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Downbeat nystagmus associated with damage to the medial longitudinal fasciculus of the pons: a vestibular balance control mechanism via the lower brainstem paramedian tract neurons

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ABSTRACT

The paramedian tract (PMT) neurons, a group of neurons associated with eye movement that project into the cerebellar flocculus, are present in or near the medial longitudinal fasciculus (MLF) in the paramedian region of the lower brainstem. A 66-year-old man with multiple sclerosis in whom downbeat nystagmus appeared along with right MLF syndrome due to a unilateral pontomedullary lesion is described. In light of these findings, a possible schema for the vestibular balance control mechanism circuit of the PMT neurons via the flocculus is presented. Damage to the PMT neurons impaired the elective inhibitory control mechanism of the anterior semicircular canal neural pathway by the flocculus. This resulted in the appearance of anterior semicircular canal-dominant vestibular imbalance and the formation of downbeat nystagmus.

From the pathogenesis of this vertical vestibular nystagmus, the action of the PMT neurons in the vestibular eye movement neuronal pathway to maintain vestibular balance was conjectured to be as follows. PMT neurons transmit vestibular information from the anterior semicircular canals to the cerebellum, forming a cerebellum/brainstem feedback loop. Vestibular information from that loop is integrated in the cerebellum,

inhibiting only the anterior semicircular canal neuronal pathway via the flocculus and controlling vestibular balance.

1. Introduction

The tegmentum on the dorsal side of the pons and medulla contains the paramedian pontine reticular formation (PPRF) and the medial longitudinal fasciculus (MLF), which are associated with eye movement control. The MLF, which is located dorsally to the PPRF, is a fiber bundle that traverses the medial region of the brainstem tegmentum and forms an important pathway for signal transmission associated with eye movement. Through it pass fibers that connect the main eye movement-related regions of the brainstem, including fibers projecting from the vestibular nucleus to the oculomotor nucleus.

Morphological studies have also shown the dense presence in the MLF and its vicinity of the cell groups of the paramedian tract that project into the cerebellar flocculus [1]. These floccular projecting neurons are known as paramedian tract (PMT) neurons.

Animal experiments have shown that these PMT neurons code vertical eye position signals accurately. They are also believed to play an important role in connecting with the neural integrator that maintains eye position or gaze holding [2]. They also receive strong excitatory input from the anterior semicircular canal, and they are believed to

exert an important action in maintaining vestibular balance via the cerebellar flocculus [2].

Clinically, it has been reported that damage to the brainstem tegmentum causes damage to these neurons resulting in the appearance of vertical nystagmus [3, 4]. It is now known, however, that PMT neurons exert an important action in controlling vertical eye movement, suggesting that symptoms may appear as a result of damage to PMT neurons in the MLF and its vicinity [2].

A clinical case of downbeat nystagmus corresponding to the vestibular balance control mechanism, based on the knowledge obtained from the animal experiments described above, is reported.

2. Report of a case

A 66-year-old man had been diagnosed with multiple sclerosis at age 60 years, and he experienced a flare-up of his symptoms, such as oscillopsia and diplopia on left gaze while driving his car.

Neurologically, right failure of adduction and left monocular nystagmus on abduction

were evident, with convergence maintained. Right MLF syndrome was diagnosed on the basis of these findings. Nystagmus was not induced during fixation, and infrared camera observation in darkness in the absence of fixation showed vertical nystagmus of both eyes with a downward rapid phase. This nystagmus intensified particularly when the eye position was rightward or downward. No other neurological signs were evident.

Cranial magnetic resonance imaging (MRI) revealed fresh plaque in the right pontine tegmentum from the superior cerebellar peduncle to the inferior cerebellar peduncle level (Fig. 1A, B). Since no MLF lesion was evident on MRIs done prior to the one shown in the figure, this was regarded as a new lesion that had recently appeared. The multiple sclerosis was treated with steroid pulse therapy (1,000 mg methylprednisolone daily for 5 days), and the patient was subsequently started on interferon-β. The nystagmus disappeared after steroid therapy, but only mild failure of adduction of the right eye persisted. An MRI image three months later showed that the lesion had shrunk.

