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The lectures summarized in this publication were presented by their authors at a workshop held on the 27th through the 29th of November, 1991, at the Fundación Juan March

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Fundación Juan March

Workshop on Neural Control of Movement in Vertebrates

Organized by

R. Baker and J. M. Delgado-García

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R. Baker
A. H. Bass
A. Berthoz
A. L. Bianchi
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269 Workshop on Neural Control of Movement in Vertebrates

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Serie Universitaria

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I N D E X

PROGRAMME

November, 27

Chairman: R.E. Burke.

W. Buño: "Crayfish stretch receptors as archetypes of mechano-sensory organs participating in motor control".

A.H. Bass: "Evolution of vocal motor pathways: species- and sex- typical characters".

S. Grillner: "Neuronal network underlying locomotion in a vertebrate, circuitry, transmitters, membrane properties and simulation".

R.E. Burke: "Spinal cord mechanisms of motor control: the role of interneurons".

Chairman: A. Berthoz.

J.M. Delgado-García: "Functional organization of the premotor system for eye movements".

S.M. Highstein: "The brainstem organization of saccadic eye movements".

G. Cheron: "The gaze holding system".

November, 28

Chairman: S.M. Highstein.

A. Berthoz: "Neural basis of orienting movements and their adaptive mechanisms".

Y. Shinoda: "Branching patterns of single axons of long descending motor tract neurons in the spinal cord".

D. Guitton: "Role of superior colliculus in the control of saccadic eye and/or eye-head gaze shifts".

A.L. Bianchi: "Neural control of respiratory movements".

Chairman: M. Steriade.

J.R. Bloedel: "The role of the sagittal zone in cerebellar operations".

F.J. Rubia Vila: "Is the cerebellum a learning device?".

November, 29

Chairman: P.L. Strick.

M. Steriade: "Thalamic oscillations and their modulation by brainstem cholinergic systems".

C. Acuña: "Role of pulvinar-latero posterior complex of behaving primates in goal directed movements. Comparison with parietal area 5a".

F. Mora: "Interactions of neurotransmitters in the basal ganglia and aging: Studies of amino acids and dopamine".

R. Caminiti: "Neural construct of space in the primate frontal lobe".

Chairman: E.E. Fetz.

E.E. Fetz: "Synaptic interactions between motor cortex neurons".

P.L. Strick. "The corticospinal system: parallel pathways for the central control of movement".

Poster oral presentations: *A.M. Pastor, F. Viana, H. Straka, J.P. Welsh.*

R. Baker: "The developmental origin of motor systems in the vertebrate CNS".

Main conclusions of the workshop.

INTRODUCTION

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Laboratorio de Neurociencia
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Universidad de Sevilla
Sevilla (Spain)

INTRODUCTION

The understanding of how vertebrates are able to stand up (i.e., maintain their forms) against gravity and to move opposing viscous-elastic forces is a very basic, albeit unanswered, objective of present-day neuroscience. Perhaps because the way we walk, speak or organize our behavior seems so obvious, the relatively little attention paid from both scientific and cultural points of view to the neural mechanisms underlying motor control is not so surprising. Nevertheless, and assuming that our behavior is in the end the result of our own brain activity, it should be stressed that, in the words of Sherrington, "*we can still endorse the old adage that to move things is all that mandkind can do, and for such the sole executant is the muscle, whether in whispering a syllable or in felling a forest*".

Both multidisciplinary and comparative approaches seem to be necessary to throw light on these intriguing questions. Knowledge about the neuronal genesis and control of movement has increased dramatically in recent years with the help of several experimental techniques. These techniques extend from the electrical recording of neuronal activity in freely moving animals to the use of retrograde, anterograde and transynaptic neuronal dyes to trace motor and premotor pathways in the central nervous system. Further improvements have also been obtained using kinematic analysis of movement, quantitative analysis of sensorimotor data, and computer modeling of the experimental results. Moreover, the comparative approach has allowed some insights into the peculiar strategies followed by different species to maintain and/or change their position in space.

The aim of the workshop was to offer a forum in which scientists with different backgrounds and technical skills could discuss about these recent developments and could propose future directions of research. The format of the workshop was designed to stimulate a short formal presentation of the selected topics and a long informal discussion. The participation in the debate of the students attending the workshop was highly encouraged.

The following main topics relative to the neural control

of movement were considered. To begin, the spinal cord organization in a primitive vertebrate (Dr. Grillner) and in mammals (Dr. Burke) was discussed. Dr. Buño presented the studies carried out by his group on the crayfish stretch receptors as an archetype of mechano-sensory organs participating in motor control. Dr. Bass presented his studies on the sonic motor system of fishes as a way to introduce the relationships between phylogeny, adaptation and nervous system organization.

Two sessions were addressed to the study of the oculomotor system in vertebrates. The first two presentations approached the brain stem organization of motor (Dr. Delgado-García) and premotor (Dr. Highstein) centers related to the control of eye movements. The functional basis of the gaze holding system (Dr. Cheron), the role of superior colliculus on gaze (Dr. Guitton), and a general perspective of orienting movements (Dr. Berthoz) were also discussed. Dr. Shinoda illustrated new findings on the branching pattern of motor axons descending to the spinal cord. As an example of a motor system with completely different functional properties, Dr. Bianchi presented the work of his group on the neural control of respiratory movements.

The roles of cerebellum on motor control and as a (possible) learning device were introduced by Drs. Bloedel and Rubia, respectively. Dr. Steriade's talk covered the electrophysiological properties of the thalamus underlying behavioral states such as alertness and quiet sleep.

The final two sessions of the workshop were devoted to the study of cortical and subcortical structures in relation to the genesis and control of movement. Dr. Acuña addressed the relationships between the pulvinar-latero posterior complex and parietal area 5a; Dr. Caminiti presented the role of the frontal cortex in reaching movements; Dr. Fetz gave due prominence to synaptic interactions in sensoriomotor cortex; and Dr. Strick presented data relative to the organization of cortical descending pathways studied with the help of new morphological techniques. The neurochemical sustrates of motor behavior with special reference to the basal ganglia were introduced by Dr. Mora. A broad perspective of evolutionary trends regarding motor systems and some concluding remarks were presented by Dr. Baker.

Last but not least, the participation of the students in the workshop was highly remarkable, not only for their contribution to the different opportunities of informal discussion, but also for the scientific level of their posters and oral presentations.

I do not want to conclude this introduction without thanking all the participants, both professors and students, for their generous and enthusiastic contributions to the fulfilment of the workshop. I also want to thank Mr. Andrés González and Mr. Eduardo Ruiz, from the Fundación Juan March, for their continuous help during the organization and development of the workshop.

Reference

Ch. S. Sherrington, *Linacre Lecture*, Cambridge, England, 1924.

NOVEMBER, 27

CRAYFISH STRETCH RECEPTORS AS ARCHETYPES OF MECHANO-SESORY ORGANS PARTICIPATING IN MOTOR CONTROL

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The slowly and rapidly adapting stretch receptor organs of crayfish (RM1 and RM2, respectively) are prototypic mechanoreceptors involved in motor control. The RM neurons are included in an extremely simple circuit with two inputs, one sensory and excitatory, the mechanical stretch stimulus (and also the contraction of the receptor muscle), and another synaptic and inhibitory, the efferent accessory neuron. The RM1 behaves as a pacemaker, while the RM2 is a prototypic phasic receptor and therefore spontaneously silent cell.

The mechanisms of sensory transduction and the coding of stimulus characteristics, as well as the efferent modulation and control by the inhibitory fiber in both receptor types will be discussed.

The participation of the oscillatory pacemaker activity in stimulus coding and the characteristics of the pacemaker-synaptic interactions will be considered. A model of the involvement of RMs and of pacemaker-synaptic interactions in motor control, applicable to other motor systems, will be proposed.

EVOLUTION OF VOCAL MOTOR PATHWAYS: SPECIES- AND SEX- TYPICAL CHARACTERS. BASS, ANDREW H., Division of Biological Sciences, Section of Neurobiology and Behavior, Cornell University, Ithaca, New York, 14853 U.S.A.

Studies of neuronal function and behavior can pose either *How* or *Why* questions. *How* questions seek to identify the cellular and molecular mechanisms, inclusive of their ontogeny, determining the generation of a behavior. *Why* questions address "ultimate" causation within the context of the contribution of a behavior to an individual's survival and reproductive fitness. For both the *How* and *Why* questions, it is important to identify the contribution of phylogenetic (i.e., mechanical/developmental) factors vs. current adaptive modifications to an extant phenotype. Evolutionary neurobiologists want to understand *How* a given neuronal trait has been altered to subserve "new" behaviors between or within species.

The aforementioned issues have been addressed within the context of comparative/interspecific and developmental/intraspecific studies of brain pathways determining the production of vocal communication signals in teleost fishes. The vocalizations are highly stereotyped, species-specific and, in some cases, sex-specific. The vocal, or sonic, motor system exemplifies basic organizational features determining the production of a rhythmic motor behavior. It may be considered a "simple" vertebrate motor system because there is a direct relationship between the patterned output of the central nervous system and the basic physical properties of the vocal signal itself, namely fundamental frequency and duration.

Vocal motor traits common to several species illustrate the phylogenetic factors influencing the evolution of this motor system. Thus, phylogenetic analyses suggest that the common ancestor of a number of teleosts had a vocal motor system characterized by: (1) ipsilateral innervation of paired sonic muscles by occipital nerve roots arising just caudal to the vagus nerve, (2) paired, sonic motor nuclei located in the caudal brainstem at the same level as the hypoglossal nucleus of tetrapods, and (3) motoneurons innervated by rhythmically-firing pacemaker neurons that determine the fundamental frequency of all vocal signals.

Sex-specific traits demonstrate the adaptive modification of the sonic motor system and vocalization behaviors within the context of the functional organization of vertebrate mating systems. For example, the plainfin midshipman, *Porichthys notatus*, has two groups of reproductively active males that can be distinguished on the basis of behavioral, endocrinological and somatic traits. One group of nest-building, egg-guarding males that we have designated as *Type I* males, generate mate calls during the breeding season to attract gravid females to their nest. The second group of smaller *Type II* males, do not build nests or guard fertilized eggs, but rather parasitize Type I males by "sneaking" into the nest of a Type I male or lying just outside it and fanning sperm into the nest while a female is depositing eggs. Type II males, like females, do not generate mate calls. There are extreme dimorphisms when comparing the vocal motor system of the mate-calling Type I males to that of the non-calling Type I males or females. For example, in Type I males, the vocal muscles are 25-fold greater in absolute mass, sonic motoneurons and pacemaker neurons are 100-300% larger, and the central

discharge frequency of the vocal pathway is 20% higher. Thus, intra- and inter- sexual differences in a rhythmically-generated behavior, i.e. vocalizations, is paralleled by both male-female and male-male differences in the morphological and neurophysiological traits of the vocal motor pathway.

Selected References

Bass, A.H. (1989) Evolution of vertebrate motor systems for acoustic and electric communication: Peripheral and central elements. *Brain, Behavior and Evolution* 33:237-247.

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NEURONAL NETWORK UNDERLYING LOCOMOTION IN A VERTEBRATE, CIRCUITRY, TRANSMITTERS, MEMBRANE PROPERTIES AND SIMULATION

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The lecture will relate to the basic features of the pattern generator network of locomotion. The example chosen in the talk is that of a lower vertebrate model, the lamprey, in which the cellular bases of the basic behaviour has been elucidated to a significant extent. The discussion should deal with general mechanisms of

- Spinal pattern generation in vertebrates.
- Network properties if importance for the pattern generation.
- Membrane properties, transmitters and post synaptic receptors in the locomotor network.
- Sensory regulation of a central pattern generator-cellular effects.
- Supra spinal initiation and control.

SPINAL CORD MECHANISMS OF MOTOR CONTROL: THE ROLE OF INTERNEURONS

Robert E. Burke
Laboratory of Neural Control, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA

Central nervous system (CNS) control of the limbs and trunk necessarily involves neural mechanisms in the spinal cord. The ability to functionally define individual primary afferents and motoneurons during experiments has produced a large body of detailed information about these essential elements. However, the vast majority of neurons in the CNS are interneurons that receive input and transmit output entirely within the CNS. A detailed understanding of motor control requires information about the connectivity (circuitry) of defined groups of interneurons and their role (functional identity) in particular motor acts. Knowledge of circuitry is necessary but not sufficient to define functional identity. The spinal cord is ideal for studying this problem because primary afferents and motoneurons are anatomically and functionally defined entities, thus serving as landmarks for interneuron identification as input sources and output targets. Interneurons in disynaptic reflex pathways that receive input directly from afferents and project directly to motoneurons ("last-order" interneurons) can be precisely defined as to circuitry, leading to inferences about functional role(s). The next steps are: 1) to examine the organization of other synaptic input systems, particularly supraspinal systems, that converge onto last-order interneurons; 2) to study the circuit organization of other categories of interneurons, using last-order interneurons as either input or target; and 3) to design experiments to examine directly the function of circuit-defined interneurons during movement performance. Pioneering work by Lundberg and colleagues in Sweden has shown that most segmental interneurons are nodal points at which "reflex" and "voluntary" motor functions intersect. The available evidence suggests that particular groups of interneurons can assume different functional roles, depending on the motor task at hand.

References:

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Recent: Hultborn, H. and Illert, M. (1991) How is motor behavior reflected in the organization of spinal systems? In: Motor Control: Concepts and Issues (ed: D. R. Humphrey and H.-J. Freund) Chichester: John Wiley & Sons. pp. 49 - 73.

FUNCTIONAL ORGANIZATION OF THE PREMOTOR SYSTEM FOR EYE MOVEMENTS

J.M. Delgado-García, Laboratorio de Neurociencia, Departamento de Fisiología y Biología Animal, Facultad de Biología, Universidad de Sevilla.

The activity of pontomedullary reticular, vestibular and prepositus hypoglossi neurons was recorded in the alert cat during spontaneous and vestibularly-induced eye movements. Neurons were identified by their antidromic activation from the abducens nucleus. Spikes of these neurons were used to trigger the recording of field potentials in the abducens nucleus. The analysis of post-spike averaging of field potentials showed the presence of a trifold system of reciprocal (excitatory and inhibitory) direct (monosynaptic) projections that originated in the above nuclei and terminated in the abducens nucleus with a distinctly graded effectiveness. This trifold afferent system is involved in the generation of fast eye movements, slow compensatory movements of vestibular origin, and eye fixation, respectively.

