# The neural control of fast vs. slow vergence eye movements

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## Abstract

When looking between targets located in three-dimensional space, information about relative depth is sent from the visual cortex to the motor control centers in the brainstem, which are responsible for generating appropriate motor commands to move the eyes. Surprisingly, how the neurons in the brainstem use the depth information supplied by the visual cortex to precisely aim each eye on a visual target remains highly controversial. This review will consider the results of recent studies that have focused on determining how individual neurons contribute to realigning gaze when we look between objects located at different depths. In particular, the results of new experiments provide compelling evidence that the majority of saccadic neurons dynamically encode the movement of an individual eye, and show that the time-varying discharge of the saccadic neuron population encodes the drive required to account for vergence facilitation during disconjugate saccades. Notably, these results suggest that an additional input (i.e. from a separate vergence subsystem) is not required to shape the activity of motoneurons during disconjugate saccades. Furthermore, whereas motoneurons drive both fast and slow vergence movements, saccadic neurons discharge only during fast vergence movements, emphasizing the existence of distinct premotor pathways for controlling fast vs. slow vergence. Taken together, these recent findings contradict the traditional view that the brain is circuited with independent pathways for conjugate and vergence control, and thus provide an important new insight into how the brain controls three-dimensional gaze shifts.

## Introduction – the Hering–Helmholtz binocular control debate

In the last century, research on the brain has provided valuable information about how we clearly see the world in three dimensions. However, surprisingly, our understanding of how the neuronal pathways, which are responsible for generating eye movements, precisely align the fovea on a visual target remains a topic of long-standing debate. This review will consider the results of recent studies that have focused on determining how individual neurons contribute to realigning gaze to targets located throughout three-dimensional space.

Over a century ago, a largely theoretical and philosophical debate arose between two German physician-scientists, Ewald Hering and Hermann von Helmholtz. On the one hand, Helmholtz argued that we learn to precisely aim both eyes at a visual target (von Helmholtz, 1962). To fully appreciate Helmholtz's argument it is helpful to consider how chameleons move their eyes. A chameleon has the unique ability to point each eye in different directions (Mates, 1978; Gioanni *et al.*, 1993; Pettigrew *et al.*, 1999; Ott, 2001). Effectively Helmholtz's proposal was that the brain is initially wired so that we, like chameleons, can move each eye independently, but that over time we learn to move our eyes together such that both are accurately aimed at the same point in space, in order to ensure optimal visual acuity in three dimensions. On the other hand, Hering argued that we are born with the ability to move our eyes in a coordinated fashion (Hering, 1977). A common analogy used to explain this argument is that our eyes are like the reins of a horse – if you pull on one side the other side moves by the same amount, in the same direction. In other words, Hering's proposal suggested that the eyes should be seen as a single organ rather than two separate entities.

Following these original theoretically based proposals, over the last five decades neurophysiologists have made more precise predictions about how the brain controls binocular eye movements through the study of eye movement behaviour and neuronal responses (Rashbass & Westheimer, 1961; Ono *et al.*, 1978; Mays, 1984; Maxwell & King, 1992; Zhou & King, 1998; Gamlin, 2002; Sylvestre & Cullen, 2002; Sylvestre *et al.*, 2003; Van Horn & Cullen, 2008; Van Horn *et al.*, 2008). Figure 1 summarizes the basic neural circuitry involved in generating horizontal eye movements. Premotor excitatory saccadic burst neurons (SBNs) innervate neurons in the abducens (ABN). Within the abducens, motoneurons innervate, via the sixth nerve, the ipsilateral lateral rectus muscle and abducens internuclear neurons innervate, via the medial longitudinal fasciculus (MLF), contralateral medial rectus motoneurons, which innervate the contralateral medial rectus eye muscle via the third nerve. Notably, it has long been appreciated that the MLF plays an important role in ensuring conjugate eye motion in many conditions. For example, the MLF ensures that vestibularly driven reflexive eye movements are conjugate