Electronystagmography was performed for detailed testing of the vertical nystagmus. Measurements were made using a direct-current (DC) recording electronystagmograph (First, Tokyo, Japan). Vertical eye movements of the left and right eyes were measured

separately on monocular recordings. Results of eye movement tests were sampled and analyzed using a data acquisition and analysis system (PowerLab, AD Instruments, Castle Hill, Australia) at 1 kHz.

Electronystagmography in darkness in the absence of gaze identified downbeat nystagmus, in which a downward rapid phase appeared after upward drift of the eye. The nystagmus waveform of the upward slow phase exhibited a linear course (Fig. 2).

3. Comment

In the present case, MRI revealed fresh demyelinated lesions in the pontine tegmentum, and MLF syndrome was present, suggesting damage to the MLF on one side and the PMT neurons in its vicinity. This caused the appearance of downbeat nystagmus, which presupposes impaired vestibular balance in the vertical direction.

Animal experiments have shown that PMT neurons receive strong excitatory input from the opposite anterior semicircular canal via the vestibular secondary neurons [2]. Experiments using muscimol, which has a selective inhibitory effect on cell bodies without affecting nerve fibers, also showed that damage to PMT neurons induced

downbeat nystagmus in which the slow phase demonstrated exponential change [2]. This finding indicated that anterior semicircular canal-dominant vestibular balance impairment also appeared at the same time as impaired eye position maintenance (Fig. 3B). PMT neurons thus also play an important role in vestibular balance control.

Among the vertical vestibular oculomotor reflex pathways, the cerebellar flocculus exerts inhibitory control over the anterior semicircular canal pathway, and it is known to have no effect on the posterior semicircular canals [5]. This mechanism of floccular selective control may therefore be involved in fast vestibular balance control.

The direction of vertical nystagmus in both this case and nystagmus induced by damage to the medial lower brainstem was the same as that induced by anterior semicircular canal-dominant vestibular balance impairment after damage to PMT neurons in animal experiments. It was thus probably due to the same mechanism. This mechanism of vestibular balance impairment was conjectured to be as follows. A slow upward phase is formed due to damage to the PMT neurons that receive excitatory input from the anterior semicircular canals via the cerebellar flocculus, and a rapid downward phase appears in compensation (Fig. 3B). It has yet to be demonstrated

electrophysiologically whether PMT-floccular projections are excitatory or inhibitory. However, the fact that, in our animal experiments, a similar pattern of downbeat nystagmus with upward drifts was observed in both experiments involving PMT neuron damage and those involving damage to the cerebellar flocculus suggests that PMT-floccular projections may be excitatory (Fig. 3B) [2, 6].

There is also a contrasting neuron group in both the nucleus of Roller and the nucleus intercalatus on the medullary side of the lower brainstem that receives input from the posterior semicircular canals and projects into the cerebellar flocculus [7-10]. Damage that mainly affects this neuron group results in the formation of nystagmus in which the slow phase is downward, and upbeat nystagmus ultimately appears (Fig. 3C) [7-10].

As we have previously reported, PMT neurons in the abducens nucleus rostralis comprise a functionally uniform neuron group with an upward ON direction. They do not include any neurons with a downward ON direction [2]. This characteristic sets them apart from other regions involved in ocular movement control, such as the interstitial nucleus of Cajal, the vestibular nucleus, and the prepositus hypoglossal nucleus. These regions contain neurons with opposing ON directions, such as up and

down. The reason that all PMT neurons have an upward ON direction and form a functionally uniform neuron group may be that these neurons are associated with the mechanism of selective inhibitory control of the anterior semicircular canals by the flocculus. Damage in this region impairs the eye position maintenance mechanism, and, on the basis of animal experiments, this would be expected to result in the appearance of gaze-evoked nystagmus or downbeat nystagmus with a slow phase that had an exponentially decreasing velocity with impairment of neural integration due to the PMT lesion. In the present case, however, this did not occur. The difference between this patient and the results of animal experiments probably arose because the symptoms observed in this patient were not the result of unilateral damage, but were due to the extent of PMT damage. Because PMT neuron damage was partial, it had only a weak effect on the overall mechanism of eye position maintenance, causing little change in the slow phase of nystagmus. This was probably why the slow phase did not change from a linear to an exponential relationship in qualitative terms.

