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Eye position and eye velocity integrators reside in separate brainstem nuclei

(gaze stabilization/motor performance/integrator rhythmicity/prepositus nucleus/lidocaine inactivation)

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ABSTRACT **Two types of central nervous system integrators are critical for oculomotor performance. The first integrates velocity commands to create position signals that hold fixation of the eye. The second stores relative velocity of the head and visual surround to stabilize gaze both during and after the occurrence of continuous self and world motion. We have used recordings from single neurons to establish that the "position" and "velocity" integrators for horizontal eye movement occupy adjacent, but nonoverlapping, locations in the goldfish medulla. Lidocaine inactivation of each integrator results in the eye movement deficits expected if horizontal eye position and velocity signals are processed separately. These observations also indicate that each brainstem compartment generates and stores these signals. Consequently, each integrator exhibits functional autonomy. Therefore, we propose that the intrinsic electrophysiological properties of the constituent neurons in each brainstem subnucleus may be sufficient for producing integrator rhythmicity.**

Maintaining gaze on targets that move relative to the observer requires that vestibular and visual reflexes detecting both self and world motion respond with appropriate eye and/or head movements. Neural integrators acting as computational elements are essential building blocks within this sensory-motor transformation (1–3). The concept of a "neuronal" integrator whose input–output characteristics could be described by a mathematical integral was first envisioned after observing the activity of abducens motoneurons during changes in horizontal eye position (4). Current hypotheses require neural networks of cascading, reverberating collaterals with positive and/or negative feedback; however, putative neuronal mechanisms, let alone causal chains of synaptic connections, are still notional in the operation of integrators for either spinal or brainstem circuits (5–7). Here we describe the precise location of hindbrain neurons that are necessary and sufficient for accomplishing two distinct types of integration in the oculomotor system.

In mammals, the prepositus hypoglossi nucleus was initially proposed to fulfill the criteria postulated as necessary for the "velocity to position" transformation (8–11). Recent pharmacological and lesion studies implicate both the vestibular and prepositus regions of the brainstem (12–14). Jointly these data suggest that all horizontal eye movement-related subsystems (e.g., saccadic, vestibular, and visual) probably share a common position integrator (15, 16). Unfortunately, it has not been possible to causally place any identified vestibular or prepositus neuron within this circuit (5).

The observations that vestibular and visual sensory signals related to self or externally generated movement are largely encoded in a velocity domain (17, 18) led to identification of a second type of integrator that could accumulate eye velocity in the horizontal plane (19, 20). In this case, neural information proportional to the velocity of the head and/or visual surround is compiled and preserved centrally (i.e., stored up). By discharging the stored velocity after cessation of the initiating sensory stimulus, this integrator extends the time for oculomotor compensation of either head or visual world motion. The location of this integrator, let alone its operation, has remained quite elusive, although most evidence suggests a crucial role for the vestibular nuclei (14, 21). In this paper, the position and velocity integrators will be shown to occupy spatially separate, nonvestibular, loci in the goldfish medulla that can be accurately identified, recorded from, and reversibly inactivated.

MATERIALS AND METHODS

Goldfish (*Carassius auratus*) were prepared under general anesthesia (tricaine methanesulfonate; 1:20,000, wt/vol) for eye movement and neuronal recording. Surgery consisted of implanting an acrylic pedestal for head stabilization and trephining a hole in the occipital bone for recording brainstem neural activity (22). Eye position was monitored with scleral search coils. After a recovery period of several days, fully alert animals were tested in a vertical-axis optokinetic and vestibular stimulator. This system consisted of a servo-controlled planetarium and rotating table interfaced by a waveform generator that produced any desired interaction in phase and/or relative velocity between the two stimuli (23). Compensatory eye velocity is nearly of equal amplitude, but oppositely directed, to head velocity and exhibits nearly 180° phase shift with respect to the stimulus [e.g., vestibuloocular reflex (VOR) gain of 1.0 in Fig. 2 *B* and *D*].