During the presentation particular attention will be paid to the neural mechanisms underlying the generation of eye position signals. Experimental data will be presented supporting the hypothesis of a transformation of the eye velocity signal in an eye position signal by neural mechanisms located in the nucleus prepositus hypoglossi. It will be proposed that prepositus hypoglossi neurons are organized in a *cascade* fashion in order to generate an eye position signal from the velocity signal present in pontine reticular long-lead and short-lead excitatory burst neurons.

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THE BRAINSTEM ORGANIZATION OF SACCADIC EYE MOVEMENTS

Stephen M. Highstein M.D., Ph.D.
Washington University School of Medicine
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Extraocular motoneurons generate rapid eye movements by firing a burst of action potentials temporally and metrically related to the ensuing saccade. These motoneurons are driven by the immediately prenuclear excitatory and inhibitory burst neurons. Horizontal burst neurons are located in the pons and medulla and vertical burst neurons in the midbrain. By studying the axonal arbors and terminals of the burst neurons it has been possible to explain the behavior of many other brainstem neurons also related to rapid eye movements. Firing patterns and synaptic inter relations of these brainstem cells provide a model for the generation and control of rapid eye movements.

Article for review: Strassman, Highstein, McCrea, Anatomy and Physiology of saccadic burst neurons in the alert monkey. I. Excitatory burst neurons. J. Comp. Neurol. 249:337-357 (1986).

THE GAZE HOLDING SYSTEM

G. CHERON

Laboratory of Neurophysiology - University of Mons, Belgium

Skavenski and Robinson, 1973 performing a saccade and the subsequent gaze-holding necessitates a pulse-step signal. The generator for making saccades, which is located in the pontine paramedial reticular formation (PPRF), provides only the pulse signal (Keller, 1974). The step signal is hypothesized to be made by processing the pulse signal in an integrator (the oculomotor neural integrator, NI). If the integration processing is missing, the resulting saccade will not be followed by a gaze-holding period but by an exponential post-saccadic drift with a time constant of about 0.16 s.

During the vestibulo-ocular reflex (VOR) at 0.10 Hz the firing rate of the abducens motoneuron is in phase with eye position while the firing rate of the primary vestibular afferent is proportional to head velocity. Consequently, it would appear that a network of neurons in the brainstem must perform a integration of this velocity signal to provide the eye position signal. In the case of a total failure of the NI the VOR phase lead would be + 93 deg at 0.10 Hz with a gain value around 0.1.

After all, it is the neural integrator that generates the slow phase of nystagmus and holds the eye eccentrically after a saccade. All these theoretical predictions were experimentaly produced for the first time in 1986 when we performed electrolytic lesions in the prepositus hypoglossi nuclei (PH) in the cat (Cheron et al, 1986). Unilateral kainic acid injection in the PH also produces a bilateral post-saccadic drift and a VOR integrator failure (Cheron and Godaux, 1987). This bilateral gaze holding failure could be interpreted on the basis of the commissural connections.

The idea is that there must exist two horizontal integration processing : one is necessary to hold an eccentric position to the left, the other is necessary to hold an eccentric position to the right. The questions are : how do these two components cooperate with each other ? Are they two complete half-integrators each of which able to perform a complete integration ? Do the commissural fibers linking the two half-integrators transform them from very bad into very good ones ? Is the commissural link the basic mechanism of the integration ?

Two possible commissural connections were proposed. The first one is a feedforward, push-pull type. The second one is a feedback closed-loop type. Galiana and Outerbridge (1984) suggested that this latter configuration could provide a positive feedback loop, the second order vestibular neurone would inhibit the contralateral second-order vestibular neurone producing a crossed desinhibition of itself. This process is clearly a positive feedback the favored mechanism with which to build an integrator. Effectively, when neuron excites themselves through a positive feedback loop their activity, once started, would be perseverated and would yield integration.

The experimental testing of this theoretical considerations was made on the cat by means of midsagittal and parasagittal sections in the pontomedullary part of the brainstem (Godaux and Cheron, 1991). On the basis of these experiments we can conclude that the commissural connections between the two PH are not crucial for the integrating process. The parasagittal incision of the vestibular commissure produced a clear syndrome of the vestibular integrator failure and an asymetrical behaviour of the holding system. The gaze-holding was good for saccades made toward the side opposite of the incision while saccades made toward the site of the incision were followed by a post-saccadic drift.

This asymetrical behaviour of the holding system argues against a sine qua non role of the vestibular commissural pathway in the saccadic integrator, but the very distorted VOR with non-linear slow phases argues in favour of an important role played by the positive feedback vestibular commissural pathway in the vestibular integrator.

The neurotransmitters involved in the neural integrator network are unknown but it is interesting to note that there are drugs that alter the gaze holding system while they spare the generator of the saccades. Intramuscular injection of a low dose of ketamine (a specific blocker of NMDA-receptors) caused a failure of the gaze holding integrator while the main sequence of the saccade was normal (Godaux et al, 1990). Moreover, unilateral microinjection of ketamine in the rostral PH produced a vertical and a bilateral horizontal gaze holding failure (Cheron et al, 1992).

In conclusion, this fact suggests that NMDA receptors play a role in the building of the position signal by the PH.

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NOVEMBER, 28

Speaker: Dr. Alain Berthoz

Main topic: Orienting movements

Title: Neural basis of orienting movements and their adaptive mechanisms

Summary and issues for discussion:

1. Neural organization of the tecto-reticulo-spinal system: What is the role of reticulo-spinal neurons in gaze control? Are they important for fina or adaptive adjustments of gaze?
2. Parallel pathways for the control of saccades: the role of of pathways which do not transit through the superior colliculus for the generation of orienting reactions
3. Which are the best methods to study the cortical control of orienting movements ? - Can positrom emission tomography help?
4. Coordinate transformation in visual capture: how are target locations represented in visuo-spatial maps?
5. Mechanisms of memory driven orienting movements: what is the role of the vestibular system in updating visual maps during navigation or locomotion?
6. What is the respective role of networks and of intrinsic properties of neurons in the mechanisms of orienting movements?

Reference:

- A. Berthoz, Adaptive mechanisms in eye-head coordination Chapter 12, pág. 177-201, in "Adaptive mechanisms in gaze control. Facts and theories. A. Berthoz and Melvill-Jones (eds.), Elsevier, 1985

BRANCHING PATTERNS OF SINGLE AXONS OF LONG DESCENDING MOTOR TRACT NEURONS IN THE SPINAL CORD

Yoshikazu Shinoda,
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Classical long descending motor tracts have been classified into two groups; lateral and ventral groups, based on anatomical and lesion studies by Kuypers and his colleagues. The lateral group consists of corticospinal (CS) and rubrospinal (RS) tracts, and the medial group of reticulospinal, tectospinal, and vestibulospinal (VS) tracts. The lateral group runs in the lateral funiculus and mainly controls the musculature of the distal extremities, whereas the medical group runs in the ventral funiculus and mainly controls the musculature of the proximal extremities, the trunk and the neck. Distribution of terminals of these long descending motor tract axons in the spinal cord has been determined, using new anatomical techniques. Axon terminals of the lateral group are mainly distributed in the intermediate zone of the spinal cord, laminae V, VI and VII of Rexed, and lamina IX of the lateral motor nuclei innervating the musculature of the extremities, whereas those of the medial group are mainly distributed in laminae VIII and VII and lamina IX of the medial motor nuclei innervating the musculature of the trunk. The morphology of single axons in these descending tracts has been visualized by intracellular staining with horseradish peroxidase. All of these descending motor tract axons have multiple axon collaterals in the cervical cord. Descending tract axons in the lateral group have common features on their branching pattern and terminal distribution, but those axons in the medial group have very different features. Both CS and RS axons have multiple axon collaterals with a wide rostrocaudal extension separated from each other at a long intervals in laminae V-VII of the cat spinal cord, whereas VS axons have multiple axon collaterals with a narrow rostralcaudal extension separated at short intervals in laminae VII-IX. It has been tacitly assumed that each motor tract consists of private lines connecting the nucleus of origin to a single muscle, as a motoneuron innervates a single muscle. But this notion is no longer tenable. Recent studies indicate that single long descending motor tract axons may innervate a functional set of interneurons and motoneurons.

Speaker: **D. Guitton**

Main Topic: Superior Colliculus and Gaze

Title of your Presentation: Role of superior colliculus in the control of saccadic eye and/or eye-head gaze shifts

The topics suggested below represent more material than can be covered in 40 minutes. I assume the session moderator will choose whatever topics(s) suit the "mood" of the meeting.

1. Respective roles of frontal eye field (FEF), supplementary eye field (SEF) and superior colliculus (SC) in saccadic eye movement control, (e.g., behavioral context, effect of lesions, etc.).

2. Role of basal ganglia: caudate nucleus (CN) and substantia nigra (SN) and relation to SC (e.g., SN inhibits SC; role of FEF-CN-SN-SC pathway etc.).

3. Cerebellar nuclei project to SC. What might be the role of this pathway?

4. Why are the visual and motor maps of the SC superimposed (e.g., implications for eye or eye-head (gaze) motor control, express saccades, etc.)

5. How are eye saccades (or gaze shifts) initiated or stopped?

6. Does the SC provide the brainstem with a signal specifying only the vector (amplitude and direction) of the desired saccadic eye (or gaze) movement or rather does the SC specify the instantaneous error vector (i.e., ongoing difference between desired and actual positions)?

7. Can the concept of feedback control of saccadic eye or gaze shifts be extended to limb motor control?

Neural Control of Respiratory Movements.

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Faculté des Sciences et Techniques Saint Jérôme
Marseille, France

Introduction

In vertebrate, the uptake of oxygen from air and the release of carbon dioxide are performed in the lung acting as a pump driven by a neuromuscular machinery which produces rhythmic movements of the diaphragm, thoracic muscles and other accessory muscles of the upper airway.

A special characteristic of this machinery is to be under the control of both automatic brainstem neuronal network, and voluntary circuitry originating in the cerebral cortex. Thus, the production of respiratory movements, i.e. respiration, works as a sensory-motor act in a way quite similar compared to that of the other motor systems. This presentation will be only devoted to the automatic circuitry.

The motoneurones driving the respiratory muscles of the thoracic pump are located at various level of the spinal cord:

-phrenic motoneurons for the diaphragm at the C4-C6 cervical level,

-motoneurons for the intercostal muscles at the T1-T12 thoracic level,

-motoneurons for the abdominal muscles at T10-T12 thoracic level and L1-L3 lumbar level,

The cranial motoneurones also receive a respiratory command. They are concerned with the control of the upper airway muscles which perform a valve regulation of the inflow/outflow of air into the thoracic pump:

-motoneurons for the pharyngeal and laryngeal muscles, the axons of which are distributed in the vagus nerve and recurrent laryngeal nerve for muscles of the bronchi and the larynx, and in the glossopharyngeal nerve and pharyngeal branch of the vagus nerve for the pharyngeal muscles.

-motoneurons in the facial nerve for the alae nasi,

All these motoneurons are also involved in many other functions other than respiration. They are involved for instance in postural control and phonation, in

protective reflexes of the upper airway (coughing, swallowing), in expulsive functions (vomiting, defecation, parturition, micturition etc...). A poster presentation devoted to the behavior of this motoneurons during respiration compared to their behavior during swallowing, vomiting and coughing has been presented during this workshop (Grélot et al., 1992).

The first goal of the modern respiratory Neurobiologists was to locate in the brainstem the so-called respiratory neurons which drive these different motoneurons in a well coordinated fashion to insure ventilation.

The notion of respiratory neurons

A respiratory neurons is defined as a neuron exhibiting a rhythmic activity with a firing discharge pattern in relation to the movements of the thorax or EMG of the diaphragm. In paralyzed animals, the favorite preparation of Respiratory Neurophysiologists, the neural gross activity of the phrenic nerve usually serves as witness of the central respiration..

Extracellular or intracellular microelectrode soundings of the brainstem have been performed in several species of mammals, and mainly in the cat, under various experimental conditions (anesthetized or decerebrate, paralyzed or spontaneously breathing animals with intact vagi or bivagotomized).

Thus, in the brainstem, it is possible to record neuronal activities related to either inspiration or expiration, hence giving two categories of respiratory neurons: Inspiratory neurons spiking in phase with the bursts of phrenic nerve activity, and expiratory neurons spiking between the bursts of phrenic nerve activity (Fig. 1).

But, characterization of the respiratory-related neurons by using only discharge pattern criterion was not sufficient to know what are the functional properties of the respiratory neurons and their role in the rhythm generation and modulation of the respiratory rhythmicity.

Other criterions are needed to separate the real respiratory neurons from the neurons exhibiting respiratory-related activity, but not associated with generation and modulation of the respiratory rhythmicity.

One important criterion is to determine their axonal destination. Neuroanatomical tracing methods can be used, but it is much more useful to know the axonal projection of the neurons at the time of recordings. For this purpose, the antidromic invasion of the soma by electrical stimulation of the axons is an useful tool to characterize the functional category of the respiratory neuron under recording (Bianchi, 1971).

Anatomo-functional properties of the respiratory neurons.

It turns out that based on the antidromic invasion following stimulation of their axons, 3 functional categories of respiratory neurons can be recognized:

- the **inspiratory and expiratory bulbospinal premotor neurons** whose axons go down to the spinal cord to drive the motoneurons of the diaphragm, and the motoneurons of the thoracic and abdominal muscles; these neurons constitute the output neuronal population of brainstem respiratory network;

- the **inspiratory and expiratory motoneurons** whose axons are distributed in either the vagus nerve and its branches, or in the glossopharyngeal nerve; these cranial motoneurons regulate the upper airway patency during the respiration. Their pattern of activities look-alike those of the respiratory neurons concern with the production of the thoracic respiratory movements, and they can be recognized solely by antidromic invasion at the time of recording.