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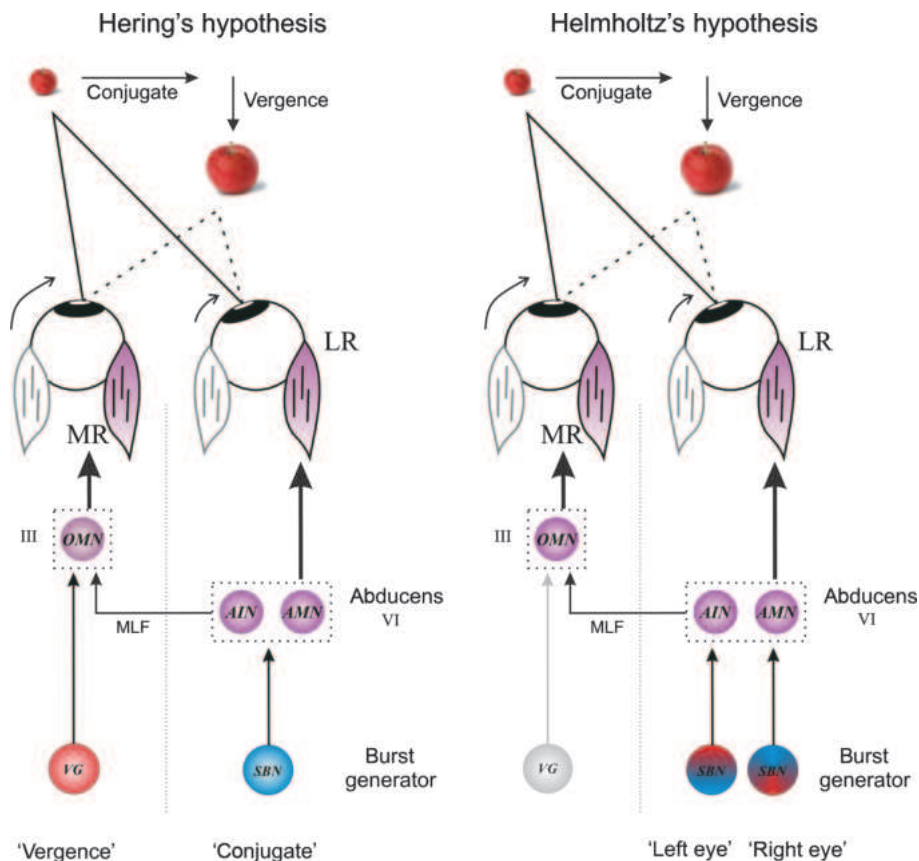E-mail: kathleen.cullen@mcgill.ca

FIG. 1. Theoretical frameworks of binocular control as inspired by Hering (left) and Helmholtz (right). Left – Vergence burst neurons project a fast vergence command directly to medial rectus motoneurons, whereas the premotor saccadic burst neurons control fast conjugate eye velocity. Note that in this schema the commands to the motoneruons innervating the right and left lateral and medial recti are yoked by the MLF. Right – Premotor saccadic burst neurons in the paramedian pontine reticular formation send a burst of action potentials to drive motoneurons and internuclear neurons [abducens internuclear neurons (AINs)] in the abducens nucleus. This premotor drive to the abducens motoneurons is not conjugate, but preferentially encodes the motion of the right eye, whereas that to the AINs preferentially encodes the motion of the left eye. LR, lateral rectus; MR, medial rectus; AMN, abducens motoneuron; VG, vergence; OMN, medial rectus oculomotor neuron.

(see Leigh & Zee, 2006 for a review). However, evolutionary pressure for enhanced stereopsis led to the development of frontal binocular vision, which in turn resulted in the ability to voluntarily shift the axis of gaze to precisely align the fovea on the feature of interest. Here we focus on the results of recent experiments that have studied the neuronal pathways that control the voluntary eye movements that are made to look between near and far targets (i.e. disconjugate saccades). Notably, during such eye movements the two eyes move by different

amounts and thus command to the eye muscles of each eye must differ. In Table 1 we provide a glossary of terms commonly used when discussing binocular eye movements.

Inspired by Hering's theory, researchers initially proposed that neurons within the classical 'saccadic' pathway should be exclusive to conjugate movements and a separate 'vergence' pathway should exist to provide the additional vergence command required to realign gaze between targets located at different depths (Mays, 1984). Accordingly,

TABLE 1. Classically defined types of binocular eye movements

| Eye movement | Description | Example |
|---|---|---|
| Conjugate | The eyes rotate in the same direction, by the same amount | Looking between far objects located > 1 m away |
| Vergence | The eyes rotate in opposite directions | Looking between near objects located along the midline |
| Disconjugate* | The eyes rotate asymmetrically | When looking between objects located near and far during rapid eye movement sleep |
| Components of disconjugate eye movements | | |
| Fast vergence | Asymmetrical saccadic eye movement | Fast, asymmetrical eye movement occurring when looking between objects located near and far |
| Slow vergence | Slow eye movement (< 60°/s) where they rotate in opposite directions | Fine binocular repositioning occurring before or after asymmetrical saccade or when looking between objects located symmetrically along the midline |

*For any disconjugate movement a vergence and conjugate component can be calculated – *conjugate* = (left eye + right eye position)/2; *vergence* = left eye − right eye position.

in this schema, the MLF would supply the medial rectus with a conjugate command signal and a summation of conjugate and vergence commands at the level of the motoneurons would result in accurate binocular positioning (Fig. 1).

In contrast, Helmholtz's theory suggested that the movement of each eye was programmed independently; rather than having separate control systems for conjugate and vergence eye movements, the brain would contain two motor control pathways comprised of neurons whose activity would explicitly command movement of the left or right eye (e.g. Fig. 1, right panel). The results of more recent experiments, including ongoing work in our laboratory, provide evidence that the neuronal pathways, responsible for generating voluntary saccadic eye movements, largely encode the motion of individual eye rather than specific conjugate and vergence commands. Here we review the existing neurophysiological literature in the context of its support for the hypothesis that brainstem saccadic neurons command the movement of each eye by encoding integrated, rather than separate, conjugate and vergence commands.