Neuronal activity was recorded during spontaneous and/or visual–vestibular-induced reflex eye movements (see Fig. 2). Instantaneous firing rate histograms were constructed as the reciprocal of the interspike interval (ref. 22; see Fig. 2 *A* and *B*, FR). To produce local anesthesia, micropipettes filled with 4% lidocaine and beveled to a tip size of 10 μm were situated at the physiological center of each identified area by recording the surrounding extracellular activity. On average, 1 nl of lidocaine was injected with 5- to 10-ms, 200-kPa air pressure pulses over 30 s (see Figs. 3 and 4). For bilateral inactivation, two separate injections were completed within 2 min.

Biocytin dissolved in 0.1 M phosphate buffer was either pressure injected or iontophoresed into the caudal lobe of the cerebellum to label brainstem nuclei (see Fig. 1 *B–E*). After perfusion with teleost saline and aldehyde fixative, 50-μm sections were reacted with avidin–biotin–peroxidase complex (Vector Laboratories) followed by diaminobenzidine histochemical analysis (ref. 22; see Fig. 1 *C–F*).

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Abbreviation: VOR, vestibuloocular reflex.

RESULTS

Four hindbrain nuclei distributed periodically at ≈500-μm intervals between the obex and the abducens nucleus were designated from caudal to rostral as areas I–IV (Fig. 1 *A* and *B*). Each subgroup contained a total of 25–40 neurons that were involved in either position (areas I and III) or velocity (areas II and IV) integration for oculomotor (areas I and II) and postural (areas III and IV) control. Biocytin injections in the vestibulocerebellar lobe selectivity labeled neurons in the inferior olive and area II (Fig. 1 *C–F*). Electrical stimulation of the cerebellum (Fig. 1*B*, CL) produced antidromic activation of area II eye velocity-only neurons described in Fig. 2 (32). Areas I and II were situated directly above the inferior olive as shown in both sagittal (Fig. 1 *C* and *F*) and coronal (Fig. 1 *D* and *E*) views of the brainstem. The longitudinal distribution of the four hindbrain nuclei could be recognized in relationship to a set of repeating vascular branches that was confirmed by neurophysiological correlates in every animal.

Neurons were identified in each of the horizontal eye movement-related areas I–IV with extracellular single unit recordings (Fig. 2). Discharge properties were highly correlated in the two posterior areas (I and II) with eye movement parameters, while relationships were less obvious in the two rostral areas (III and IV). In the most caudal subnucleus (area I), neuronal firing rate during spontaneous eye movements increased in proportion to the angle of eye deviation toward the ipsilateral side of recording. During divergent saccades, area I neurons encoded the position of the ipsilateral eye (Fig. 2*A*; dashed lines). The majority of area I neurons (70%) demonstrated a sensitivity proportional to the velocity of the eyes during saccades (Fig. 2*A*, arrow). Some of these neurons were purely position related (30%) since the velocity sensitivity during rapid eye movements was negligible (Fig. 2*B*, arrows). During the slow phase of either vestibular (Fig. 2*B*) or optokinetic nystagmus, firing rate of neurons in area I was proportional to eye position, exhibiting little eye velocity sensitivity.

Area II was located immediately rostral to area I. Neurons in this area either remained silent or showed a steady firing rate during spontaneous saccadic eye movement (Fig. 2*C*). Area II neurons modulated in phase with eye velocity directed toward the ipsilateral side of recording during the slow component of either optokinetic (Fig. 2*D*) or vestibular nystagmus. The two main types of neuronal responses detected in area II were eye velocity only (51%) and eye combined with a head velocity sensitivity measured during visual suppression of the VOR (49%). Some of these neurons also paused for all fast phases (eye velocity pause, 25%). During either sinusoidal optokinetic or vestibular stimulation, the firing rate of neurons in area I peaked in phase with eye position (Fig. 2*B*, dotted line), while neurons in area II modulated in phase with eye velocity (Fig. 2*D*, dotted line). Thus, the main physiological difference between areas I and II was an exquisite segregation of eye position and eye velocity signals. Nevertheless, neurons in both areas were considered premotor since they fired 15–20 ms prior to the