- finally, even if the above criteria are used, number of the respiratory neurons had their axonal projections undetected. However, antidromic mapping of their axons within the brainstem have revealed that these neurons can be defined as **propriobulbar inspiratory and expiratory interneurons**, a name which assumed an intramedullary course for their axons. This definition gives these neurons an inferred position of higher order interneurons involved either in the central pattern generator or, at least, in interconnective pathways between groups of output identified medullary respiratory neurons, i.e., bulbospinal premotor neurons and cranial motoneurons. Certain of their connections with output respiratory neurons have been shown by antidromic, cross-correlation and spike triggering-averaging methods. However, since these propriobulbar neurons where detected by means of negative criterion, the absence of antidromic activation, it is better to give them the label of **not antidromically activated (NAA) neurons.**

Localization of the respiratory neurons.

These respiratory neurons are concentrated into two well-defined distinct regions of the medulla oblongata (Feldman, 1986).

One termed the **dorsal respiratory group (DRG)** constitutes the ventrolateral division of the nucleus of the solitary tract. It is composed of a population of multipolar cells morphologically and functionally homogeneous, but quite restricted in number (Berger et al.1984; Otake et al.1989). Studies involving extracellular recordings and antidromic stimulation of the cervical spinal cord have given an estimate of 50 to 80% of inspiratory bulbo-spinal neurons within the DRG (Bianchi, 1971; Euler et al.1973).

The second aggregate of medullary respiratory neurons is commonly referred to as the **ventral respiratory group (VRG)**. It corresponds to a bilateral longitudinal column of neurons extending from the facial nucleus to the first cervical roots in a region of the lateral medulla associate with the nucleus ambiguus (Bianchi, 1971). The VRG is usually

subdivided into three divisions which support anatomical and functional peculiar characteristics. The caudal division or caudal VRG (cVRG) extending from the limit between spinal cord and medulla to the obex, has been also named the retroambigualis nucleus. This region is characterized by the presence of a high concentration of expiratory bulbospinal neurons.

The intermediate division of the VRG (iVRG) includes the nucleus ambiguus and para-ambiguus whose distinction is more due to functional than anatomical consideration. The nucleus ambiguus includes the laryngeal motoneurons driving the intrinsic laryngeal muscles and part of the pharyngeal muscles which exhibit various kind of respiratory pattern of activities, either expiratory or inspiratory, but which cannot be considered as element of the central respiratory rhythm generator. The nucleus para-ambiguus includes respiratory bulbospinal premotoneurons which can be considered as the output neurons of the "respiratory center" involved in the control of spinal motoneurons driving the thoracic respiratory muscles. This nucleus also includes respiratory propriobulbar interneurons. The relative location of the bulbospinal neurons with respect to the laryngeal motoneurons of the nucleus ambiguus have been studied by means of retrograde fluorescent double labeling or electrophysiological methods. Bulbospinal neurons were described to be arranged both within the nucleus ambiguus, and ventromedially and ventrolaterally to it.

The rostral division of the VRG (r-VRG) includes the rostral pole of nucleus ambiguus which take the name of retrofacial nucleus due to its proximity with the facial motor nucleus. This division includes pharyngeal motoneurones exhibiting expiratory or inspiratory pattern of discharge (Grélot et al.1988; Bianchi et al.1988; Grélot et al.1989). In addition to these pharyngeal motoneurons, the rostral VRG also include respiratory interneurons interconnected with the caudal medulla and spinal cord. Some of the latter are neurons exhibiting an expiratory augmenting pattern of activity, and are referred to as the "Bötzinger Complex" which constitutes a functional rather than anatomical division.

The pattern of discharge of the respiratory neurons

Examination of the pattern of discharge of respiratory neurons shows the existence of several sub-categories larger than the simple characterization into only two types, i.e. inspiratory and expiratory neurons. The various sub-categories have been recognized by examination of the time course of the discharge, in addition to the period in inspiration or expiration, at which the neurons fired (augmenting or constant, and decreasing), and the time in the respiratory cycle, at which minimum or maximum frequency occurred (early or late) (Cohen, 1979).

Hence, it was possible to distinguish at least 5 or 6 subtypes of respiratory neurons (Fig 1):

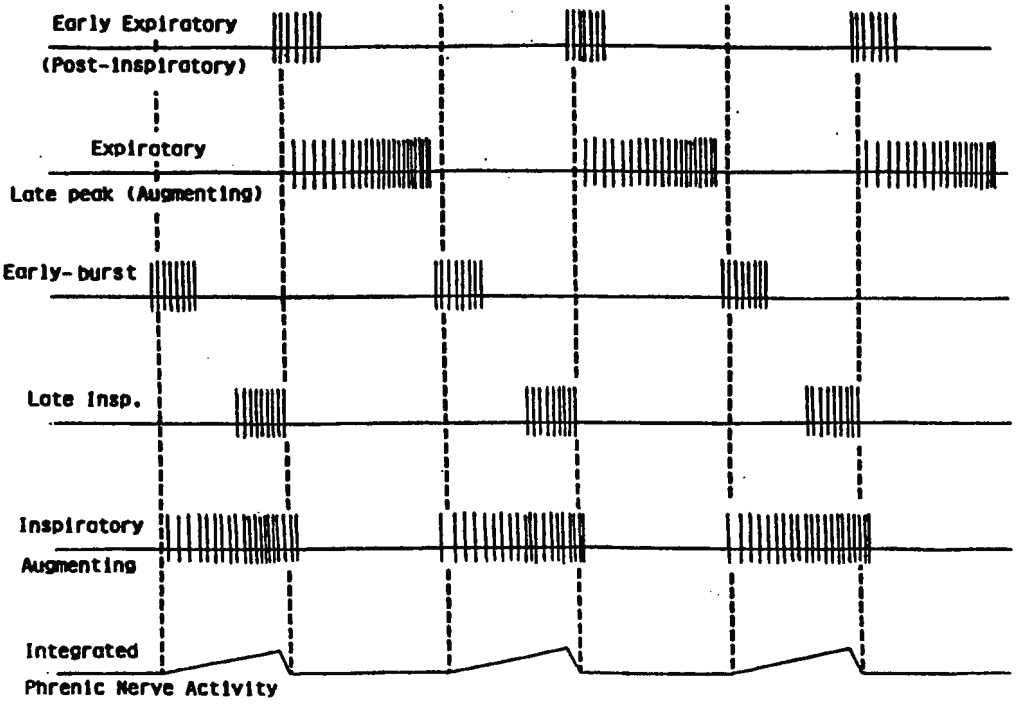

Figure 1: *Sketch showing firing patterns of respiratory neurons*

- inspiratory neurons with an augmenting pattern of discharge reaching a frequency peak in late inspiration (I augmenting, I ramp, I late), or with a decrementing or early peak pattern of discharge frequency (I early burst, I decrementing),

- expiratory neurons with an augmenting (E augmenting, or E constant) or with a decreasing discharge pattern (E early or Post-inspiratory neurons).

Intracellular recordings give indication on the time course and intensity of excitatory and inhibitory post-synaptic potentials of the sub-groups of medullary respiratory neurons previously described by extracellular recordings,

Comparing the pattern of the membrane potential trajectories during period of inhibition to the pattern of respiratory neurons firing at the same time, it has been possible to assume how the various subgroups of the respiratory neurons within the network are interconnected (Richter, 1982; Richter et al.1987).

An augmenting pattern of excitatory synaptic inputs was observed in inspiratory ramp (I_R) and late inspiratory (/-I) neurons. Close examination of the membrane potential trajectories permitted to distinguish not only the period at which these neurons received waves of excitatory inputs, and fired, but also the period at which the same neurons received waves of inhibitory inputs, and are silent.

The method to reveal that the period of repolarization of the membrane potentials is due to a wave of active inhibition, is to raise intracellular chloride by passing negative current (ionophoretic injection) through the microelectrode filled with KCl.

This maneuver induced the hyperpolarization to flatten and finally to reverse in a large depolarizing wave of inhibitory post-synaptic potentials by displacing the equilibrium potential of chloride to more positive values. Such reversal of the membrane potentials in expiration (Fig. 2A2) implies the presence of an augmenting and summing pattern of IPSPs during second part of expiration the origin of which is assumed to be the expiratory augmenting neurons firing at this time (Fig. 2B1).

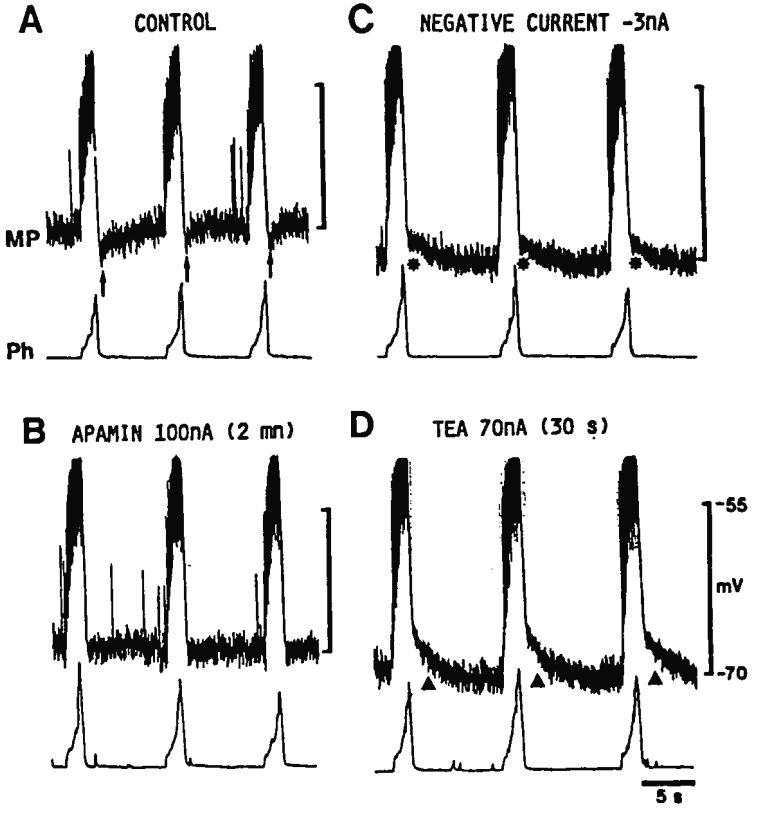

Figure 2: *Membrane potential trajectories of a medullary NAA inspiratory neuron of the VRG during microionophoretic injection in its extracellular environment of apamine and TEA.*

In each panel, MP, membrane potentials; Phr, integrated phrenic nerve activity. A: control condition 2 min after cell impalement, note the large and transient hyperpolarization in post-inspiration. B: extracellular injection of apamine during 2 min. (100 nA) canceled the post-inspiratory period of hyperpolarization. C: intracellular injection of chloride by negative current (3 nA, 2 min) induced a small depolarization by reversal of inhibitory post synaptic potentials. D: extracellular injection of TEA during 30 s. (70 nA) after the chloride injection enhanced the depolarization in the post-inspiratory period. (unpublished results obtained with F. Issa and J.E. Remmers)

It had been proposed the existence of a three phases theory in the respiratory cycle (Richter, 1982), assuming the existence of a phase of passive expiration beginning at end inspiration (called stage I of expiration), followed by a phase of active expiration or stage II expiration.

A second rhythmic patterns of inhibition were related to expiration, during the period which is referred to as post-inspiration, early expiration or stage I of expiration. This stage I expiratory inhibition appears in several of the sub-categories of neurons, and especially in some inspiratory neurons where this inhibition has a very pronouncing decreasing profile.

This post-inspiratory inhibition is the result of inhibitory inputs which are reversed by negative current. It is assumed that this inhibition is coming from the post-inspiratory neurons firing during this period of the respiratory cycle.

However, the inspiratory interruption is not solely the result of this wave of inhibitory input. Indeed it appears that at least in some neurons membrane current conductances are involved. One is TEA sensitive, and could correspond to a potassium voltage-dependent conductance. The other is apamine or EGTA sensitive, and could correspond to a potassium calcium-dependant conductance (Fig 3).

Thus, the interruption of the discharge of inspiratory neurons, the so-called off-switch mechanisms, could be the combination of both synaptic inputs and intrinsic membrane properties of the respiratory neurons.

An augmenting pattern of excitatory synaptic inputs was also observed in expiratory ramp neurons. Close examination of the membrane potential trajectories permitted to distinguish not only the period at which these neurons received waves of excitatory inputs, and fired, but also the period at which the same neurons received waves of inhibitory inputs, and are silent.

Two rhythmic patterns of inhibition were related to inspiration, which developed in this expiratory neurons in early and late inspiratory phases. Indeed, it is possible to observe in the membrane potential trajectory two waves of inhibitory post-synatic potentials which could be reversed by intracellular chloride injection (Fig. 2B2). One in early inspiration, correspond to a rapid onset, decreasing pattern of inhibitory synaptic inputs: it is assumed that this inhibition come from the early inspiratory neurons. A second wave of inhibition appears in late inspiration and exhibits an augmenting pattern indicating that these neurons receive a wave of inhibition coming from the augmenting inspiratory neurons.

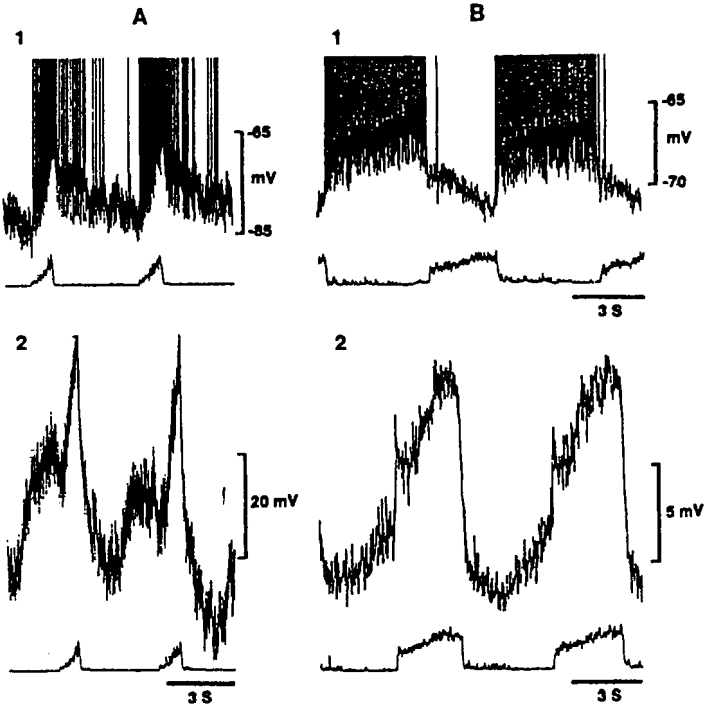

Figure 3: *Membrane potential trajectories of one inspiratory (A) and one expiratory (B) medullary bulbospinal neurons.* A1, B1 control activities just after impalement. A2, B2 changes in membrane potentials after intracellular chloride injection.