In an analysis of 33 patients with torsional-vertical nystagmus and internuclear ophthalmoplegia (INO) due to MLF damage, in 3 patients with pontine lesions,

downbeat nystagmus was observed only in the eye on the same side as the lesion [11]. In experiments involving what was regarded as unilaterally localized PMT neuron damage, however, nystagmus appeared bilaterally rather than unilaterally [2].

The reason for the appearance of bilateral nystagmus, rather than unilateral nystagmus resulting from MLF damage, is that when only the PMT neurons are damaged and there is no damage to the MLF fibers, an action is exerted on the IIIrd nerve nuclei via the flocculus, as described below [2]. The PMT neurons project ipsilaterally into the flocculus, and the flocculus projects ipsilaterally into the vestibular nucleus [12–14]. Unilateral PMT neuron damage thus acts on the ipsilateral flocculus and subsequently acts on the ipsilateral anterior semicircular canal system vestibular nuclei from the flocculus. The anterior semicircular canal system vestibular nuclei then act on the oculomotor neurons of the IIIrd nerve nuclei, finally acting on the superior rectus muscle of the eye on the side with PMT damage and the inferior rectus muscle of the contralateral eye to produce bilateral upward slow drifts [15]. When damage from pontine lesions encompasses not only MLF fibers but also the PMT neurons, bilateral downbeat nystagmus may be observed.

One presumed possible explanation as to why downbeat nystagmus is not seen more often with INO is that when PMT neurons are damaged, the decrease in stimuli to the flocculus Purkinje cells reduces the inhibition of vestibular secondary neurons by Purkinje cells (Fig.3B). This simultaneously leads to an increase in excitatory input to the PMT neurons via the vestibular secondary neurons. This brainstem-cerebellar-brainstem feedback loop might contribute to the compensation of the vestibular imbalance, which is induced by the damage of PMT neurons in and around the MLF.

This case report suggests that PMT neurons may also play an important role in the vertical vestibular balance control mechanism in humans. The symptoms of downbeat nystagmus resulting from lesions in the ponto-medullary tegmentum of the lower brainstem may be masked and overlooked if the nystagmus occurs concurrently with MLF syndrome, and caution is required in clinical practice.

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FIGURE LEGENDS

Fig. 1. Cranial MRI images

Axial T2-weighted images from the abducens nucleus of the ponto-medullary sulcus to the rostral pons

Fig. 1A shows the pons at the level of the superior cerebellar peduncle. Fig. 1B shows the pons at the level of the inferior cerebellar peduncle. A high-intensity plaque lesion is evident in the right paramedian region adjacent to the fourth ventricle of the pontine tegmentum. This lesion includes the MLF. R: right, L: left.

Fig. 2. Electronystagmography (DC recording)

Vertical eye movement from monocular recordings of the right and left eyes in darkness in the absence of fixation

The top rows show vertical eye position, and the bottom row shows the speed of eye movement.

RV: Vertical eye movement of the right eye. LV: Vertical eye movement of the left eye.

Downbeat nystagmus is evident, with the induction of downward eye movement

forming a rapid phase after upward eye movement (slow phase).

Fig. 3. Diagram illustrating the mechanism of vestibular balance control by brainstem neurons projecting into the cerebellar flocculus, and the pathogenesis of nystagmus if these are damaged

P: Purkinje cells, G: granule cells, PMT neurons: paramedian tract neurons. White squares (□) denote excitatory neurons, and black squares (■) inhibitory neurons. The plus sign indicates excitation, and the minus sign inhibition. The sizes of the plus and minus signs denote the strength of their actions.

Fig. 3A. Vestibular balance control mechanism by brainstem floccular projecting neurons

PMT neurons receive excitatory input from the anterior semicircular canals via vestibular secondary neurons and project into the cerebellar flocculus in an excitatory fashion. Neurons in both the nucleus of Roller and the nucleus intercalatus that receive input from the posterior semicircular canals also project into the cerebellar flocculus.