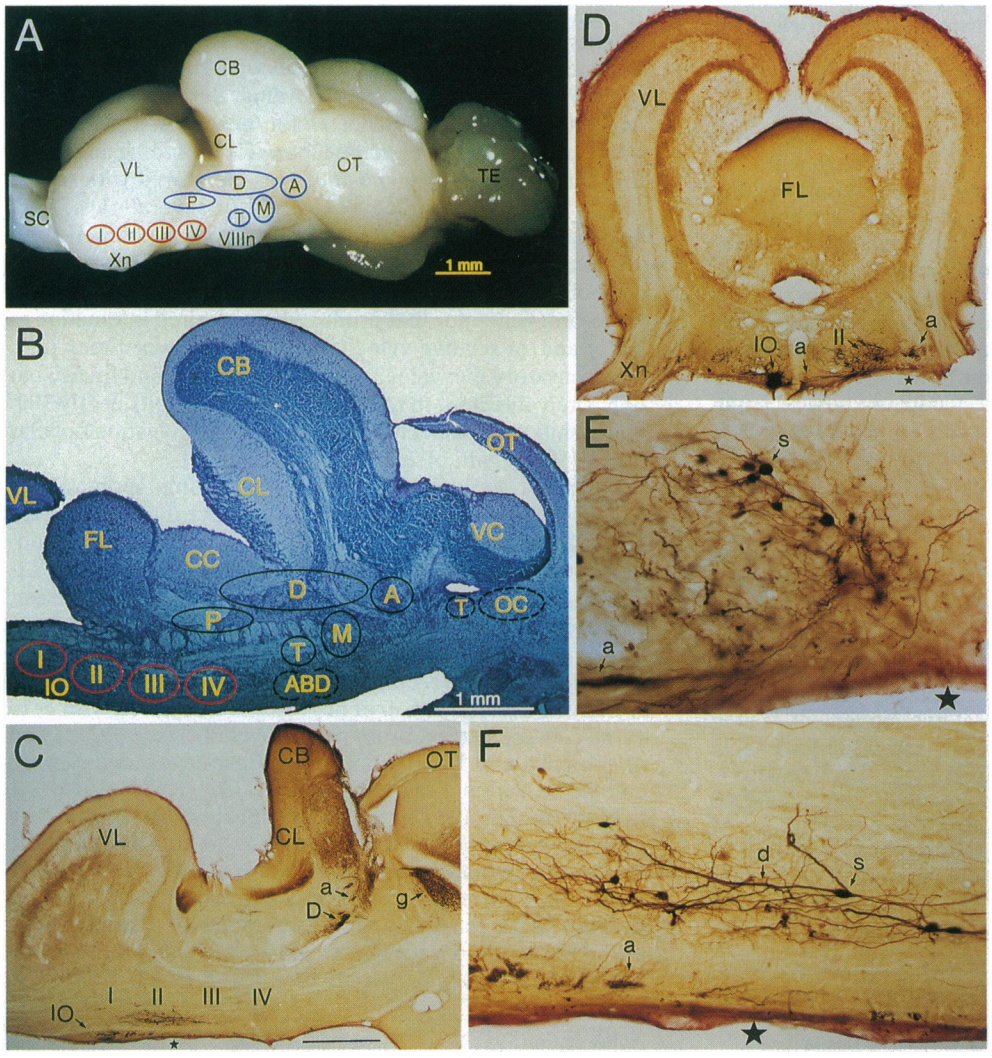

FIG. 1. Organization of hindbrain nuclei in the goldfish. Whole brain (*A*) and sagittal Nissl sections (*B*) showing the rostrocaudal and ventral location of the major vestibular subdivisions (24) and areas I–IV. (*C–F*) Neurons, axons, and processes labeled after biocytin injection into the vestibulocerebellum (CL). (*C*) Parasagittal section 300 μm from the midline showing the rostral inferior olive (IO) decussation and neurons in area II. Mossy fiber pathways (a) and granule cell (g) clusters are marked. (*F*) High magnification of area II (star in *C*) illustrating soma and dendrites of putative eye velocity integrator neurons. (*D*) Coronal section showing axons (a) of labeled contralateral IO neurons crossing the midline and the ipsilateral ventromedial location of putative area II eye velocity neurons. (*E*) Clustered somas (s) and dendrites (d) of area II neurons are shown at higher magnification (star in *D*). A, D, P, M, and T, anterior, descending, posterior, magnocellular, and tangential subdivisions of vestibular nuclei; VC, CL, CC, and CB, valvula, caudal lobe, cerebellar crest, and corpus of the cerebellum; ABD, abducens; OC