Examination of the time-intensity profiles of the state of depolarization of these neurons indicate the presence of a sort of accomodation the origin of which is not yet known. The existence of such a declining pattern of excitatory drive for some respiratory neurons (post-inspiratory and early burst inspiratory we shall see just after) is probably not simply due to synaptic interactions, but it is suggestive of a non-synaptic intrinsic membrane conductance. This behavior suggests the existence of a potassium outward current which is activated by the calcium (I_C current). These neurons are rapidly hyperpolarized in inspiration, and the membrane potential trajectory follows a declining profile. This inhibitory synaptic activity in the post-inspiratory neurons can be reversed by intracellular chloride injection. We can assume that they received waves of inhibitory post-synaptic potentials from the early inspiratory neurones.

Regarding the early burst inspiratory neurons, these neurons exhibit a declining pattern of membrane trajectory in inspiration followed by a rapid repolarization at the end of inspiration. This hyperpolarization can be reversed by intracellular chloride injection indicating the existence of waves of inhibitory post-synaptic potentials. The neurons which are spiking at this time are the post-inspiratory neurons candidate for this inhibition.

The observations of the pattern of synaptic activity of various types of respiratory neurons within the brainstem indicate that they are likely reciprocally interconnected. This observation allows to tentatively explain **that the respiratory rhythm is generated and controlled by a neuronal network rather than cells having pacemaker activity.** Especially, it has been inferred by Richter and his colleagues (1986) that **I early burst** and **post-inspiratory (post-I) neurons** "constitute populations of common inhibitory interneurons with widely divergent outputs to all other neurons within the [respiratory] network".

Putative neurotransmitters have been demonstrated to be involved in this interconnective pathways. The role of excitatory amino acids (glutamate) has been demonstrated in the bulbospinal transmission of the inspiratory drive (McCrimmon et al.1989). Glycine and GABA ($GABA_A$) acting on chloride channels mediate the inhibitory post-synaptic actions (Haji et al.1990). However, a mechanism only based on synaptic interactions is not enough to explain the rhythmic character of respiration. It is likely that additional mechanisms based on intrinsic membrane properties may be involved to organize on-switch and off-switch functions in the neuronal network producing respiratory movement.

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THE ROLE OF THE SAGITTAL ZONE IN CEREBELLAR OPERATIONS

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This presentation explores the premise that the function of the cerebellum is best approached by attempting to understand the operation performed across its structurally homogeneous subdivisions, the cerebellar sagittal zones. Each zone contains a subset of neuronal elements whose projections are topographically organized within this structural unit. These include the projection of Purkinje cells to the cerebellar nuclei, the nucleocortical projection, and the projection of climbing fibers originating from discrete regions within the inferior olive. An hypothesis is developed attempting to reconcile the sagittal organization of these afferent and efferent systems with the widely distributed somatotopy characterizing the mossy fiber projections carrying information from various regions of the body surface and specific descending pathways.

Studies from our laboratory support a heterosynaptic action of climbing fibers on the responses to its other dendrite inputs. This action consists of a short-lasting modification in the gain of Purkinje cell responses to modulated inputs mediated by the mossy fiber-granule cell-parallel fiber system. Specifically, these experiments, which used a variety of passive paradigms in decerebrate cats, demonstrated that there is an enhanced simple spike responsiveness of Purkinje cells following the activation of its climbing fiber input and that this enhancement lasts at most only a few hundred msec.

Multiple single unit recording experiments demonstrated that perturbation of the locomotor cycle results in the synchronous activation of climbing fiber inputs to sagittally-aligned Purkinje cells. Furthermore the modulation of the population's simple spike response to the perturbation was directly related to the fraction of these neurons responding with synchronous complex spikes. Based on these observations and our previous studies reviewed above, the dynamic selection hypothesis was proposed. This view suggests that the activation of sagittally-distributed climbing fiber inputs may spatially select populations of Purkinje cells which will be most highly modulated by mossy fiber inputs distributed across multiple sagittal zones. Because the distribution of the activated climbing fibers would be task-specific, this enhanced modulation would occur in the groups of Purkinje cells most critical to the coordination of the specific movement being performed.

Based on the findings reviewed above and additional data which are inconsistent with the cerebellum serving as a required storage site for the plastic changes produced during motor learning, it is further argued that the cerebellum participates in regulating motor behavior through the real time, on-line integration of inputs characterizing external target space information about the intended movement, the internal representation of body scheme, and the inputs from the periphery and descending pathways.

IS THE CEREBELLUM A LEARNING DEVICE?

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It has been shown that different lesions in the cerebellum can abolish the conditioning of the nictitating membrane response of the rabbitt. So do the lesions of the middle cerebellar peduncle, the dentate and interpositus nuclei, the superior cerebellar peduncle and the inferior olivary complex without affecting the unconditioned response. Similar results have been obtained from studies investigating the vestibulo-ocular reflex, the withdrawal reflex and the conditionied autonomic reflexes.

On the basis of these results it has been proposed that the cerebellum is an esential element in motor learning.

However, in other experiments it has also been shown that these results are probably due to deficits in motor performance rather than motor learning, since also deficits in the unconditioned response were observed after lesions in the cerebellum. Moreover, naive decerebrate rabbits could acquire the conditioned nictitating membrane reflex with inyections of local anesthetics into the cerebellar nuclei during training. It was, therefore, concluded that the cerebellum has an important role in regulating sensorimotor processes which are necessary for the performance of both the unconditioned and conditioned responses.

Finally, experiments performed on decerebrate-decerebellate rabbits have shown that the decerebrate animals that were previously conditioned could execute the conditioned reflex behavior following complete removal of the cerebellum.

In our own experience, it is difficult to adscribe to the climbing fiber system the role of a teacher or instructor of the Purkinke cell, since we found that this system is able to transmit to the cerebellum very precise information about peripheral events, like the mossy fiber system. Working on the decerebrate cat or the awake monkey, we have been able to show that the climbing fiber system can convey to the cerebellum information about position, velocity and acceleration of a passive movement applied to the animal's forepaw as well as the direction of the movement.

In awake monkeys, a similar passive movement could elicit also similar responses. By comparing passive with similar active movements we found that during voluntary movements the sensory feedback information from the periphery via the climbing fiber system was cancelled or strongly reduced and that the same olivary cell responded to the command signal from the motor cortex.

From this type of experiments we concluded that the climbing fiber system seems to be another sensory afferent system like the mossy fiber system. Presumably, the information conveyed by the climbing fiber system is involved in transmitting information about the sensorimotor context from which a precise movement has to start.

NOVEMBER, 29

THALAMIC OSCILLATIONS AND THEIR MODULATION BY BRAINSTEM CHOLINERGIC SYSTEMS

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There are three types of thalamic oscillations occurring during behavioral states of alertness and quiet sleep.

1. The beta (25-40 Hz) oscillation appears during waking immobility while animals are watching a prey and humans perform a complex task. Thalamocortical cells display rhythmic fast prepotentials (FPPs) within the beta frequency range that are either intrinsic or arising in afferent projections. Brainstem cholinergic systems potentiate beta oscillation by acting on muscarinic receptors of cortical-projecting thalamic neurons.

2. The spindle (7-14 Hz) rhythm is the epitome of brain electrical synchronization at sleep onset and is associated with loss of consciousness. It is a synaptically generated oscillation due to the pacemaking properties of GABAergic reticular (RE) thalamic neurons that impose rhythmic IPSPs onto thalamocortical cells, followed by rebound spike bursts transferred to the cerebral cortex. Spindles are blocked upon arousal, mainly by the actions of brainstem cholinergic afferents that decouple the synaptic networks of the spindle pacemaker, the RE nucleus.

3. The delta (0.5-4 Hz) rhythm prevails during late sleep stages. It is an intrinsic oscillation due to the interplay between 2 currents (I_h and I_t) and is generated at more hyperpolarized levels than spindles. Then, I will postulate that a progressive hyperpolarization of thalamic cells with the deepening of sleep accounts for spindling during early stages and delta waves during late stages. While the 0.5-4 Hz oscillation is intrinsically generated in individual thalamic cells, it is potentiated and unrelated thalamic cells become synchronized by corticothalamic volleys engaging RE thalamic neurons. Brainstem cholinergic modulatory systems block this slow oscillation by depolarizing thalamocortical cells, thus bringing them out of the voltage range required for delta genesis.

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MAIN TOPIC: pulvinar-latero posterior complex and goal directed movement.

TITLE : Role of Pulvinar-latero posterior complex of behaving primates in goal directed movements. Comparison with parietal area 5a.

Goal directed movements are voluntary unconstrained arm movements directed to targets situated in the immediate extrapersonal space. Here we present evidence of the participation of the pulvinar-latero posterior (pv-lp) complex of behaving monkeys in *goal directed arm movements*[1,3].

The extracellular unit activity in the pv-lp was recorded in monkeys during the execution of goal directed movements in a previous learned task. Because of area *5a has been related to reaching behavior*[3], the same paradigm was used in area 5a in order to compare the thalamic and cortical responses. A study of area 5a-pv-lp connections at the places of recording was made with HRP-WGA.

The cell discharge of the majority of the pv-lp cells (95/123, 77%) is related *to the movement itself,* but not to the direction of the goal. Only 28/123 (23%) were *goal direction sensitive*. On the contrary, the majority (62/109, 76%) of area 5a cells are *goal direction sensitive,* and only 20/109 (24%) are related *to the movement itself*. The HRP-WGA study revealed that the area 5a and pv-lp places were the activity of these cells were recorded, *are connected together*.

The pv-lp complex would integrate cortical and subcortical information for the execution of visual guided movements. Cortical areas would be more directly related to directional movement information, whereas the pv-lp would belong to a distributed system subserving attentional functions.

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INTERACTIONS OF NEUROTRANSMITTERS IN THE BASAL GANGLIA AND AGING: Studies of amino acids and dopamine.

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The basal ganglia has been the focus of research in relation to the interaction of several types of neurotransmitters (1). In particular, the possible interaction between dopamine and acidic amino acids has been a matter of controversy in recent years(2). In fact, the hypothesis accepted up to very recently was that dopamine, released in the neostriatum through the terminals of the nigrostriatal pathway was inhibitory of the release of glutamate through the corticostriatal pathway (3). This hypothesis has recently been questioned (2).

Based on recent findings it has been hypothetized the possibility that dopamine releases glutamate and/or aspartate through a corticostriato-thalamocortical negative feedback loop (2). In fact our experiments (see in this same issue Exposito et al. 1991) show that dopamine perfused directly into the neostriatum produces a concentration-related release of glutamic acid and also aspartic acid (at the higher concentration) and that this release is blocked by the D1-D2 dopamine receptor blocker haloperidol.

These last experiments coupled with those published by Freeman and Gibson (4) in which a release of dopamine and glutamic acid along with a decrease of acetylcholine is produced in the basal ganglia as a result of aging suggest the possible participation of the cortico-striato-thalamo-cortical circuit in the neurochemical mechanisms underlying aging of the basal ganglia.

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NEURAL CONSTRUCT OF SPACE IN THE PRIMATE FRONTAL LOBE

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In both premotor and motor cortices, individual arm-related neurons are broadly tuned around a preferred direction of movement. This implies that coding of arm movement direction occurs at the population level. Experimental data suggest, in fact, that neuronal movement population vectors (NMPV) describe well the direction of an incoming arm movement.

When arm movements of similar directions are made within different parts of space, in both motor and premotor cortices the cell preferred directions shift their orientation to follow the orientation of the arm in space. This suggests that coding of direction of movement occurs within a coordinate system centered on the shoulder joint and rotating with it. In these conditions, where patterns of muscle activity and joint angles change notably, NMPV do not change their spatial orientation, suggesting that they reflect movement kinematics more than movement dynamics.

These results support the hypothesis that cortical circuits compute the appropriate motor command by combining the visual information about movement trajectory with the proprioceptive one concerning the orientation of the arm in space. This combination can be learned by a neural network during spontaneous movements of the arm. The network, composed of units mimicking cortical columns, learns a computation similar to a bilinear combination of inputs which can predict the invariant properties of neuronal activities in an arm-centered coordinate system.

Synaptic Interactions between Motor Cortex Neurons

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Previous studies have elucidated the response properties and post-synaptic effects of premotoneuronal cells on motoneurons in behaving monkeys[1]. Similar techniques have now been used to study synaptic interactions between motor cortical neurons, as measured by cross-correlating the spike activity of neighboring cells and by spike-triggered averages of membrane potentials[2]. Intracellular studies in neocortical slices have elucidated the relationship between these two measures by showing that excitatory post-synaptic potentials affect firing probability of cortical neurons in two ways: by direct threshold crossing and by turning on an inward current that also shortens the interspike interval[3].

In vivo extracellular recordings in behaving monkeys have documented the response patterns of motor cortex neurons whose synaptic linkages to each other were revealed by cross-correlation[2]. The correlogram feature encountered most often is a central peak, due to common synaptic input to both recorded neurons from the same presynaptic cells or from synchronized inputs. *In vivo* intracellular recordings with spike-triggered averages have provided more sensitive measures of the synaptic potentials mediated by connections between motor cortex neurons[4]. Cells in different cortical layers have excitatory and inhibitory serial connections, but again the most frequent observation is common synaptic input to both cells, particularly in awake monkeys.

A new mode of synchronous activation of large populations of neurons has recently been investigated. In behaving monkeys sensorimotor cortex neurons and local field potentials can exhibit oscillatory activity at 25 - 35 Hz during finely controlled hand movements that require attention and sensorimotor integration[5]. These transient oscillations occur in phase over large cortical regions, suggesting effective recruitment of many neurons into coherent discharge. Intracellular recordings reveal depolarizing potentials during these oscillatory episodes and interspike interval trajectories of some cells suggest an intrinsic tendency to repolarize at 30 - 40 ms.

