral balance of activity across the brainstem).

Consistent with this, our analysis suggests that head rotations elicited by stimulation of the INC often occur about axes aligning with the vertical canal sensitivity axes, and which remained head-fixed at different head positions (Klier et al., 1999), much like those of a Fick coordinate system. To complete this story, it would be necessary to explore the brainstem sites involved in the control of horizontal head rotation, and see if they employ a body-fixed vertical axis like that observed in the behavioral Fick constraint.

Where are the transformations?

The picture that emerges from the previous sections is that a fairly simple 2-D eye-centered gaze control signal emerges from the SC, which must then be used to drive 3-D brainstem control signals in coordinate systems appropriate for control of the eye and head. This leaves a considerable amount of complexity to the intervening transformations, including solutions to the problems of eye-head coordination, the degrees of freedom problems for both the eyes and head, and the reference frame transformations described in the previous section. We know remarkably little about how these transformations are performed. Although we can speculate that a number of brainstem areas are involved (i.e., NRTP, cMRF, LLBN, cerebellum, etc.), this seems to leave a lot of the job to occur across a very few serial synaptic connections.

So how could the brainstem handle this complexity, in effect asking it to do much of the job reserved for the parietal-premotor-motor cortex arc in arm movement control? One answer — demonstrated most neatly by neural network simulations — is that a large number of neurons arranged in parallel with even a modest inherent non-linearity (like thresholds and saturations) can perform quite complex operations across only a few synapses (Van Opstal and Van Gisbergen, 1989). For example, we have recently trained a three-layer neural network to transform retinotopically coded visual signals and

eye orientation signals into the correct motor error commands for accurate saccades in Listing's plane, with the latter coded in the canal-like Listing's coordinates described above (Smith and Crawford, 2001b). The network learns the transformation with only a handful of hidden units, employing a solution similar to the classic 'gain field' story (Fig. 7) (also see Krommenhoek et al., 1993; Van Opstal et al., 1995). When one considers that the real network has millions of neurons, a considerably greater diversity of computational power at the synaptic level, and re-entrant pathways through the cerebellum and other side loops, the power and complexity of this transformation is perhaps not so surprising. But it also hints that the working out the details of these transformations, as opposed to just identifying the major milestones like we have so far, will not be a straightforward task.

Conclusions and future directions

In our view, the neural control systems for 3-D gaze are organized along principles much like those proposed by founding fathers of neurophysiology like Sherrington and Bernstein. In particular, the coding of potential or desired gaze targets at the level of topographic or pseudo-topographic maps in the SC and cortex is only made possible by considerable complexity in the forward serial transformations and parallel modules of the downstream brainstem motor control mechanisms. A certain level of similarity between the brainstem oculomotor and head control mechanisms may help us to understand these transformations, and how the eye and head work together as one system to produce gaze shifts. Conversely, if detailed kinematics information is necessary for the spatial updating of the higher-level representations — as our work suggests — then a similar level of complexity is required in the reverse bottom-up transformations, which in turn must interact with local cortical representations to produce a dynamic, 3-D representation of visual space. Our future work will focus on these forward and reverse transformations, as well as continuing to understand the basic control signals for 3-D eye-head coordination and head control.

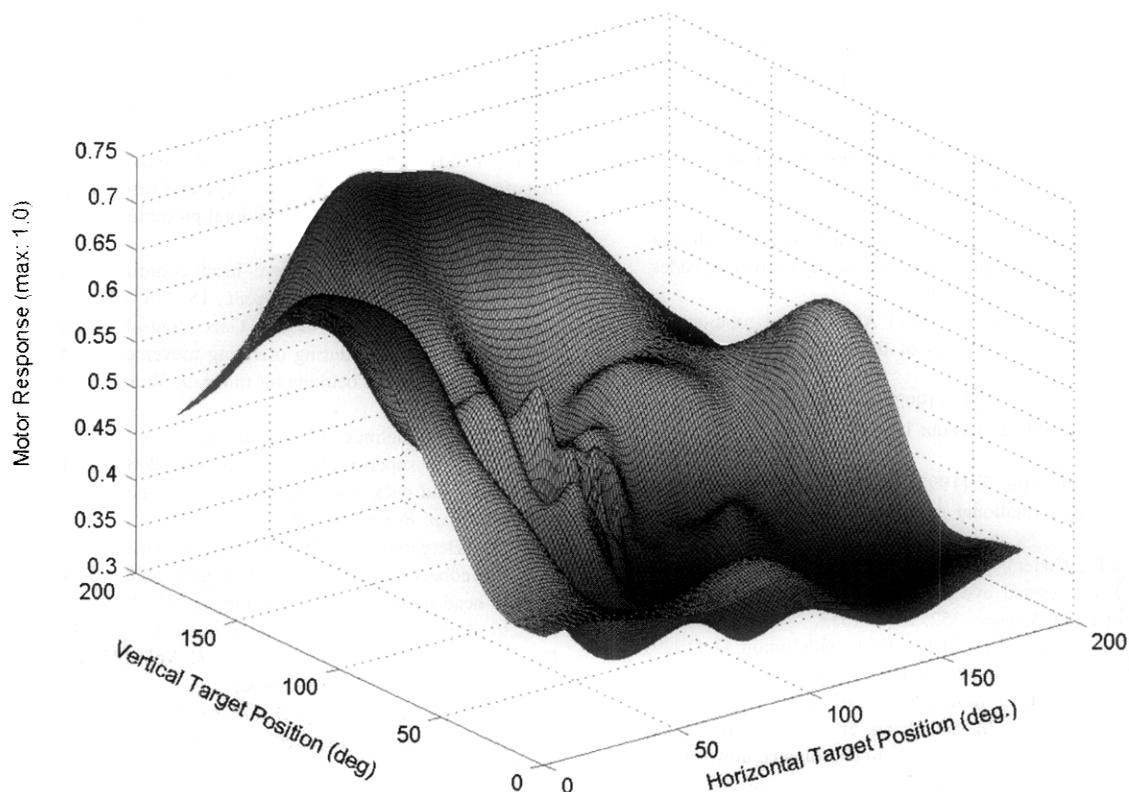


Fig. 7. Typical movement field of a hidden layer unit in our 3-layer neural networks. Our networks took in a 2-D visual target and a 3-D eye orientation and produced the correct motor output which would generate a saccade to the selected visual target. As in physiological studies, we are able to map the visual (input) and movement (output) fields of each of the hidden layer units. The movement fields were generated by stimulating all possible 2-D visual target locations and recording the output of each hidden layer unit. The floor of the graph (X and Y axes) indicate the horizontal and vertical components of possible 2-D target locations while the height of the graph (Z axis) represents the magnitude of response throughout the movement field. Although complex, these movement fields exhibited preferred (highest regions) and anti-preferred (lowest regions) areas of activity. In order to account for the eye-position-dependent modification of motor error, the neural networks used a bias mechanism whereby the entire movement field was shifted upward when eye position was in the preferred direction of the unit.

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