and T, oculomotor and trochlear nuclei; FL, facial lobe; I–IV, areas I–IV of the hindbrain; OT, optic tectum; SC, spinal cord; TE, telencephalon; VIIIn, octavolateralis nerve; Xn, vagal nerve; VL, vagal lobe.

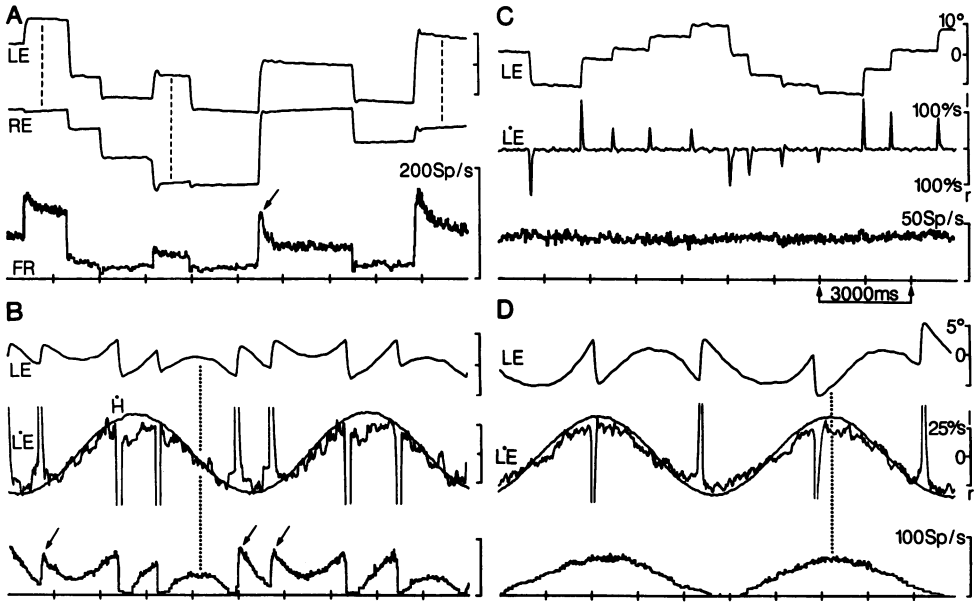

FIG. 2. Discharge characteristics of area I (*A* and *B*) and area II (*C* and *D*) neurons. (*A*) Firing rate (FR) of an area I neuron during spontaneous eye movements. Discharge was correlated to left eye position (LE) during fixation (dashed lines) and some neurons also exhibited saccade sensitivity (arrow). (*B*) FR of a purely position-related area I neuron (arrows) during sinusoidal head rotation ($\dot{H}$) in the dark. Head velocity is inverted in *B* and *D* to facilitate comparison to eye velocity. FR was associated with horizontal eye position (LE) but not eye velocity (dotted line). (*C*) Area II neurons were not modulated during spontaneous eye movements. (*D*) During head rotation area II neurons modulated in phase with eye velocity ($\dot{L}E$, dotted line) but not eye position (LE). Calibrations are indicated.

occurrence of saccades, fast phases, or eye responses to sudden step rotations of the head (data not shown).