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THE CORTICOSPINAL SYSTEM: PARALLEL PATHWAYS FOR THE CENTRAL CONTROL OF MOVEMENT

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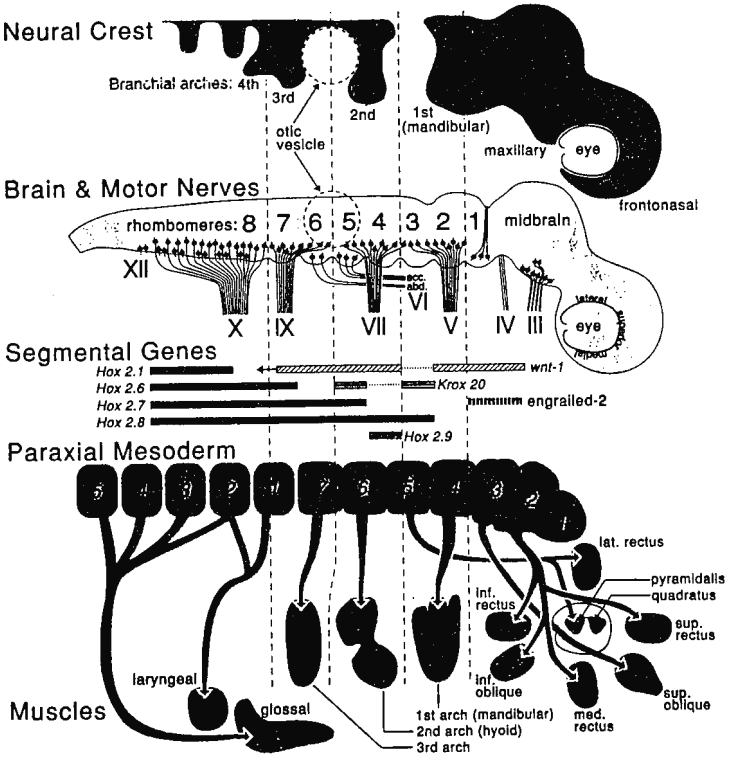
The results of recent studies indicate that *premotor cortex* is composed of multiple, spatially separate 'premotor areas'. Each premotor area receives a unique pattern of inputs from the parietal lobe and from subcortical motor nuclei like the cerebellum and basal ganglia. Furthermore, each promotor area projects not only to the primary motor cortex, but also to the spinal cord. This arrangement provides each premotor area with a 'motor' output which is independent of the primary motor cortex. These findings suggest that the anatomical organization of the premotor areas and the primary motor cortex should be viewed from a new perspective. We propose that these cortical motor areas represent the nodal points for parallel pathways to the spinal cord. Thus, each motor area should be considered as part of a functionally distinct efferent system which may differentially generate and/or control a specific aspect of motor behavior.

THE DEVELOPMENTAL ORIGIN OF MOTOR SYSTEMS IN THE VERTEBRATE CNS. Dr. Robert Baker, Dept. of Physiology and Biophysics, New York University Medical Center, 550 First Avenue, New York, NY 10016

One of the most challenging problems in biology is to identify the developmental mechanisms responsible for the arrangement and interconnections of cells in the vertebrate sensory-motor system. Recent evidence suggests that the hindbrain region consists of a series of nearly identical compartments each acting as a species-typical developmental template underlying the generation of unique neurogenic patterns. According to this scenario each hindbrain compartment (neuromere) is critical for producing a segmentally unique pattern of neurogenesis and subsequently imparting that positional identity upon adjacent paraxial mesoderm through the migration of neural crest derivatives as illustrated in the accompanying figure.



Homeobox genes give rise to a group of sequence-specific DNA-binding proteins that have been implicated as the molecular pre-pattern underlying compartmentalization. At issue, is how the segment-restricted code of Hox gene expression becomes established in the neuronal epithelium and the adjacent migrating neural crest to then impart a Hox-code in cranial ganglia and paraxial mesoderm. The concept of causal instructive interaction between the above autonomous tissue types can be utilized to test the hypothesis that the developmental basis for establishing fundamental vertebrate networks is founded upon early embryonic spatial programming of motoneurons in brain neuromeres coupled with instructive spatial cues available in the muscle-specific template.

POSTERS

NOVEL HYPERPOLARIZATION-ACTIVATED K^+ CURRENT MEDIATES INWARD RECTIFICATION IN CRAYFISH MUSCLE.

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1. The ionic current underlying inward rectification in opener muscle fibres of crayfish was studied under two-electrode voltage-clamp.

2. Hyperpolarizing voltage command pulses from a holding potential of -60 mV evoked an instantaneous voltage-independent linear current (I_L) followed by a time- and voltage-dependent inward current (I_{IR}) which reached a steady-state within 500 ms.

3. The mean reversal potential of I_{IR} (E_{IR}) at an extracellular K^+ concentration ($[K^+]_o$) of 5.4 mM was -61.78 mV. E_{IR} shifted towards positive potentials by 50.78 mV for a tenfold increase in $[K^+]_o$.

4. The conductance underlying I_{IR} (G_{IR}) increased sigmoidally with hyperpolarization, starting close to the RP, saturating at a $G_{IR}max$ of about -140 mV, and showing a mean half-activation at -94.43 mV. The activation curve of G_{IR} shifted 53.56 mV towards positive potentials with a tenfold increase in $[K^+]_o$. $G_{IR}max$ did not increase in raised $[K^+]_o$.

5. The activation and deactivation kinetics of I_{IR} were accurately described by single exponentials with similar time constants (<100 ms). Time constants changed as an exponential function of the membrane potential.

6. I_{IR}, its time course, G_{IR} and E_{IR} were not modified in the following conditions: (1) Na^+- and Ca^{2+}-free solutions, (2) intracellular EGTA, (3) extracellular (100 mM) or intracellular TEA, (4) extracellular Cs^+ (up to 50 mM), Rb^+ (up to 10 mM), Ba^{2+} (13.5 mM) or Mn^{2+} (13.5 mM).

7. Low extracellular concentrations of Cd^{2+} or Zn^{2+} (<5 mM) strongly and reversibly reduced both I_L and I_{IR}.

8. We conclude that inward rectification in crayfish muscle is generated by a voltage- and time-dependent K^+ current I_{IR}. This current displayed many electrophysiological and pharmacological characteristics which distinguish it from all others mediating inward rectification described previously.

This work was supported by DGICYT and CEC grants to W.B. A.A. is a CajaMadrid fellow.

DISCHARGE PATTERNS IN DENTATE NUCLEUS DURING VISUALLY GUIDED STEPPING.

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The dentate nucleus is the output nucleus for the cerebellar hemisphere and there is abundant evidence in man and monkeys that lesion (both permanent and reversible) greatly impairs the accuracy of visually guided movements of the upper limb (Brooks et al, 1973; Miall et al, 1987), which implies an important role for the lateral cerebellum in the control of such movements. Furthermore, some neurones in dentate nucleus and the hemispheral cortex projecting to it exhibit early responses to visual stimuli, and sometimes complex properties in which the behavioural significance of visual inputs appears important (Marple-Horvat & Stein, 1990). Connections to and from dentate nucleus in the cat establish that it is essentially a functional homologue to primate dentate nucleus; there are massive visual cortical projections to the lateral cerebellum via the pontine nuclei (Baker et al. 1976). There is, however, a lack of data regarding unit discharge patterns in dentate nucleus during visually guided forelimb movements in the cat. We therefore record discharges of these neurones in cats trained to walk on the rungs of a horizontal ladder, which requires a high degree of visuo-motor coordination. In addition, two rungs around the ladder can be made to move up or down 3 or 6 cm from the level of the walkway. Rung movement can be made to occur at different times during the cat's approach. Using this mechanism we are able to look at the neural discharges for components related to stepping (limb movement), eye movement (spontaneous, step-related or evoked by the moving rung) and visual stimuli whose significance to the animal can be varied.

We have recorded 33 neurones, 7 of which were identified as cerebellar projection neurones by antidromic stimulation in brachium conjunctivum. Histological verification showed all electrode penetrations passed through dentate nucleus (none through nucleus interpositus). Eight cells discharged rhythmically during normal ladder locomotion.

Twenty-one neurones were tested against the pre-displaceable rung. Several of these showed short latency responses to the visual stimulus of rung movement. This altered discharge can be seen in isolation by subtracting the normal step-cycle related modulation in cells which discharged rhythmically during ladder walking.

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BEHAVIOR OF PREPOSITUS HYPOGLOSSI AND VESTIBULAR NEURONS PROJECTING TO THE ABDUCENS NUCLEUS IN THE ALERT CAT

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Extraocular motoneurons present a burst of activity during rapid eye movements in the pulling direction of the active muscle and a resting frequency proportional to eye position in the orbit. Both, velocity and position signals are thought to be generated in the premotor ocular system. It has been proposed that eye position signal is achieved by the integration of eye velocity signal. Electrophysiological and behavioral studies have pointed out that the integrator is located in the prepositus/vestibular nuclear complex. The goal of this work was to study oculomotor signals carried by both structures to the abducens (ABD) nucleus during spontaneous, vestibular- and visual-induced eye movements. Animals were chronically implanted with stimulating electrodes on the VIth nerve, and with recording and stimulating electrodes in the ABD nucleus. Eye movements were recorded with the scleral search-coil technique. Neural activity and field potentials were also recorded with glass microelectrodes. Neurons in both nuclei were identified by their antidromic activation from the ABD nucleus, the averaged field potentials induced in the ABD nucleus by the recorded spike and their activity during vestibular sinusoidal stimulation.

Vestibular neurons shown an irregular frequency, with a very low position coefficient, during spontaneous and optokinetic eye movements and a phase lag of 90º respect to eye position, during vestibular stimulation. Prepositus hypoglossi neurons were more regular and their activity was highly correlated with eye position in the orbit during all types of eye movements. We propose the prepositus hypoglossi as the nucleus giving the eye position signal to the ABD nucleus.

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INTERACTION OF ACIDIC AMINO ACIDS AND DOPAMINE IN THE BASAL GANGLIA OF THE "IN VIVO" CONCIOUS RAT.

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Previous studies (Carlsson and Carlsson, 1990) have shown that glutamatergic terminals arising from the cerebral cortex terminate in the caudate putamen in the rat. Also dopaminergic terminals exist in the basal ganglia arising from the substantia nigra pars compacta in the mesencephalon. The basal ganglia also contains intrinsic aminoacidergic neurones (Ottersen and Storm-Mathisen, 1984) together with neurones containing acethylcholine, GABA and several types of peptides neurotransmitters among them neurotensin.

Several hypothesis have postulated a possible type of interaction between glutamatergic terminals, and/or neurones and dopaminergic terminals. However, the controversy still remains as to the exact type of this interaction.

In this comunication we present a series of experiments in which the effects of apomorphine, an agonist of dopaminergic receptors, have been perfused directly into the basal ganglia and analyzed its effects on the release of acidic amino acids in the concious rat by means of an "in vivo" "push-pull" perfusion system. In these experiments apomorphine at the doses of 3, 1.5 and 0.75 ug/ml produced a dose-response curve in the release of glutamic acid. Higher doses of 6 and 12 ug/ml produced an inhibitory effect on the release of this same amino acid. Only the dose of 3 ug/ml increased significantly the release of aspartic acid. Paradoxically, the extracellular levels of the main precursor of these acidic amino acids, mainly released from astrocytes, also was increased under the effects of apomorphine. The effects of apomorphine were blocked by the D1-D2 dopamine receptor antagonist, spiroperidol. These results suggest that dopamine directly or indirectly through GABAergic neurones could interact with aminoacidergic neurones and/or terminals in the basal ganglia.

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Postural adjustments in cats during conditioned movements in form of a single step

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The aim of our current research is to study restitutional processes in the sensory motor system of the cat following different types of lesions.

We used the conditioned movement paradigm in order to correlate behavior with neuronal activity in the cerebellar cortex. This was done before and after experimentally applied lesions. The aim of the present study was to obtain evidence for expected changes in the neuronal activity within the cerebellum.

In the behavioral approach, we trained co-operative cats to stand still on four platforms within a pre-defined resting period. The platforms were equipped with strain gauges to monitor the forces produced by each limb. Following a tone signal, the animal had to perform a single step with the forelimb to a fifth platform positioned directly in front of the others. The position of the moving limb was also measured. From the force signals the trajectory of the center of gravity was calculated. Evaluation of measurements from four cats revealed that each cat used its own strategy to perform the step. This could be derived from the individual forms of trajectories which were typical for each animal as well as from the related times and velocities of these signals.

In the electrophysiological approach, we implanted chronically a multi channel recording electrode in the cerebellar cortex. The electrode was inserted into lobule V, which represents the sensory forelimb area of the animal. During the implantation procedure the ipsilateral superficial radial nerve was electrically stimulated and evoked potentials were recorded.

UNITARY ACTIVITY IN THE CAT FRONTAL CORTEX DURING CONDITIONED LOCOMOTION

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The activity of a high proportion of frontal cells in cats changes during locomotion on a moving rubber band. However, this type of motor activity did not require that this portion of the cortex should be intact. Questions thus arise concerning the function of this area. In primates, the frequency changes observed in motor cortex are related with fine finger movements, the modulation of active force and/or the amplitude and direction of visually guided movements. In cats, unitary recordings of frontal neurons show that many of them discharge rhythmically during locomotion; this pattern may be essential for control of the step cycle. Other cells show changes that might not be related with any of the controlled parameters; in such a case, these neurons could be related to more complex locomotor control. Our aim was to demonstrate the participation of frontal cells during preparation for locomotion. For this purpose, frontal unitary activity was recorded in two cats previously trained to walk on an exercise belt running at a speed of 0.5 m/sec and to follow an experimental protocol in which the walking and rest periods were conditioning by perception of an auditory stimulus.

The results show that in 38 frontal cells recorded (group A), the frequency of discharge under control conditions was 28 Hz. This value increased during the period following the perception of an auditory stimulus, eventhough neither an evoked potential nor movement were present. Thirteen neurons decreased their activity (group B) and 5 did not show any change (group C). Some of the neurons (31) included in group A increased their discharge frequency even more during the first 1500 ms of locomotion, thereafter returning to lower values.

These observations show that some frontal cortical neurons change their discharge frequency prior to the start of locomotion. This suggests a possible role of these cortices in preparation for movement. The observed effect of an increase in discharge during the beginning of locomotion could be a prolonged preparatory effect or could be related to the start of the locomotion program.