## A specific neural circuit for the control of slow (saccade-free) vergence – evidence for Hering's law?

Initially, neurophysiological evidence accumulated in favour of Hering's hypothesis. The premotor pathways controlling conjugate saccades and saccade-free vergence eye movements (i.e. symmetric vergence) were studied in isolation and this subsequently led to the identification and characterization of neurons appropriate for encoding conjugate saccades and a separate population of neurons encoding slow saccade-free vergence. For example, the paramedian pontine reticular formation was found to contain a population of neurons, known as SBNs, whose neural activity was related to conjugate saccadic eye movements (i.e. when both eyes moved the same amount in the same direction) (for a review see Scudder et al., 2002). Another distinct group of neurons, called near-response neurons, was identified in the midbrain reticular formation whose discharge was proportional to the vergence angle when tracking visual targets located along the midline (i.e. symmetric vergence) (Mays, 1984; Judge & Cumming, 1986; Zhang et al., 1992).

Near-response neurons were found to either increase (i.e. convergence neurons) or decrease (i.e. divergence neurons) their activity during symmetric convergence such that their firing rates were proportional to the vergence angle. Importantly, these neurons were unresponsive during conjugate saccades. Electrophysiological studies further showed that near-response neurons could be antidromically activated from the medial rectus subdivision of the oculomotor nucleus (Zhang et al., 1991, 1992). Additionally, a second related class of vergence-related neurons, termed 'vergence velocity neurons', was identified in the midbrain (Mays et al., 1986). These neurons generated a burst of action potentials that was correlated with instantaneous vergence velocity, and the number of spikes in the burst was correlated with the size of the vergence movement. Both convergence and divergence neurons were described, although far fewer divergence neurons than convergence neurons were reported. Vergence velocity neurons were found in two regions of the midbrain reticular formation. One group was located in proximity to the neurons that encode vergence angle (i.e. the near-response cells) and a second group was located in a more ventral area. It has been proposed that these neurons provide the extraocular motoneurons with a vergence velocity command. To date, however, the exact anatomical projection of these neurons remains unknown. Furthermore, our more recent study in the central mesencephalic reticular formation has shown that the majority of central mesencephalic reticular formation neurons,

which were traditionally thought to encode conjugate saccadic eye movements, in fact encode integrated conjugate and vergence commands during disconjugate saccades (Waitzman et al., 2008). The proximity between the central mesencephalic reticular formation and the vergence velocity neurons described by Mays et al. (1986) raises the question of whether these are the same population of neurons, and whether neurons originally characterized as 'vergence velocity neurons' might also make a contribution to generating conjugate saccades.

Overall, these initial findings supported Hering's proposal that there exist independent neural pathways dedicated to generating conjugate and vergence eye movements (Mays, 1998). However, as noted above and as will be further detailed below, although these results appeared to suggest an elegant solution to the problem of binocular control, the findings of more recent experiments provide reason to question this view.

## Behavioural and neuronal responses during disconjugate saccades – evidence against 'Hering's law'

To quickly and accurately redirect gaze between near and far targets we typically combine saccadic and vergence eye movements. These eye movements, termed disconjugate (i.e. disjunctive) saccades, are characterized by the two eyes rotating by different amounts with different trajectories. Behavioural studies have shown that, during disconjugate saccades, vergence velocities reach far greater values than would be expected. For example, when vergence eye movements are made alone (i.e. saccade-free), eye velocities reach maximum values of $\sim 60°/s$ (Fig. 2, left panel), whereas vergence velocities during disconjugate saccades can reach values of $> 200°/s$, even when the required change in vergence angle is identical (Fig. 2, right panels) (Ono et al., 1978; Enright, 1984, 1992; Maxwell & King, 1992; Zee et al., 1992; Oohira, 1993; Collewijn et al., 1997; van Leeuwen et al., 1998; Busettini & Mays, 2005a; Van Horn & Cullen, 2008). These behavioural findings have challenged the traditional 'Hering' view that there exist separate vergence and conjugate oculomotor subsystems and suggested that saccadic conjugate and vergence commands are not independent, but are integrated upstream of the level of the motoneurons.