During spontaneous eye movements, most neurons in area III (75%) exhibited an irregular firing rate poorly correlated ($r < 0.7$) with ipsilateral eye position. A weak eye velocity sensitivity was detected during vestibular and optokinetic reflexes. The second type (25%) exhibited a similar profile but paused for saccades and fast phases in all directions. Area IV (100%) was composed of eye velocity-like neurons that increased firing during contralateral eye movement. Three separate clusters of medially located bursting neurons were situated between areas I and IV. Every burst neuron between area I and II fired 30–40 ms before the occurrence of all ipsilaterally directed fast phases and saccades. Burst neurons located between areas II and III exhibited a variable latency and correlation with saccades while those between areas III and IV were bidirectional.

Selective lidocaine inactivation of the four medullary areas was used to assess the potential contribution of constituent neurons to the integration process. The inactivation of either area I or II, but not area III or IV, produced qualitatively distinct changes in eye movement parameters (Figs. 3 and 4). Bilateral lidocaine injection of area I produced severe gaze-holding deficits for horizontal eye movements. By 2 min after the injection, and during the 20 min of effective inactivation, horizontal saccades for both eyes and in both directions were followed by an exponential drift directed asymptotically toward a null point (Fig. 3*A*). The exponential time course of the drift can be interpreted as the passive recentering of the eye due to orbital viscoelastic tissue forces. The time constant of the exponential drift was progressively shortened toward a minimum of 0.3 s over the first 10 min (Fig. 3*B*, 10 min). Then the time constant progressively recovered to control over the next 20 min (Fig. 3*B*, 30 min). Thus, inactivation of the integrator appears to remove the position signals available to the motoneurons for maintaining the horizontal angle of gaze.

Bilateral inactivation of area I also produced devastating effects on both the VOR and optokinetic reflex. Sinusoidal stimulation at low frequency (≤0.25 Hz) greatly reduced VOR gain from 1.0 to an average of 0.2 and eye velocity led table velocity by 70° (Fig. 3*C*, dotted lines). At higher rotational frequencies, gain and phase progressively approached typical values (Fig. 3*D*, dotted line). Consequently, VOR measurements at ≈1 Hz exhibited a normal sensory to motor transformation in the absence of any central neuronal processing of velocity to position signals.

Eye movement deficits induced after unilateral lidocaine inactivation of area I were never as marked as those following bilateral injection and the time constant of the postsaccadic drift was never lowered to <1.0 s. Comparison of data after many reversible uni- and/or bilateral inactivations demonstrated that a single intact area I could process position signals capable of driving both eyes. Independent integrity of the bilaterally located position integrators implies that the interconnections between the two are not critical for the velocity to position transformation. By contrast, unilateral vestibular and/or prepositus lesions in mammals were reported as sufficient to produce a total gaze-holding failure (21, 25).

Lidocaine inactivation of area II also produced distinct oculomotor abnormalities. A single unilateral lidocaine injection in area II caused a nystagmus of the two eyes with fast phases always directed toward the side of the inactivation (Fig. 4*A*). The sawtooth movement of the eyes likely originated from imbalancing the velocity output from the bilateral area II nuclei (Fig. 2). The resulting eye velocity bias was maximal in the dark, 16–22°/s during the slow phase of nystagmus; however, in the presence of an illuminated stationary background, the bias was reduced to ≈4°/s, indicating visual suppression through the intact area II (Fig. 4*A*, dashed line). This ramp-like eye movement (Fig. 4*B*) was clearly distinguishable from the exponential drift in eye position following inactivation of area I (Fig. 3*B*). During sinusoidal head rotation in the dark, the velocity bias shifted the eye velocity by a constant value of ≈20°/s (Fig. 4*C*, arrows). All the fast phases of nystagmus occurred in the direction opposite the velocity bias because eye velocity could not cross zero value (Fig. 4*C*, $\dot{L}E$).