TWO EXAMPLES OF INTEGRATIVE PROCESSES: (I) DIPOLE LOCALIZATION DURING HUMAN VISUAL SELECTIVE ATTENTION AND (II) A MODEL OF POSSIBLE MECHANISMS OF RESPONSE SELECTION IN RATS

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Individuals must finally integrate the neural activities and produce an unified behavior. Attention and goal directed behavior are two processes clearly related with the unifying of action.

In the attentional paradigm the neural generators underlying the visual event related potentials have been inferred using voltage maps, current source density maps and dipole localization during a task that involved selective attention to specific location of the visual field. The dipole localization technique modelled the N70 component as a tangential dipole situated contralateral to the stimuli in a location that could be coherent with the calcarine fissure. The subsequent components were localized in areas that could be considered as extraestriate (In collaboration with Steve Hillyard, Department of Neuroscience, San Diego).

In the response selection process a mathematical model of competition between neural nets is proposed. The model proposes that the neural network controlling the lever pressing response during variable-interval schedules of reinforcement should compete with all the other behavior-controlling networks. The network with the highest activity would be expressed as a behaviour by a winner-take all mechanism. This theoretical model fits the interresponse time distributions.

BEHAVIOR OF NEURAL ELEMENTS OF THE RESPIRATORY NETWORK DURING REFLEXES INVOLVING RESPIRATORY MUSCLES.

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The rhythmic alternating contractions of the diaphragm and abdominal muscles, the main respiratory muscles, induces airflow within the lungs. However, these muscles also appear as essential in the realization of common expulsive behaviors such as coughing and vomiting.

During vomiting, the alternating activations of the inspiratory phrenic (cervical rootlets, C4-C6) and expiratory abdominal (lumbar rootlets, L1-L3) nerves, which innervate the diaphragm and the abdominal muscular wall respectively, are converted into a series of large co-activations also observed on some of the upper airway motor nerves. During these synchronous large bursts, the inspiratory bulbospinal neurones (IBSNs), which normally transmit the central respiratory drive to the phrenic motoneurones, are strongly hyperpolarized by waves of chloride-dependent inhibitory post-synaptic potentials. These results might suggest that during vomiting the respiratory central pattern generator (CPG) is inhibited. However, the inspiratory interneurones, possibly involved in the generation of the respiratory rhythm, exhibit a different behavior which evolves in two stages. First, throughout the early part of vomiting (e.g. the retching phase), their membrane potentials stay nearly constant indicating likely that these interneurones are disfacilitated, then, they exhibit a large depolarization during the expulsive phase. The latter observation suggest that some neural elements of the respiratory CPG might be involved in the realization of a motor activity which cannot be developed simultaneously with breathing.

During coughing, the activity of the phrenic nerve is also changed. The duration, the rate of rise and the amplitude of the phrenic discharge, compared with that observed during breathing, are drastically increased. Intracellular recordings of IBSNs during coughing revealed that these premotoneurones are strongly activated and exhibit a high frequency of discharge. Such an activation of IBSNs was also observed during the single or rhythmic buccopharyngeal stages of swallowing induced by activation of the laryngeal afferents. The mechanical significance of the latter behavior is still unknown.

The question which arises from our results is to determine if the neural elements of the respiratory CPG which are activated during a reflex are really essential for its accomplishment or if they follow passively the activation of another CPG. This point is fundamental since the former hypothesis implies that a single neurone of the mammalian CNS could belong to different networks and thus, serve to the realization of several motor activities.

BEHAVIOR OF BRAIN STEM AND CEREBELLAR NUCLEI NEURONS DURING EYE RETRACTION IN THE ALERT CAT

AGNES GRUART I MASSO

The activity of identified accessory abducens motoneurons (Acc Abd Mns) and brain stem and cerebellar nuclei neurons were recorded in the alert cat paradigm. Animals were implanted with scleral and palpebral stainless-steel coils. Eyelid and rotational and retractional eye movements were recorded with the search-coil technique. Animals were also implanted with stimulating electrodes on the left abducens nerve and in the levator palpebrae (LP) subdivision of the oculomotor complex. Recordings were carried out with glass micropipettes using a transcerebellar approach. Quantifiable stimuli of vestibular, visual, acoustic and trigeminal origin were applied and correlated to firing rate of recorded neurons.

Main results were as follows: i) Acc Abd Mns fired a high frequency burst during eye retraction, but showed no noticiable activity at the intervals; they were not activated from the LP electrode; ii) following cytotoxic destruction of lateral rectus muscle fibers and of the Abd Mns innervating them, putative Acc Abd Mns showed an increased firing rate during eye retraction and also the appearance of some tonic activity in absence of eye retraction;iii) reticular neurons located around the Acc Abd area and below the main Abd nucleus responded to air-puff stimulation and to one or more of the following stimuli: vestibular rotation, optokinetic stimulus and sounds of several frequencies. Acoustic, trigeminal or visual stimuli strongly blocked the neural response to any other stimulus for 150-200 msec. Most of these neurons were antidromically and/or synaptically activated from the LP electrode; and iv) neurons located in the fastigial and in the medial part of the interpositus nucleus also fired in response to air-puff stimulation and/or to acoustic stimuli. These cells were antidromically activated from the LP electrode. Neurons described in iii) and iv) could be related to the conditioning of the nictitating membrane response.

NEURONES IN LAMINA 7 AND 8 OF THE TURTLE SPINAL CORD: Ca^{++}-MEDIATED PLATEAU POTENTIALS.

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Here we identify a plateau generating subgroup of neurones in lamina 7 and 8 of the spinal cord. Intracellular recordings in this region were carried out in an in vitro preparation of the lumbar enlargement of turtle spinal cord from a total of 155 neurones. Based on the response pattern evoked by depolarizing current pulses these neurones were divided into two groups.

In one group consisting of 75 neurones, adaptation or steady firing was seen, together with a hyperpolarization following the pulse. Plateau potentials were not seen in these cells. Among the 80 plateau generating neurones forming the other group, some cells fired with increasing frequency during the pulse, while a plateau potential was recruited in others before the onset of steady firing. In more than half of the plateau generating cells the pulse was followed by a voltage sensitive afterdepolarization. This afterdepolarization sometimes exceeded spike threshold to sustain firing beyond the duration of the pulse. The plateau potential was insensitive to TTX but blocked by nifedipine and by Co^{++}.

It is concluded that complex active membrane properties as represented by plateau potentials are found in many of the cells that, based on their location in the grey matter close to the motor nuclei, presumeably constitute an important part of the turtle spinal motor system.

SYNAPTIC INFLUENCES OF PYRAMIDAL AND CORTICOSPINAL COLLATERALS OVER RETICULOSPINAL NEURONS IN THE CAT*.

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Data were obtained from 25 cats anaesthetized with α-chloralose (60 mg/Kg, i.p), artificially respired, and paralyzed (Pavulon 1mg/Kg/h, i.v). Pyramidal (PTNs) and corticospinal (CSNs) neurons were extracellularly recorded within the intermediate precruciate motor cortex and identified by stimulation of the ipsilateral pyramids (PT) ,ventrally approached at mid-bulbar level, and the contralateral dorsolateral funiculus (DLF) at C_2 level. The entire cerebellum was suctioned to expose the floor of the fourth ventricle, and micropipettes for intracellular recording of reticulospinal cells (ReSNs) were introduced into the nucleus reticularis gigantocellularis (nRG) contralaterally to the recording in the motor cortex. ReSNs were antidromically identified by stimulating the ipsilateral ventromedial funiculus at C_3. In order to detect pyramidal and corticospinal collaterals to the nRG, a fine tungsten microelectrode was introduced together with the recording micropipette (tips separation about 300 μm). When a pyramidal or corticospinal cell, spontaneously active, was isolated from the recording in the cortex, stimulation of the contralateral nRG was achieved to search for collateral branches. A total of 56 pyramidal non-corticospinal cells sent their axons to or through the nRG, which represented 21% (56/268) of tested. A similar percentage of corticospinal axons (29/136 or 21.3% of tested) sent branches to nRG. In order to study the postsynaptic effects of both PTNs and CSNs on ReSNs, two procedures were followed and compared: a) electrical stimulation of both PT and DLF, and b) the rising phases of the spontaneous pyramidal and corticospinal spikes were used to trigger an averager whose input was the intracellular signal recorded in the nRG. Comparison of results obtained using both methods demonstrated that while the total of corticospinal collaterals detected (n=10) produced monosynaptic excitatory potentials (EPSPs) upon reticulospinal neurons, the pyramidal non-corticospinal cells elicited disynaptic (n=8) and monosynaptic (n=4) EPSPs. In no case did we find monosynaptic inhibitory potentials.

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J.A.Lamas is a fellow of the FPI program (Spain).

PLASTICITY OF THE GOLDFISH VESTIBULO-OCULAR REFLEX. Angel M. Pastor. Lab. de Neurociencia. Dept. de Fisiología y Biología Animal. Universidad de Sevilla. 41012 Sevilla. Spain.

The Vestibulo-Ocular reflex (VOR) is subjected to long-term plastic changes that can be induced by altered visuo-vestibular interactions. Examination of the eye velocity profile in response to a step of head velocity reveals the presence of an early "dynamic" component followed by a "sustained" response. Modifications of the VOR gain (the eye to head velocity ratio) using velocity steps as the training paradigm produces robust changes in both phases of the step response that have differential sensitivities to cerebellectomy. Thus, acute cerebellectomy after VOR modifications reveals that part of the dynamic response is retained whereas the sustained response returns close to the pretrained levels. Training after long-term cerebellectomy shows that the dynamic response can no longer be modified; but moderate changes can be observed in the sustained component. The shortest latency changes of the eye velocity profile in response to the step argues for a site of plasticity located in the vestibular nucleus that requires an intact cerebellar machinery to attain VOR modifications.

In order to determine how activity in the vestibulo-cerebellum contributes to the adaptive process Purkinje cells were recorded during periods of VOR modification. The simple spike data revealed that Purkinje cells altered their response in parallel to the eye velocity changes. However, the simple spike sensitivity measured separately in relation to both head and eye movements did not changed for periods of training up to 24 hrs that involved eye velocity changes of up to 64°/s. It is concluded that the cerebellum functions as a parallel pathway of the VOR that supports the eye velocity change, but the variable gain element is not the Purkinje cell postsynaptic membrane.

SOMAESTHETIC PROJECTION TO THE MOTOR CORTEX MEDIATED BY THE SPINOTHALAMIC SYSTEM. J.L. RELOVA. Departamento de Fisiología, Facultad de Medicina, Universidad de Santiago. 15705 Santiago de Compostela. Spain.

The motor cortex receive short latency somaesthetic responses. As this projection constitute the afferent link of a peripheral feedback onto the cells at the origin of the motor cortical efferent pathways which control the limb musculature, it might play an important functional role in continuosly updating the motor command, particularly during the performance of precise manipulatory movements. However, the ascending pathway involved in transmitting the sensory messages to the motor cortex has been a matter of debate due to controversial experiments, and it has still not been unanbigously identified.

In a previous series of experiments using intracellular recording techniques using intracellular recording techniques it was shown that, after excluding all the *classic* inputs to the motor cortex, the cells at the origin of the corticospinal pathway could still be excited and/or inhibited by electrical or natural stimulation applied to the limbs. The motor cortical area was isolated from its cortico-cortical connections, the cerebellum was isolated also and, in addition, a transverse section of the dorsal half of the spinal cord excluded the dorsal columns and the spinocervical tract. The only surviving pathway which could transmit the sensory responses to the motor cortex was identified as a component of the spinothalamic system.

The thalamic region of this pathway was delineated subsequently using electrophysiological methods involving field potenctial mappings of the antidromic responses after motor cortex stimulation and postsynaptic responses after stimulating the spinothalamic system ascending in the spinal cord.

This particular somaesthetic pathway may be an essential part of the sensory-motor integration system allowing a fast correction of the motor command during ongoing movements so as to precisely fit the physical and temporal characteristics of the environment.

MORPHOLOGICAL AND PHYSIOLOGICAL EFFECTS OF TARGET REMOVAL ON ADULT CAT ABDUCENS INTERNUCLEAR NEURONS

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The degree of dependence of adult central nervous system neurons on trophic retrograde influences was evaluated following specific target removal. Abducens (ABD) nucleus internuclear neurons (Ints) represent a good model for such a purpose, as they innervate almost exclusively the medial rectus (MR) motoneurons (Mns) subdivision of the oculomotor nucleus. MR Mns death was induced by means of a single injection of Ricinus communis agglutinin II into the MR muscle. This toxic ricin produced a complete and specific Mn death within 2 days, leaving ABD Int presynaptic axon terminals uninjured. Adult cats were prepared for chronic recording of extracellular single unit activity and eye movements. ABD Ints were identified following their antidromic activation from the contralateral medial longitudinal fasciculus. The electrical activity of ABD Ints following target removal showed several abnormalities and a significant reduction in their firing-related parameters, i.e., their sensitivities to eye position and eye velocity. However, after a critical period of abnormal behavior (15-20 days), ABD Ints recovered their typical discharge pattern which continued normal up to 1 year later. Morphological analysis of the ABD nucleus at different times following MR Mns lesion showed no evidence of either ABD Int loss or cell degeneration. The anterograde tracing of biocytin has demonstrated that the axonal terminations of the ABD Ints remain in location up to 1 year following target removal, with absence of sprouting toward other subdivisions within the oculomotor nucleus. The labelling of the terminals at different survival times revealed a progressive reduction in the density of boutons, which was especially low 1 year after target removal. It can be concluded that ABD Ints continue alive and functionally active in the absence of their target MR Mns.

PHYSIOLOGY AND PHARMACOLOGY OF VESTIBULAR INPUTS TO IDENTIFIED ABDUCENS MOTONEURONS AND INTERNUCLEAR NEURONS IN FROGS

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Anatomy: The principal abducens nucleus of frogs consits of about 75 motoneurons (ABMOT) that project via N.VI to the lateral rectus muscle. Following injection of HRP into the oculomotor nucleus a subpopulation of about 30-40 interneurons within the pool of contralateral ABMOT was labeled retrogradely. Injection of H^3-leucine into the abducens nucleus resulted in anterograde labeling of axon terminals within the contralateral oculomotor nucleus. Thus, these interneurons represent most likely abducens internuclear neurons (ABINT) that project to the contralateral oculomotor nucleus.