To directly probe the validity of Hering's hypothesis at the level of single neurons, researchers next investigated how neurons in the commonly assumed, 'conjugate' saccadic pathway respond during disconjugate saccades during which the eyes are rapidly shifted to targets located at different depths and eccentricities. In particular, recent experiments focused on the analysis of these rapid movements during which the two eyes rotate by differing amounts have yielded new insights into the question of whether the electrical activity of an individual neuron was related to the movement of one eye or the other. In 1998, King et al. made the first observation that the number of action potentials produced by the SBNs of the paramedian pontine reticular formation during a disconjugate saccade was better correlated to the movement of an individual eye than to the conjugate component of the movement (Zhou & King, 1998). More recently, experiments in our own laboratory have addressed two key questions. (i) What eye movement command signals are dynamically encoded by SBNs and other premotor neurons (e.g. the burst-tonic neurons of the nucleus prepositus hypoglossi, which are involved in the neural integration for horizontal eye movements) during conjugate saccades vs. disconjugate saccades? (ii) Do the commands encoded by these neurons provide a significant drive to the extraocular motoneurons (i.e. abducens and medial rectus) during these behaviours?
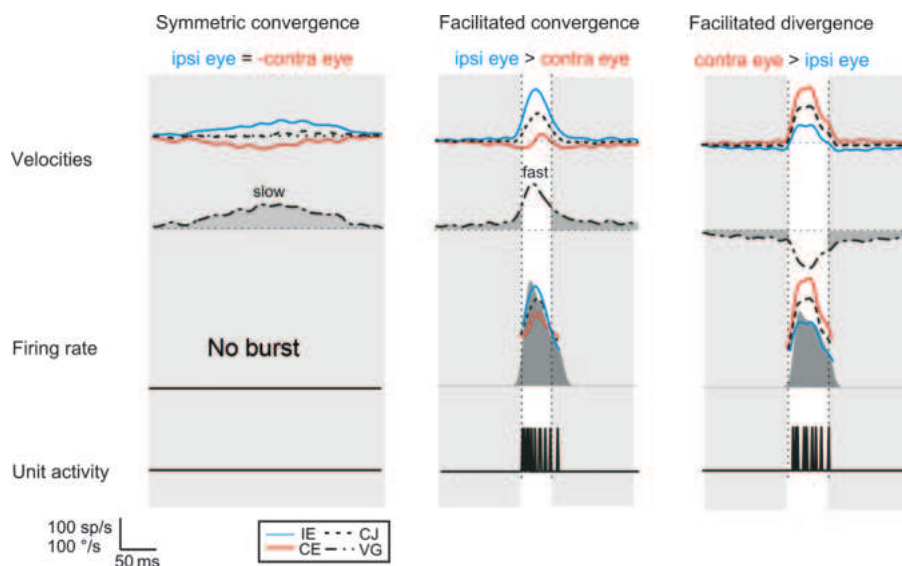
Fig. 2. Example neural activity for an SBN during symmetric (i.e. saccade-free) vergence. Conjugate (CJ), vergence (VG) as well as the velocity traces of each eye [ipsilateral (IE) and contralateral (CE) eye] are shown in the first row and vergence velocity is shown in the second row. The grey shaded areas in the third row represent the firing rate of the neuron and the representative model predictions using the IE (blue trace), CE (red trace) and CJ eye (black dotted) velocity are superimposed on the firing rate. The corresponding unit activity is shown in the fourth row. The light grey shaded boxes highlight the areas of slow vergence.

First, in order to determine whether neuronal commands encoded at the level of the extraocular motoneurons themselves were more consistent with a Hering (i.e. conjugate/vergence commands) or Helmholtz (i.e. right eye/left eye commands) inspired framework, Sylvestre & Cullen (2002) tested whether the same simple dynamic model of a given abducens motoneuron's response during conjugate saccades could also be used to quantify its firing rate during disconjugate saccades. First, in the case that Hering's hypothesis was true, one might expect to find two classes of motoneurons – one that preferentially received input from vergence pathways and another that preferentially received input from conjugate pathways. In this case, if a individual motoneuron received a pure conjugate drive, then the simple first-order model describing the relationship between its firing rate (FR) and the conjugate component of the movement [e.g. $FR(t - t_d) = b + kE(t) + r\dot{E}(t)$, where $b$, $k$ and $r$ are the bias, and eye position and velocity sensitivities of the neuron, respectively] should be the same for both types of eye movements. Instead, this prediction generally failed. Specifically, the neuronal responses of abducens motoneurons typically encoded the movement of an individual eye rather than the conjugate component of each eye movement during disconjugate saccades (Sylvestre & Cullen, 2002; Sylvestre et al., 2003). Similar results were also obtained for the analysis of the antagonist motoneurons of the medial rectus (Van Horn & Cullen, 2009) and analysis of the premotor burst-tonic neurons (Sylvestre et al., 2003). Taken together, these results indicate that the neuronal commands encoded at the level of the saccadic neural integrator as well as the extraocular motoneurons themselves are more consistent with a Helmholtz (i.e. right eye/left eye commands) inspired framework.

## Does the brainstem premotor saccadic pathway provide a significant contribution to vergence during disconjugate saccades?