After bilateral lidocaine inactivation of area II, saccades and fixations exhibited little sign of either bias or gaze-holding failure (Fig. 4*D*). Nevertheless, bilateral anesthesia of area II maximally compromised both the VOR and the optokinetic reflex. Eye velocity processing was totally abolished during either sinusoidal or step rotation of the head. The normal time constant of the velocity storage integrator was reduced from 10–12 s (Fig. 4*E*, arrow) to 0.3 s (Fig. 4*F*, arrows). By contrast, the position integrator continued to perform one-step integration of the velocity-related signals because both eyes followed with an eye position step resembling the stimulus velocity profile (Fig. 4*F*, RE and LE).

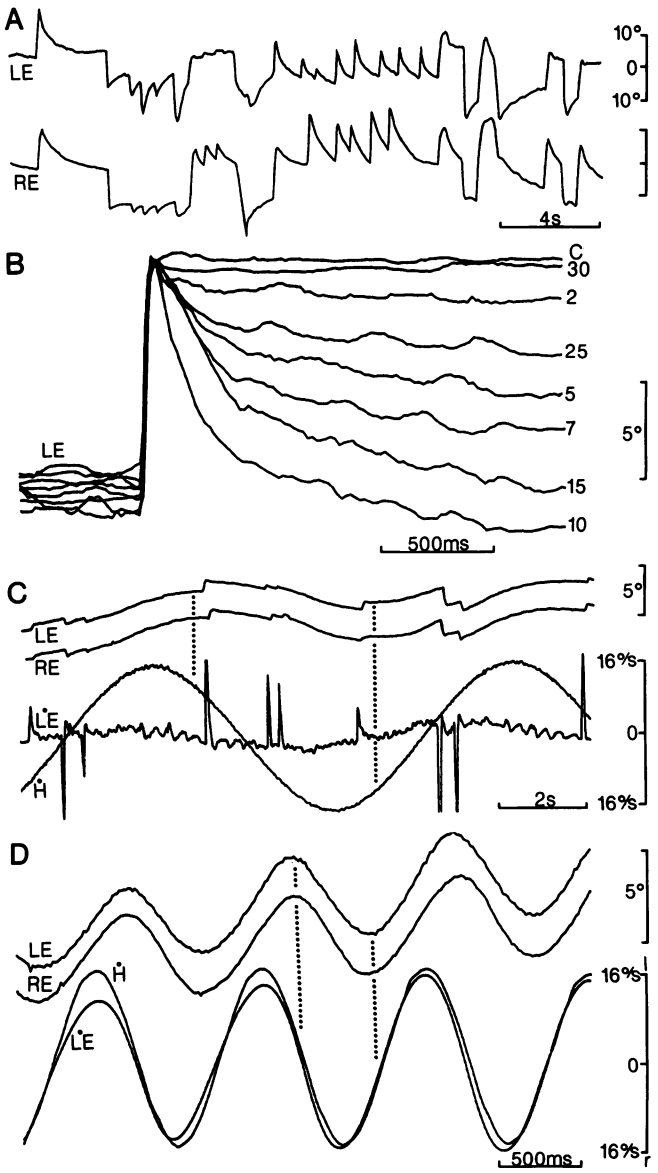

FIG. 3. Effects of bilateral lidocaine injection in area I. (*A*) Horizontal position of the left (LE) and right (RE) eyes 12 min after area I inactivation. After saccades in both directions the eyes drifted centripetally with an exponential profile exhibiting a time constant of 0.3 s. (*B*) Time course in minutes illustrating inactivation and recovery after bilateral area I lidocaine injection. Saccades of similar size directed leftward were superimposed at the point of peak amplitude to illustrate shortening of the velocity to position integrator time constant. (*C* and *D*) Effects of area I inactivation on the VOR at low (0.125 Hz; *C*) and high (1 Hz; *D*) frequency. Lidocaine injections of 1 nl into either area III or area IV did not influence eye movements. Large amounts (10 nl) produced some drift and velocity bias, likely due to spread into adjacent nuclei and/or fiber tracts. Lidocaine injections of 1 nl into the medial burst neurons between area I and II nearly abolished saccades and fast phases but did not affect integrator operation.