Physiology and Pharmacology: Synaptic vestibular inputs of ABMOT and ABINT were studied in the isolated brain following antidromic identification by electrical stimulation of the ipsilateral N.VI and of the contralateral Ncl. III, respectively. Conduction velocities of ABMOT ranged between 0.45 and 2.55 m/s (N = 48) and of ABINT between 1.45 and 2.2 m/s (N = 10). Stimulation of the contralateral N. VIII evoked disynaptic EPSPs in ABMOT (N = 41) and ABINT (N = 10). The times to peak were very similar in both groups of neurons (ABMOT: 5.48 ms ± 3.10; ABINT: 5.99 ms ± 2.98).

Stimulation of the ipsilateral N. VIII evoked disynaptic IPSPs in most of the ABMOT (N = 35 out of 41) and in all ABINT (N = 10). Rise times of IPSPs were very similar again (ABMOT: 6.83 ms ± 3.20; ABINT: 6.25 ms ± 1.59). These IPSPs were blocked by the addition of 50 µM strychnine to the bath (N = 8). This effect was reversible as evidenced by a partial recovery of IPSPs subsequent to the washout of strychnine. Bath application of the GABA antagonist picrotoxin (100 µM) had no significant effect on these IPSPs (N = 5), suggesting that they were mediated by a glycinergic compound. Ongoing experiments indicate that the EPSPs are mediated by a glutamatergic compound.

In few ABMOT (N = 6) stimulation of the ipsilateral N. VIII evoked disynaptic EPSPs instead of IPSPs with times to peak (5.44 ms ± 0.57) similar to those evoked by stimulation of the contralateral N. VIII. These ipsilateral EPSPs are unlikely to represent reversed IPSPs, since their reversal potential is at about 0 mV (N =2) and their amplitude is strychnine insensitive (N = 1).

In vivo, abducens motoneurons can be activated by horizontal angular as well as by horizontal linear acceleration. This excitation originates in both cases in the contralateral labyrinth, i.e. in hair cells of the horizontal canal and of the macula utriculi, as evidenced by recordings in hemilabyrinthectomized frogs. The uncrossed excitation might originate in the ipsilateral macula utriculi. Its functional role for the linear vestibulo-ocular reflex is unclear at present.

MEMBRANE AND FIRING PROPERTIES OF NEONATAL AND ADULT RAT BRAINSTEM MOTONEURONS. Félix Viana, Douglas E. Bayliss and A.J. Berger. Department of Physiology & Biophysics, University of Washington School of Medicine, Seattle, WA 98195.

The firing behavior of mammalian motoneurons results from the interplay between synaptic inputs and intrinsic electrical properties defined by various ionic conductances. Since generation of tension by muscle fibers is determined by the pattern and frequency of discharge of innervating motoneurons, a detailed knowledge of the ionic basis of repetitive firing is a necessary step in understanding the neural basis of movement (i.e. behavior). We chose to approach this problem from a developmental perspective, by characterizing the changes that occur in the firing behavior of motoneurons during maturation of the neuromuscular system.

We used a brainstem slice preparation to record intracellularly from rat hypoglossal motoneurons (HMs) during different stages of postnatal development (P0 to P12 and adult). These motoneurons innervate the muscles of the tongue. HMs were identified by their location and/or by antidromic stimulation. Some motoneurons were also labeled intracellularly with biocytin. Compared to adult, neonatal HMs were characterized by lower rheobase current, lower input conductance and a more linear current-voltage relationship. The increase in the time and voltage-dependent sag (anomalous rectification) in adult HMs was associated with the development of an inward current that resembled the I_h current in other neurons (i.e. slow activation with hyperpolarization, absence of inactivation, block by extracellular Cs^+ and unaffected by Ba^{2+}).

At the earliest age studied (~12 hours postnatal) HMs were already capable of firing repetitively in response to current injection. Firing was blocked by application of the sodium channel blocker TTX. The level of holding potential greatly influenced the firing behavior of neonatal HMs. From a depolarized potential the response to a positive current pulse was characterized by steady tonic firing. A negative prepulse modified the pattern to an early burst of action potentials riding on a slow depolarization, followed by steady repetitive firing. The amplitude of the slow depolarizing envelope was dependent on the duration and amplitude of the negative prepulse, insensitive to TTX and blocked by zero Ca^{2+}, suggesting that a low-threshold Ca^{2+} conductance contributed to burst behavior in neonatal HMs. Such bursting was not observed in adult HMs.

The action potential of HMs was followed by an afterdepolarization (ADP) and a two phase afterhyperpolarization (AHP). After repetitive firing a third, slower time course AHP was sometimes observed. The ADP was specially prominent in young motoneurons. This ADP was voltage-dependent, increasing from negative holding potentials. It was reduced in zero Ca^{2+} and enhanced by high Ca^{2+} and by Ba^{2+}. Bath application of TEA (1 to 10 mM) caused a dose-dependent prolongation of the action potential and a blockade of the fast AHP. The medium AHP was calcium dependent; it was reduced in zero Ca^{2+} and blocked by apamin, ω-conotoxin and Ba^{2+}. The duration of the mAHP decreased from more than 100 ms in the neonate to about 75 ms in adult HMs. The contribution of the mAHP to slow repetitive firing was also investigated. Blockers of the mAHP caused a strong increase in peak firing frequency and in the slope of the f-I relationship at steady state.

Calcium currents in neonatal HMs were characterized using whole-cell patch-clamp recordings in thin medullary slices. Calcium currents were isolated using a combination of potassium and sodium channel blockers. Depolarizing steps from about -100 mV evoked a transient, low-voltage activated (LVA) calcium current. The LVA calcium current inactivated fully at holding potentials positive to -60 mV. This current was selectively attenuated by 1mM amiloride. Stronger depolarizations evoked a larger calcium current (HVA). The HVA calcium current had both inactivating and non-inactivating components. A fraction of this HVA current was sensitive to 1 μM ω-conotoxin.

In conclusion, we report alterations in the subthreshold and firing behavior of rat HMs during postnatal development. These changes are likely due to modifications in the expression and/or characteristics of several ionic conductances in HMs with age, and serve to match the firing frequency of the motoneurons with the mechanical properties of the developing muscle.

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ORGANIZATION AND SYNAPTIC CONNECTIONS OF PREMOTOR NEURONES RELATED TO VERTICAL SACCADIC EYE MOVEMENTS IN THE CAT. Shwu-Fen Wang and Robert F. Spencer, Department of Anatomy, Medical College of Virginia, Richmond VA 23220, U.S.A.

Premotor neurones that control different types of eye movements (saccadic, vestibulo-ocular, optokinetic, smooth pursuit, and vergence) differ on the basis of brainstem location and involvement in horizontal versus vertical movements. Morphological, physiological, and clinicopathologic studies have established that the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) is the location of premotor neurones that control vertical upward and downward saccadic eye movements. Toward the goal of delineating an intrinsic organization of neurones in the riMLF, microinjections of biocytin have been made in different regions of this nucleus and the soma-dendritic distribution of labelled synaptic endings in relation to vertical *upward* [superior rectus (SR) and inferior oblique (IO)] and *downward* [inferior rectus (IR) and superior oblique (SO)] motoneurones in the oculomotor and trochlear nuclei has been examined by light and electron microscopy. Injections confined to *rostral* regions of the riMLF label synaptic endings that target predominantly *IR and SO* motoneurones. By contrast, injections confined to *caudal* regions of the riMLF label synaptic endings that target predominantly *SR and IO* motoneurones. Projections to SO motoneurones are predominantly *ipsilateral*, while those to IR and SR motoneurones are *bilateral*. In all cases, two populations of synaptic endings are labelled: presumed inhibitory synaptic endings that contain pleiomorphic synaptic vesicles and establish symmetrical synaptic contacts, and presumed excitatory synaptic endings that contain spheroidal synaptic vesicles and establish asymmetric synaptic contacts. Both populations of synaptic endings overlap in the same motoneurones subgroups. The mode, pattern, and soma-dendritic distribution of riMLF synaptic inputs to vertical motoneurones differ from those previously established for the inhibitory and excitatory second-order vestibular inputs. Furthermore, the organization of riMLF projections to vertical motoneurones differs from the characteristic reciprocal inhibitory and excitatory synaptic connections in the vertical vestibular or horizontal eye movement system.

A RELATIONSHIP BETWEEN OLIVO-CEREBELLAR ACTIVITY AND SKILLED MOVEMENT AS REVEALED BY MULTI-ELECTRODE RECORDING OF PURKINJE CELLS IN THE AWAKE RAT.

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It is generally agreed that the inferior olive plays a fundamental role in some aspect of motor function, even though the precise nature of that role is unresolved. Although "motor control" can be generally conceived to be a continuous function, essential at all times for all movements, many hypotheses envision the function of the inferior olive to be discontinuous, arising *only* after particular sensory events or during motor learning. Another hypothesis is that the inferior olive has a continuous role in the control of movement that derives from its persistently rhythmic activity and direct access to motor systems through the cerebellum (Llinás, 1970). Specifically, it has been hypothesized that the inferior olive serves as a clocking element that continuously modulates motoneurons so that muscle groups can be recruited quickly and synchronously any time that behavior is required. In order to test this hypothesis, new paradigms and modifications of the multiple electrode recording technique (Sasaki *et al*, 1989) were developed to permit the recording of complex spikes in arrays of Purkinje cells in rats while they performed highly skilled movements of the tongue.

Rats were trained to protrude their tongues 7 mm in response to a 750-ms, 2-kHz tone in order to receive 40 μl of water. Training was accomplished with a procedure that employed 6 days of autoshaping and up to 70 days of operant conditioning. Increasing lengths of tongue protrusion were shaped by successive approximation during the operant phase. Mouth opening and tongue protrusion occurred in a highly coordinated, stereotypic, and repetitive fashion following tone onset, with both movements demonstrating robust 6-7 Hz rhythms that persisted for up to 1500 ms after the first mouth opening. Complex spikes (CSs) within cerebellar folium Crus IIa were recorded extracellularly with glass microelectrodes from rats prepared for the simultaneous recording of up to 45 Purkinje cells over a 2 mm^2 surface of the cortex.

In 2 rats trained to protrude their tongues in response to the tone there was a dramatic increase in the probability of CSs occurring after the tone and before the movement. The average probability of any Purkinje cell firing a CS 30-80 ms after tone onset was 13% for the trained rats and 4% for a naive control rat. Summing across all of the trials, 3 different frequencies of CS activity (range 6-11 Hz) occurred in distinct populations of Purkinje cells following the initial occurrence of CSs after the tone. The resonant frequencies of these 3 populations of cells were partially coherent, the superposition of which indicated a rhythmic 6.5 Hz activity in the ensemble. This ensemble rhythm was highly correlated to (r=0.67) and maintained a constant phase relationship with repetitive tongue protrusions such that CS probability increased 10-30 ms after the tongue reached the target. The activity was not necessarily the consequence of contacting the target because oscillatory activity of the ensemble continued to occur for up to 700 ms after the final contact.

These results support the hypothesis that the inferior olive operates continuously and in real-time in order to ensure the proper coordination of movement. We propose that olivary rhythmicity is reset by descending premotor systems prior to skilled movement and that, following resetting, subpopulations of olivary neurons with different resonant frequencies oscillate in a partially coherent manner so as to confer upon ensembles of Purkinje cells a rhythmic output that complements the demands of the motor task.

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Sasaki, K., Bower, J.M. & Llinás, R. (1989). Multiple purkinje cell recording in rodent cerebellar cortex. *Eur J Neurosci*, 1, 572-586.

CONCLUSIONS

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The Juan March Foundation meeting on the neural control of movement in vertebrates lived up to expectation! Hardly a channel, voltage or ligand, was mentioned throughout the three days and nearly all the discussion centered around the neuronal processing of sensory-motor information. A different central theme was addressed on each day of the meeting and the speakers blended their particular experimental insights into a colligative tutorial agenda.

Clearly oscillatory pacemaker activity and stimulus coding characterized the firts day. In the very firts invertebrate presentation, Buño reviewed the central afferent/efferent control of a beautiful, segmentally organized motoneuronal pool in which inhibitory fiber frequency enhances position detection by regulating stretch receptor set-point. In essence, long before the appearance of real vertebrates, all the necessary ionic conductances were present and they were nicely packaged within the appropriate synaptic circuitry. Bass distinguished between the phylogenetic and ontogenetic traits that underlie vertebrate rhythmic behavior. At issue was how the CNS might be put together from the genetic vs epigenetic construct. The viewpoint that small changes in the timing of constant genetic events could produce even larger changes in behavior was put forward and defended well.

The above evolutionary points were placed into context by Grillner who schematized the circuitry underlying lamprey locomotion. Adding in the intrinsic membrane properties led to an unavoidable contemplation of central pattern generation. Subsequent discussion generated the opinion that 'it (the CPG) exists because it must" and concluded with "should it be of concern at the moment". According to Burke, both the analysis and circuitry in the mammalian spinal cord is the same after 40 years; however, neuronal processing is being viewed quite differently these days. More credence is now given to the ubiquitous role of the 'interneuron' as the significant player. The central pattern generator still appeared ephemeral in the ensuing discussion.

When the disciplinary topic moved to the vestibulo-oculomotor system it became apparent that all of the neurons necessary for eye movements have been recorded, analyzed and shelved (Delgado-García and Highstein). By use of classical techniques, Cheron placed particular oculomotro behaviors into different brain areas. For all three advocates, the assumption was explicit that some intrinsic order exists to perform precise eye movement. In the discussion, each attempted to generate the most efficient construct of circuitry and intrinsic properties to explain eye movement; however, nature, quite resolutely, has not yet chosen to reveal any sifnificant principle of design. Did the difficulty experiments obtain too simple answers? Or the reverse? The portent of this uncertainty anticipated the second day.