During this time, substantial behavioural and neurophysiological evidence began to accumulate in favour of the proposal that the

saccadic premotor pathway (i.e. SBNs, burst-tonic neurons, and their target motoneurons) encodes the movement of an individual eye rather than separate conjugate or vergence commands (Cova & Galiana, 1995; King & Zhou, 2002; Sylvestre & Cullen, 2002; Sylvestre et al., 2003; Van Horn & Cullen, 2009). However, the initial evidence that neurons within the saccadic pathway were monocularly tuned was met with some scepticism. In particular, it was suggested that left and right eye signals are averaged out at the level of the motoneurons such that a vergence signal is still needed at the level of the motoneurons to produce a disconjugate saccade (Mays, 1998). In other words, the finding that SBNs were monocular could not rule out the alternative possibility that the overall contribution of the saccadic circuitry to the control of the vergence component of eye motion was relatively unimportant compared with the contribution of the vergence subsystem. In fact, prevailing models of binocular control still assumed that SBNs predominantly encoded conjugate saccadic dynamics, with projections from these conjugate SBNs to the vergence premotor pathway mediating the vergence facilitation observed during disconjugate saccades (Zee et al., 1992; Busettini & Mays, 2005b). Accordingly, to further our understanding of the neural pathways that control disconjugate saccades, our laboratory has quantified the timing and dynamics of the SBN command during conjugate vs. disconjugate saccades (Van Horn & Cullen, 2008; Van Horn et al., 2008). Our results, based on four main lines of evidence: (i) timing, (ii) spike train dynamics, (iii) computer simulations, and (iv) the analysis of vertical-facilitated vergence by premotor SBNs, provide strong support that the SBN command alone encodes the vergence-related information required to drive disconjugate saccades.

### 1. The SBN discharge timing is appropriate to facilitate vergence during disconjugate saccades

First, to objectively quantify the command produced by the saccadic circuitry during disconjugate sacades, we compared neuronal firing and vergence velocities during disconjugate saccades, and found that

the onset of facilitated vergence was synchronized with the burst onset of both excitatory and inhibitory brainstem SBNs. The activity of an example SBN is shown in Fig. 2 during symmetric vergence and disconjugate saccades. We found that SBNs do not fire action potentials during saccade-free vergence (Fig. 2, left panel), but are active during the saccade component of the disconjugate saccades (Fig. 2, two right panels). No action potentials were observed before or following this interval, despite the presence of a significant but much slower vergence velocity (grey shaded areas in Fig. 2). Notably, slow vergence movements occurring after the disconjugate saccades are important to binocularly position the two eyes (see Table 1). Burst duration was tightly correlated with saccade duration during both conjugate and disconjugate saccades. In contrast, burst duration was significantly less well related to the total duration of the vergence movement during disconjugate saccades (i.e. where the total vergence duration included the combined duration of both the saccade and any slow vergence movement that preceded or followed it) (Van Horn *et al.*, 2008).

## 2. The SBN spike train dynamics preferentially encode the movement of one eye consistent with a role in facilitating vergence during disconjugate saccades

System identification techniques were next used to quantitatively characterize the dynamic signals encoded by the brainstem saccadic burst generator during conjugate and disconjugate saccades. During conjugate saccades, the SBN activity is well described by the simple model [$\text{FR}(t - t_{\text{d}}) = b + r\,\dot{E}(t)$, where $b$ and $r$ are the bias and conjugate eye velocity sensitivities of the neuron, respectively] (Cullen & Guitton, 1997). In contrast, during disconjugate saccades, the neuron's activity was best predicted when ipsilateral (Fig. 2, superimposed blue trace; $\text{VAF}_{\text{pred–ipsi}} = 0.62$) rather than conjugate or contralateral (superimposed black and red traces; $\text{VAF}_{\text{pred–conj}} = 0.49$ and $\text{VAF}_{\text{pred–contra}} = 0.13$) eye velocities were the model inputs for eye velocity. As a result, the firing rate prediction based on the neuron's response during conjugate saccades tended to overshoot the firing rate when the preferred eye moved less (i.e. during the diverging movements for this example neuron) and to undershoot when the preferred eye moved more.

Across the population of recorded neurons, the results of this prediction-based analysis revealed that the majority of SBNs preferentially encode the movement of one eye rather than the conjugate eye velocity. Van Horn *et al.* (2008) then investigated whether estimating a more complex model, namely a binocular expansion of the conjugate model, might provide an improved description of neuronal discharges during disconjugate saccades

$$\text{FR}(t - t_{\text{d}}) = b + r_i\,\dot{\text{IE}}(t) + r_c\,\dot{\text{CE}}(t) \quad \text{(binocular estimation model)}$$

where $b$, $r_i$ and $r_c$ are the bias, ipsilateral and contralateral eye velocity sensitivities of the neuron, respectively (subscripts $i$ and $c$ refer to the ipsilateral and contralateral eyes relative to the recording site, respectively), and $\dot{\text{IE}}(t)$ and $\dot{\text{CE}}(t)$ are instantaneous ipsilateral and contralateral eye velocities, respectively. When the parameters were freely estimated, a very good description of the example SBN's (i.e. Fig. 2) discharge patterns was obtained. The 95% bootstrap confidence intervals revealed that only the ipsilateral eye velocity sensitivity term ($r_i$) and bias were significantly different from zero. Thus, removing the contralateral eye velocity sensitivity term ($r_c$) had a negligible impact on our ability to fit this neuron's discharge. This neuron was therefore concluded to be a monocular neuron with a preference for the ipsilateral eye. Overall, the majority of SBNs (> 70%) preferentially encoded the velocity of an individual eye during disconjugate saccades.