Inactivation of area II did not interrupt the vestibular connection to the position integrator. These results are not consistent with models (26) or lesion studies (21) that place the site for velocity storage in a system of reciprocal commissural connections between the vestibular complex.

DISCUSSION

Our data demonstrate that the neural mechanisms required for both velocity to position and velocity storage integration reside in adjacent medullary nuclei clearly isolated from, but likely intimately connected to, the vestibular nuclei. The spatial discreteness of these integrators corresponds to constant morphological landmarks in the goldfish medulla that reflect the adult retention of a segmental blueprint described in larval zebrafish (27). We propose that these hindbrain nuclei in goldfish are analogous in function to the mammalian prepositus nuclei and that homologous neuronal types can be eventually recognized. Therefore, the hindbrain topography in teleosts (Fig. 1 *A* and *B*) is more advantageous for resolving neurophysiological correlates as well as investigating the developmental and genetic plans underlying assembly of hindbrain horizontal eye movement pathways (28).

In each discrete nonoverlapping compartment, the quantitative analysis of discharge characteristics and oculomotor deficits after lidocaine injections were complementary. Area I and area II neurons were correlated with eye position and velocity, respectively. Signal processing appeared to be autonomous to each nucleus. Since area I responses were correlated to saccades, VOR, and visually induced reflexes, the position integrator is indeed common for all eye movements (15). Nevertheless, area I probably represents the summing junction for two quite different modalities of eye velocity signal because fast phases and spontaneous saccadic eye movements were spared after bilateral lidocaine inactivation of area II (Fig. 4*D*). Thus, vestibular and optokinetic eye velocity signals processed in area II reach area I by a pathway distinct from that of burst neurons producing saccades. An equally likely supposition is that area II also represents a summing junction for vestibular and visual eye velocity, because these neurons do not fire for either saccades or fast phases (Fig. 2 *C* and *D*).

Homogeneity of discharge pattern and inactivation with lidocaine argues that area II plays two sequential roles in eye movement. We suggest that the neurons first generate and then store eye velocity since lidocaine inactivation not only abolished velocity storage but also reduced the VOR time constant to values less than the average vestibular afferent time constant (0.3 s vs. 3–4 s, respectively). Inactivation of area II greatly impairs both vestibular and optokinetic reflexes because all neurons in area II exhibit a continuous level of tonic activity (Fig. 2*C*). Hence, the VOR time constants are lower than that expected from predictions based on averaged primary afferent discharges (29), and, in fact, many species of teleost exhibit typical VOR time constants far less than mean afferent values (30). This lowered VOR time constant was accompanied by a marked compromise in the VOR when tested with lower frequency sinusoidal stimuli. By contrast, the direct, presumed three-neuron, VOR pathway remained intact as indicated by the latency and amplitude of the eye position step (ref. 23; Fig. 4*F*). We suggest that area II velocity neurons comprise a brainstem loop that supports the direct VOR pathway located in the descending octaval nucleus (Fig. 1 *A–C*).

Overall, the most straightforward argument is that area I and area II are independent eye position and velocity generators. Assuredly, area I is the requisite position integrator. Principally, area II converts sensory signal velocity (vestibular and visual) to motor (eye) commands as well as assuming the important role of eye velocity storage. Therefore, the patterns of neural activity within each integrator can be proposed to arise from intrinsic properties of their constituent neurons as opposed to interactions with extrinsic synaptic circuitry.

One-step signal generation and storage is an attractive idea because the same neurons used to create can also store the neural activity correlated with either position or velocity. Such neuronal behavior is predicted based on the structural uniqueness, homogeneity, and clear separation of the individual areas from each other and the vestibular nuclei (Fig.