The neural basis for orienting movements and adaptivo mechanisms was thoroughly reviewed by Berthoz, Shinoda and Guitton. Clearly at issue from the outset was the concept of 'multiple' neuronal compartments and axon collaterals at different hindbrain and spinal levels. Actually each of these speakers, in their own context, elaborated on the precise organization of networks without much concern as to either genetic or epigenetic organization. For example, to demonstrate how the superior colliculus might provide the brainstem with a signal specifying only the vector of a gaze movement, Guitton delineated a replicating pattern of tectal and hindbrain neuronal elements. Berthoz corroborated this plan and illustrated a computation loop within the colliculus to produce gaze shifts. Shinoda elaborated on the topic of neuronal targeting within multiple compartments, but also did not pursue any causal rationale. Although most of these interpretations were found tobe, in general, pausible, at issue was how to further understand the structural/functional organization of gaze-related neurons, given the limit of current experimental tools? This point was particulary salient after Bianchi's description of the rhythmical 'gaze/burst-like' discharge properties for respiratory neurons. The generation and control of respiratory movement was portrayed to be largely the result of distributed properties that convert tonic drives into oscillation. Comparisons between brainstem motor systems (respiration, eye, head, vibrissae and locomotion) were extensively debated and few discussants agreed on which system exhibited the most robust compartmental organization in the vertebrate hindbrain.

Late in the afternoon, Bloedel and Rubia addressed the timely, and controversial, question of how the cerebellum operates and whether it might participate in learning. The demonstration of the point-to-point climbing fiber projections onto Purkinje cells overlain by the fractured mossy fiber somatotopy was, as usual, memorable. The necessity for such somatotopy to co-ordinate transformations from the sensory to the motor motric was argued well, but closure has not yet been reached. The discussion centered on the apparent (in fact, real) multiple zonal organization underlying the structural heterogeneity of the cerebellum. This overcomplete desing was proposed to reflect either new or branching zonal compartments that are manifestations of phylogeny. Although it was argued that cerebellar circuitry shows little evolutionary change, the point had little bearing on whether the cerebellum could learn. Both speakers stressed the real time characterization of sensory inputs and agreed to the absence of cerebellar memory traces (no LTP, LTD, ITO, etc.). Climbing fiber afferents to the cerebellum were envisioned to represent a geometry predicting the context of movement as opposed to the detection of features. If such CF signals accompany all events, the what might be then interaction with the Purkinje cells, and for what purpose? The subsequent discussion closely paralleled, and occasionally, challenged the presenters biases. In the end, the means by which the cerebellum actually regulates sensory/motor metrics again proved elusive. Certainly the third day would be decisive.

From the outset, the three types of thalamic oscillations observed during the behavioral states of alertness

and quiet sleep were at the forefront of the discussion. Steriade's evidence for spindling to originate from reticular thalamic neurons was presented as overwhelming, but at issue was the autonomy of the trait and its suffciency to deactivate the cortex. Later, Acuña expounded on the role of the pulvinar in execution tasks and the clear pan-directionality of neuronal responses begged the question of "who drives who"; nevertheless, Steriade's scheme remained clear. Subsequent focus was on the delta waves, conceived of as the putative interplay between, largely, only two currents. Cortical-thalamic pathways were proposed to synchronize the thalamic slow waves and brachial meso-pontine multisensory inputs to block the slow oscillation. The overiding message was - 'inhibition is essential' for all thalamic behaviors. Discussion arose as to the nature of sleep and extended from roles in consolidating memories to include whether the behavior itself might have been an inopportune selection (not just a waste of time!). The identification of neuronal response types *vis a vis* afferent/efferent projections to delineate putative non-specific activity was debated, and of course, so also, was the specious attributes of interpretations from single species. Many noted that all the preceding excellent caveats are extensively and frequently used in the study of gaze. Any lingering physiological impressions where diluted by Mora's enumeration of transmitter candidates in the basal ganglia. Characterization of biochemical machinery is rendered best in cartoon fashion, and this reductionist approach was favored by everyone. Neurochemists are acutely aware that many more neuronal phenotypes exist in the brain than any physiologist would admit to (at this meeting). Excitatory amino acid release patterns were thought to be intriguing, albeit unexplainable, within the context of behavior. No one, at least at the moment, questioned this contention.

The concluding set of speakers reminded everyone that the cerebral cortex may be coincident with the final motor command site (?). Strick pointed out that the pre-motpr cortex is composed of multiple, spatially separate, pre-motpr areas that may, or may not, exhibit similar behavior. Fetz's videotape, showing synchronous activation of large populations of neuorns exhibiting oscillatory activity at 25-35 Hz, suggested, but did not prove, that such multiple areas may be coherent in their read-out. At least, the rhythmical activity (a resonance?) may be combinatorial in the sense that each area alone may be necessary, but not sufficient for a particular sensory-motor behavior. How migth space be represented, abstractly or absolutely? Caminiti argued for a body-centered co-ordinate hypothesis (ie. shoulder for arm/hand motion) in which cortical cells predict movement directions. Collectively, these neurons are Carlesian in reference frame, but not easily correlated to either body or space. The nature of extrinsic/intrinsic reference frames generated a lengthy, vociferous discussion that even included the world of art, but at least in the latter case, opinions were unanimous - the 'eye of the artist' prevails!

In sumary, all 20 presentations at this meeting focussed in common on the structure/function specifity of given neuronal types based on their intrinsic properties and activity profile in defined synaptic circuits. Quite possibly, with the

exception of the thalamus, the meeting's conclusions were dominated by the idea of hierarchic, multiple representations - especially in respect to axonal targets, neuronal phenotypes and the compartmental organization of circuits. The final speaker alluded to such 'iterative components' as phylogentic endpoints that clearly were of natures desing, but certainly arrived at in clear disregard to any efficiency of neuronal construct (ie. the result of ratcheting neurons into behavior). Dissimilarities between compartments represent developmentally-sculpted remnants of that species mutational history. This outcome is exactly that expected from the separate embryological origin of tissues wherein neuronal phenotypes, museles and their unique geometrical representations are all independently derived. What does all of this mean? Don't ever think about replaying the master tape leading to the generation of vertebrate diversity!

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Workshop on
NEURAL CONTROL OF MOVEMENT IN VERTEBRATES

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240 **Genetic Strategies in Development.**
Symposium in honour of Antonio García Bellido. Lectures by S. Ochoa, S. Brenner, G. S. Stent, E. B. Lewis, D. S. Hogness, E. H. Davidson, J. B. Gurdon and F. Jacob.

244 **Course on Genome Evolution.**
Organized by E. Viñuelas. Lectures by R. F. Doolittle, A. M. Weiner/N. Maizels, G. A. Dover, J. A. Lake, J. E. Walker, J. J. Beintema, A. J. Gibbs, W. M. Fitch, P. Palese, G. Bernardi and J. M. Lowenstein.

246 **Workshop on Tolerance: Mechanisms and implications.**
Organized by P. Marrack and C. Martínez-A. Lectures by H. von Boehmer, J. W. Kappler, C. Martínez-A., H. Waldmann, N. Le Douarin, J. Sprent, P. Matzinger, R. H. Schwartz, M. Weigert, A. Coutinho, C. C. Goodnow, A. L. DeFranco and P. Marrack.

247 **Workshop on Pathogenesis-related Proteins in Plants.**
Organized by V. Conejero and L. C. Van Loon. Lectures by L. C. Van Loon, R. Fraser, J. F. Antoniw, M. Legrand, Y. Ohashi, F. Meins, T. Boller, V. Conejero, C. A. Ryan, D. F. Klessig, J. F. Bol, A. Leyva and F. García-Olmedo.

248 Beato, M.:
Course on DNA - Protein Interaction.

249 **Workshop on Molecular Diagnosis of Cancer.**
Organized by M. Perucho and P. García Barreno. Lectures by F. McCormick, A. Pellicer, J. L. Bos, M. Perucho, R. A. Weinberg, E. Harlow, E. R. Fearon, M. Schwab, F. W. Alt, R. Dalla Favera, P. E. Reddy, E. M. de Villiers, D. Slamon, I. B. Roninson, J. Groffen and M. Barbacid.

251 **Lecture Course on Approaches to Plant Development.**
Organized by P. Puigdoménech and T. Nelson. Lectures by I. Sussex, R. S. Poethig, M. Delseny, M. Freeling, S. C. de Vries, J. H. Rothman, J. Modolell, F. Salamini, M. A. Estelle, J. M. Martínez Zapater, A. Spena, P. J. J. Hooykaas, T. Nelson, P. Puigdoménech and M. Pagès.

252 **Curso Experimental de Electroforesis Bidimensional de Alta Resolución.**
Organizado por Juan F. Santarén. Seminarios por Julio E. Celis, James I. Garrels, Joël Vandekerckhove, Juan F. Santarén y Rosa Assiego.

253 **Workshop on Genome Expression and Pathogenesis of Plant RNA Viruses.**
Organized by F. García-Arenal and P. Palukaitis. Lectures by D. Baulcome, R. N. Beachy, G. Boccardo, J. Bol, G. Bruening,

J. Burgyan, J. R. Díaz Ruiz, W. G. Dougherty, F. García-Arenal, W. L. Gerlach, A. L. Haenni, E. M. J. Jaspars, D. L. Nuss, P. Palukaitis, Y. Watanabe and M. Zaitlin.

254 **Advanced Course on Biochemistry and Genetics of Yeast.**
Organized by C. Gancedo, J. M. Gancedo, M. A. Delgado and I. L Calderón.

255 **Workshop on The Reference Points in Evolution.**
Organized by P. Alberch and G. A. Dover. Lectures by P. Alberch, P. Bateson, R. J. Britten, B. C. Clarke, S. Conway Morris, G. A. Dover, G. M. Edelman, R. Flavell, A. Fontdevila, A. García-Bellido, G. L. G. Miklos, C. Milstein, A. Moya, G. B. Müller, G. Oster, M. De Renzi, A. Seilacher, S. Stearns, E. S. Vrba, G. P Wagner, D. B. Wake and A. Wilson.

256 **Workshop on Chromatin Structure and Gene Expression.**
Organized by F. Azorín, M. Beato and A. A. Travers. Lectures by F. Azorín, M. Beato, H. Cedar, R. Chalkley, M. E. A. Churchill, D. Clark, C. Crane-Robinson, J. A. Dabán, S. C. R. Elgin, M. Grunstein, G. L. Hager, W. Hörz, T. Koller, U. K. Laemmli, E. Di Mauro, D. Rhodes, T. J. Richmond, A. Ruiz-Carrillo, R. T. Simpson, A. E. Sippel, J. M. Sogo, F. Thoma, A. A. Travers, J. Workman, O. Wrange and C. Wu.

257 **Lecture Course on Polyamines as modulators of Plant Development.**
Organized by A. W. Galston and A. F. Tiburcio. Lectures by N. Bagni, J. A. Creus, E. B. Dumbroff, H. E. Flores, A. W. Galston, J. Martin-Tanguy, D. Serafini-Fracassini, R. D. Slocum, T. A. Smith and A. F. Tiburcio.

258 **Workshop on Flower Development.**
Organized by H. Saedler, J. P. Beltrán and J. Paz Ares. Lectures by P. Albersheim, J. P. Beltrán, E. Coen, G. W. Haughn, J. Leemans, E. Lifschitz, C. Martin, J. M. Martínez-Zapater, E. M. Meyerowitz, J. Paz-Ares, H. Saedler, C. P. Scutt, H. Sommer, R. D. Thompson and K. Tran Thahn Van.

259 **Workshop on Transcription and Replication of Negative Strand RNA Viruses.**
Organized by D. Kolakofsky and J. Ortín. Lectures by A. K. Banerjee, M. A. Billeter, P. Collins, M. T. Franze-Fernández, A. J. Hay, A. Ishihama, D. Kolakofsky, R. M. Krug, J. A. Melero, S. A. Moyer, J. Ortín, P. Palese, R. G. Paterson, A. Portela, M. Schubert, D. F. Summers, N. Tordo and G. W. Wertz.

260 **Lecture Course Molecular Biology of the Rhizobium-Legume Symbiosis.**
Organized by T. Ruiz-Argüeso. Lectures by T. Bisseling, P. Boistard, J. A. Downie, D. W. Emerich, J. Kijne, J. Olivares, T. Ruiz-Argüeso, F. Sánchez and H. P. Spaink.

261 **Workshop The Regulation of Translation in Animal Virus-Infected Cells.**
Organized by N. Sonenberg and L. Carrasco. Lectures by V. Agol, R. Bablanian, L. Carrasco , M. J. Clemens, E. Ehrenfeld, D. Etchison, R. F. Garry, J. W. B. Hershey, A. G. Hovanessian, R. J. Jackson, M. G. Katze, M. B. Mathews, W. C. Merrick, D. J. Rowlands, P. Sarnow, R. J. Schneider, A. J. Shatkin, N. Sonenberg, H. O. Voorma and E. Wimmer.

263 **Lecture Course on the Polymerase Chain Reaction.**
Organized by M. Perucho and E. Martínez-Salas. Lectures by D. Gelfand, K. Hayashi, H. H. Kazazian, E. Martínez-Salas, M. Mc Clelland, K. B. Mullis, C. Oste, M. Perucho and J. Sninsky.

264 **Workshop on Yeast Transport and Energetics.**
Organized by A. Rodríguez-Navarro and R. Lagunas. Lectures by M. R. Chevallier, A. A. Eddy, Y. Eilam, G. F. Fuhrmann, A. Goffeau, M. Höfer, A. Kotyk, D. Kuschmitz, R. Lagunas, C. Leão, L. A. Okorokov, A. Peña, J. Ramos, A. Rodríguez-Navarro, W. A. Scheffers and J. M. Thevelein

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Organized by T. A. Springer and F. Sánchez-Madrid. Lectures by S. J. Burakoff, A. L. Corbi-López, C. Figdor, B. Furie, J. C. Gutiérrez-Ramos, A. Hamann, N. Hogg,

L. Lasky, R. R. Lobb, J. A. López de Castro, B. Malissen, P. Moingeon, K. Okumura, J. C. Paulson, F. Sánchez-Madrid, S. Shaw, T. A. Springer, T. F. Tedder and A. F. Williams.

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Organized by J. M. Mato and J. Larner. Lectures by M. V. Chao, R. V. Farese, J. E. Felíu, G. N. Gaulton, H. U. Häring, C. Jacquemin, J. Larner, M. G. Low, M. Martín Lomas, J. M. Mato, E. Rodríguez-Boulan, G. Romero, G. Rougon, A. R. Saltiel, P. Strålfors and I. Varela-Nieto.

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