## 3. The SBN spike train dynamics encode the vergence-related information required to drive disconjugate saccades – computer simulations

To directly test whether the command produced by the saccadic circuitry during disconjugate saccades is sufficient to produce the vergence component of eye motion, our experimental results were implemented into a computer-based simulation (for details see Van Horn *et al.*, 2008). Notably, we found that the drive from the premotor saccadic circuitry carries all the vergence drive that is necessary to shape the activity of the abducens motoneurons to which it projects. This finding did not support the alternative hypothesis that an additional input (i.e. from a separate vergence subsystem) was required to shape the activity of abducens motoneurons during disconjugate saccades.

## 4. The SBN spike train dynamics encode the vergence-related information required to drive disconjugate saccades – the analysis of responses during vertical-facilitated vergence

Finally, these results were further validated in a complementary study, which recorded the discharge dynamics of SBNs during vergence facilitated by a vertical saccade (Fig. 3A). Whereas prior single-unit studies had exclusively focused on neural correlates during horizontal disconjugate saccades (Zhou & King, 1998; Van Horn *et al.*, 2008), vergence is similarly facilitated during vertical saccades (Enright, 1984; Maxwell & King, 1992; Zee *et al.*, 1992; van Leeuwen *et al.*, 1998; Kumar *et al.*, 2005; Van Horn & Cullen, 2008). Understanding how the brain drives vertical saccades between near and far targets is particularly interesting in terms of the current debate regarding the premotor control of vergence during saccades. Although these saccades require a vertical conjugate command, which would originate from the vertical burst neurons of the rostral interstitial nucleus of the MLF (Buttner *et al.*, 1977; King & Fuchs, 1979; Crawford & Vilis, 1991, 1992; Moschovakis *et al.*, 1991a,b; Missal *et al.*, 2000), they do not require the simultaneous production of a horizontal conjugate command. Instead, a command to generate a rapid horizontal movement of the two eyes in equal and opposite directions (i.e. fast vergence) is needed.