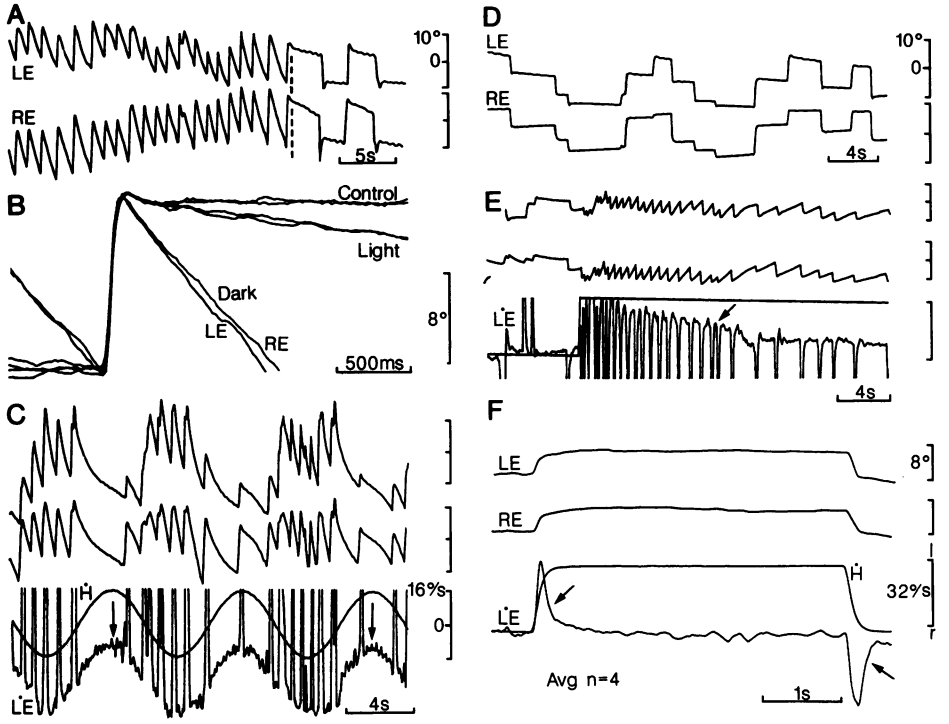

FIG. 4. Effects of unilateral (*A–C*) and bilateral (*D–F*) lidocaine inactivation of area II. (*A*) Unilateral inactivation of the left area II produced nystagmus to the left in the dark, but slow phases were attenuated in the light (dashed line). (*B*) Superimposition of fast phases demonstrates ramp-like eye movements after inactivation. (*C*) During head rotation in the dark velocity bias added to the sinusoidal nystagmus in both eyes. (*D*) Bilateral lidocaine injection produced neither drift nor velocity bias during spontaneous eye movements. (*E*) Per-rotatory nystagmus (arrow) during constant head velocity exhibited a normal time constant of 10–12 s. (*F*) Bilateral lesion of area II virtually eliminated velocity storage in both directions (VOR time constant shown by arrows) but velocity to position integration was unaffected [left eye (LE) and right eye (RE)].

1). Midline sagittal lesions between these areas do not block either position or velocity storage (data not shown); however, vestibular pathways are highly probable through more rostral commissures (Fig. 1*B*). The medioventral location of these hindbrain nuclei and their separate inactivation clearly demonstrate that neither axonal pathways nor neurons within the vestibular complex were affected by lidocaine (Figs. 3 and 4). We believe, therefore, that all of the structural and functional characteristics expected of each integrator are embodied by neurons centralized within a single nucleus.

Since these unusual compartments are necessary and presumed sufficient to process the neuronal operations elementary for integration, we hypothesize that transformations within each compartment confer autorhythmic characteristics that are largely modulated, not commanded, by external synaptic circuitry. In principle, the inherent electroresponsive properties of the neurons alone may be sufficient to produce integration (31). Therefore, we propose that signal transformations may largely arise from the intrinsic electrophysiological properties of constituent neurons (32). The diversity of eye movements and the varied integrator time constants that exist between teleostean species should permit these structural and neurophysiological hypotheses to be satisfactorily settled.

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