By recording the discharges of horizontal SBNs (Fig. 3B) during this dissociation task, Van Horn & Cullen (2008) were able to address whether neuronal commands from the horizontal saccadic pathway dynamically encode the movement of an individual eye even when no horizontal conjugate saccade command is required. Notably, Van Horn & Cullen (2008) found that, although horizontal SBNs discharge little if at all during vertical conjugate saccades, these same neurons generated robust responses during the vertical-facilitated vergence. Specifically, neuronal responses were tightly linked to the onset of facilitated vergence velocities associated with a vertical saccade and the majority of SBNs consistently encoded the velocity of the ipsilateral eye during this task (Fig. 3C). Taken together, the results strongly supported the hypothesis that monocular premotor commands from the brainstem saccadic circuitry are sufficient to control rapid shifts of gaze in three dimensions (Cova & Galiana, 1996; King & Zhou, 2000, 2002; Sylvestre *et al.*, 2003).
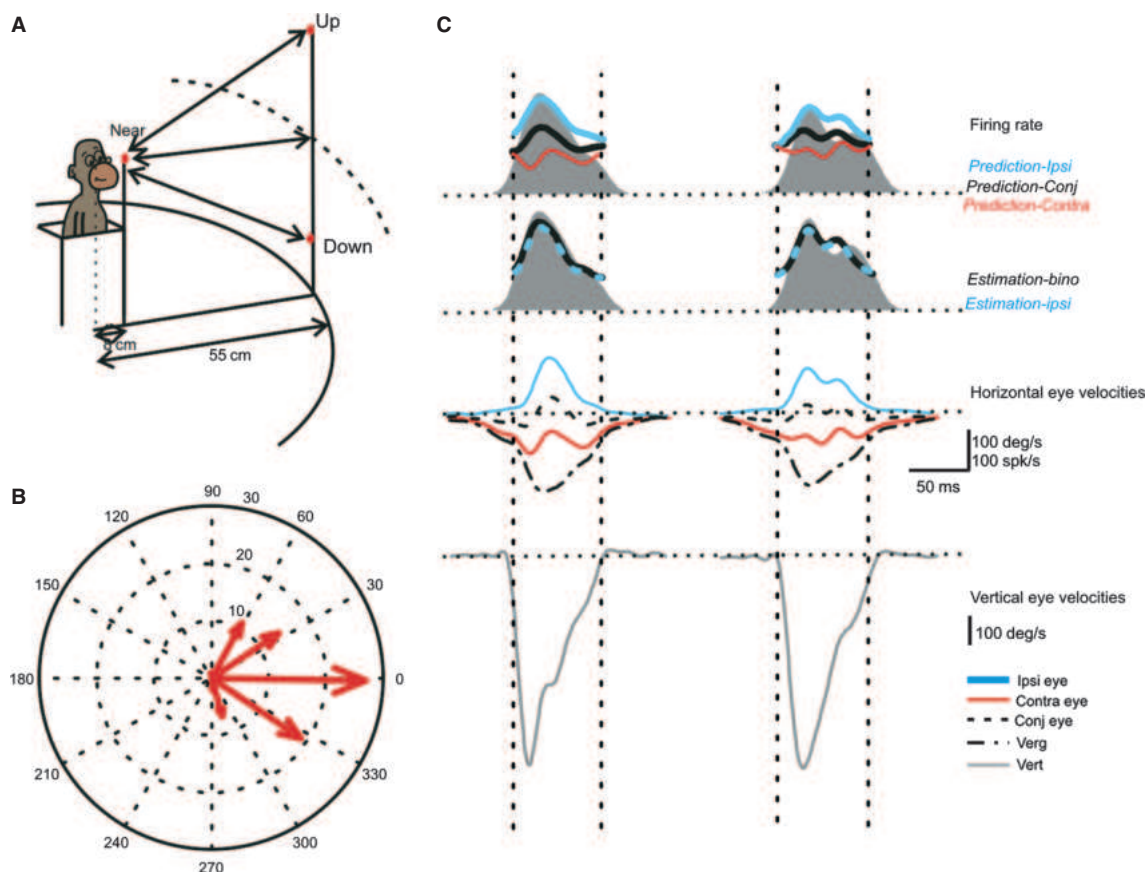
FIG. 3. (A) Schematic representation of the paradigm used to generate combined vertical-vergence movements. (B) A polar plot representing the average discharge for a typical SBN during numerous ipsilateral (i.e. 0°), oblique and vertical (i.e. 90°, 270°) saccades. The neuron was completely silent (i.e. no burst) during saccades in the contralateral direction (i.e. 180°) and during vertical saccades. (C) Neuronal responses and model fits when a vertical saccade is combined with a vergence movement (diverging-down). The left and right columns illustrate two example movements. The firing rate of the neuron is shown as the grey shaded area (top row, and reproduced in second row for clarity). Predicted model fits using ipsilateral, conjugate and contralateral eye velocities are shown in the top row in blue, black and red, respectively. Estimated model fits using the binocular model and reduced ipsilateral model are shown in the second row. Dotted vertical lines represent vertical saccade onsets and offsets of 20°/s.
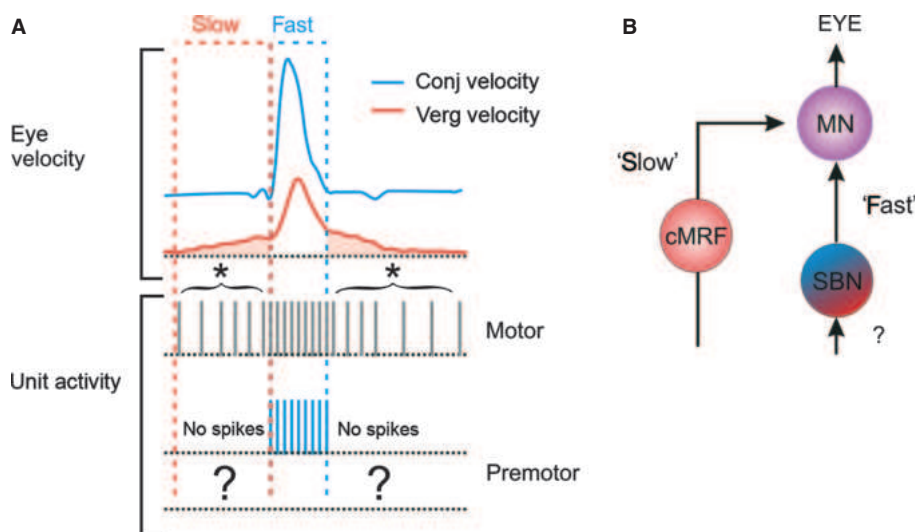


FIG. 4. Premotor control of vergence. (A) Two top traces illustrate an example disconjugate eye movement that has a period of fast vergence to quickly redirect the eyes (i.e. fast vergence; blue dashed box) as well as initial and late periods of slow vergence to binocularly position the eyes and ensure accurate visual perception (i.e. slow vergence; red dotted box). Bottom traces illustrate the typical unit activity of motoneurons (motor; grey units) and SBNs (premotor; blue units) associated with this movement. Note that motoneurons fire during periods of slow (see asterisks) and fast vergence and SBNs are only active during the fast component of the movement. (B) Proposed neural circuitry encoding vergence eye movements. The premotor saccadic circuitry has been shown to encode signals appropriate for fast vergence although an additional slow vergence input is needed. MN, Motoneuron; cMRF, central mesencephalic reticular formation.

## Clinical implications – further evidence for Helmholtz

Additional support for the hypothesis that the brainstem burst generator plays a vital role in generating disconjugate saccades comes from a recent clinical study (Chen *et al.*, 2010). Eye movements were recorded in patients who suffer from multiple sclerosis, which causes a lesion of the MLF due to demyelination of the axons. Normally, the MLF carries signals from the abducens nucleus to medial rectus motoneurons to generate a fast adducting saccade. Chen *et al.* (2010) reasoned that if vergence neurons were the sole source of vergence information to the medial rectus motoneurons then adducting eye movements generated during disconjugate saccades should be faster than saccades made between equidistant targets as the medial rectus neurons would be only missing a saccadic drive from the abducens, whereas the vergence drive would be still be appropriate. However, Chen *et al.* (2010) showed that the movement of the adducting eye was similar during saccades made between equidistant targets as compared with disconjugate saccades. Thus, these results further support the proposal that the fast component of a disconjugate saccade is primarily driven by SBNs rather than a separate group of vergence velocity neurons.

## Conclusions – implications for the neuronal control of fast vs. slow vergence – directions for future work

Studies within this last decade have clearly shown that the majority of neurons within the saccadic premotor circuitry encode the movement of an individual eye rather than the conjugate component of a saccadic eye movement (Zhou & King, 1998; King & Zhou, 2002; Sylvestre & Cullen, 2002; Sylvestre *et al.*, 2003; Van Horn & Cullen, 2008; Van Horn *et al.*, 2008). Moreover, as reviewed above, characterizations of the discharges of extraocular motoneurons have revealed that the majority of abducens and medial rectus motoneurons dynamically encode the movement of the ipsilateral eye.

We have also shown that the population response generated by motoneurons during disconjugate saccades is similar, albeit slightly smaller (~10%), than that generated during conjugate saccades (Sylvestre & Cullen, 2002; Van Horn & Cullen, 2009). This result has led to the suggestion that other mechanisms, such as selective weighting, or a sampling bias may be responsible for the apparent 'missing' motoneuron drive during disconjugate saccades (Sylvestre & Cullen, 2002; Van Horn & Cullen, 2009).

There is some evidence to suggest that different motoneurons may contribute more to certain oculomotor behaviours than others. In particular, the results of retrograde labelling studies suggest that small 'c-group' motoneurons, which tend to lie separately around the periphery of the abducen's nucleus, preferentially receive their innervations from premotor sources involved in executing slow eye movements (e.g. vestibular nucleus, prepositus hypoglossi and supraoculomotor nucleus) and, in turn, project to 'slow' or multiply innervating fibres of extraocular muscle (Buttner-Ennever *et al.*, 2001; Wasicky *et al.*, 2004; Ugolini *et al.*, 2006). These findings have led to the proposal that different populations of motoneurons are specialized for driving either fast or slow vergence movements. To date, however, there have been no reports of recordings from motorneurons that fire exclusively for either type of behaviour. In fact, we have found that both abducens and medial rectus motoneurons respond during periods of slow and fast vergence (see asterisk in Fig. 4A) (Sylvestre & Cullen, 2002; Van Horn & Cullen, 2009). Although it is important to note that our studies probably undersampled the smaller 'c-group' motoneurons hypothesized to play a specialized role in generating slow vergence movements, our results show that the majority of motoneurons (i.e. corresponding to 'A and B group' motoneurons) (see Buttner-Ennever & Akert, 1981; Buttner-Ennever, 2006) are significantly involved in executing both types of behaviours.

Motoneurons receive important dynamic vergence-related information from upstream SBNs, which we have shown drives disconjugate saccades. However, it is also important to emphasize that SBNs are silent during slow vergence movements. For example, SBNs do not fire any action potentials during periods of slow vergence that precede or follow disconjugate saccades (Fig. 4A; premotor). Notably, this is in sharp contrast to motoneurons, which modulate during periods of slow as well as fast vergence as discussed above (Fig. 4A; motor). Thus, although the SBNs function to effectively and rapidly redirect the eyes during disconjugate saccades, an additional slow vergence command is required at the level of the motoneurons to binocularly position the two eyes to ensure stereopsis. Near-response neurons located near the oculomotor nucleus, which project to medial rectus motoneurons and have been shown to be responsive during slow vergence eye movements, are the likely source for medial rectus motoneurons (Zhang *et al.*, 1992). However, no such input to abducens motoneurons has been identified to date, although a brief report has described neurons encoding slow vergence information near the abducens nucleus (Gnadt *et al.*, 1988). A detailed analysis of the discharge characteristics of these neurons, as well as a description of their anatomical projections, is needed to understand whether they produce the necessary slow vergence premotor command. It has also been proposed that inputs from the central mesencephalic reticular formation, which have been shown to encode integrated conjugate and vergence information (Waitzman *et al.*, 2008), could contribute to the premotor pathway that mediates slow vergence (Fig. 4B).

Taken together, recent findings including those of our own laboratory, emphasize the existence of distinct premotor pathways encoding fast vs. slow vergence. In particular, it has been proposed that the saccadic premotor circuitry functions to rapidly redirect the eyes, whereas an additional command (i.e. from a separate pool of premotor neurons) is required to finely align the fovea of each eye on a target after the saccade to ensure accurate binocular perception (Fig. 4B). Future work is needed to fully understand how coordinated inputs from distinct fast and slow premotor pathways work together to ensure accurate gaze positioning.

## Abbreviations

MLF, medial longitudinal fasciculus; SBN, saccadic burst neuron.

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