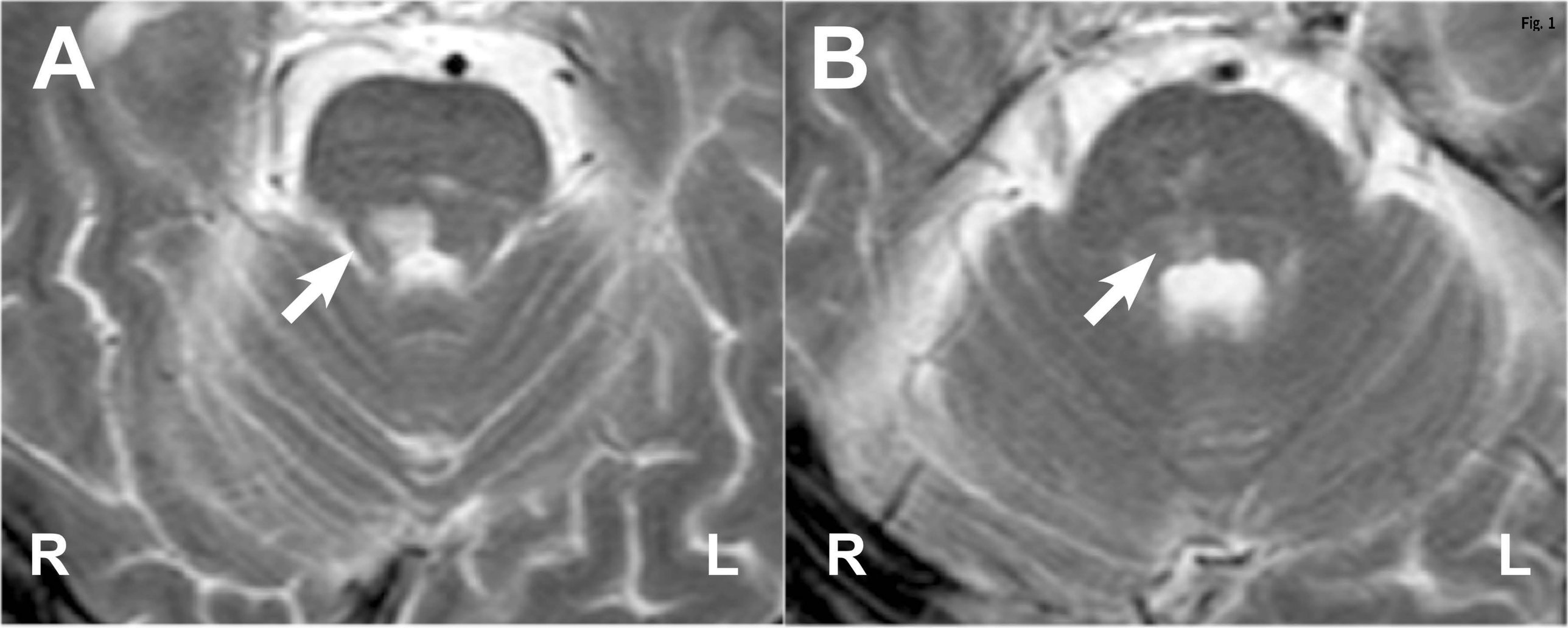
Vestibular information from the anterior and posterior semicircular canals is input into the cerebellum via the group of brainstem floccular projecting neurons. This input information is then integrated in the cerebellum, and commands for maintaining appropriate vestibular balance are transmitted from the flocculus to the motor neurons of the extraocular muscle via the anterior semicircular canal neuronal pathway.

Fig. 3B. Damage to brainstem floccular projecting neurons that receive excitatory input from the anterior semicircular canals

When PMT neurons are damaged, the decrease in stimuli to the flocculus Purkinje cells reduces the inhibition of vestibular secondary neurons by Purkinje cells. This leads to increased activity of the external ocular muscle motor neurons that excite the superior rectus muscle and decreased activity of the motor neurons that excite the inferior rectus muscle, causing the appearance of upward eye movement that forms the slow phase. In compensation for this eye movement, a rapid phase of downward eye movement appears, and downbeat nystagmus occurs through the repetition of this process.

Fig. 3C. Damage to brainstem floccular projecting neurons that receive excitatory input from the posterior semicircular canals

When the group of neurons in both the nucleus of Roller and the nucleus intercalatus is damaged, the process is the opposite of that illustrated in Figure B, with increased Purkinje cell activity in the flocculus inhibiting the activity of vestibular secondary neurons in the anterior semicircular canals. This leads to the appearance of downward eye movement that forms the slow phase. In compensation for this eye movement, upward eye movement appears that constitutes the rapid phase of upbeat nystagmus [7-10].


A
R
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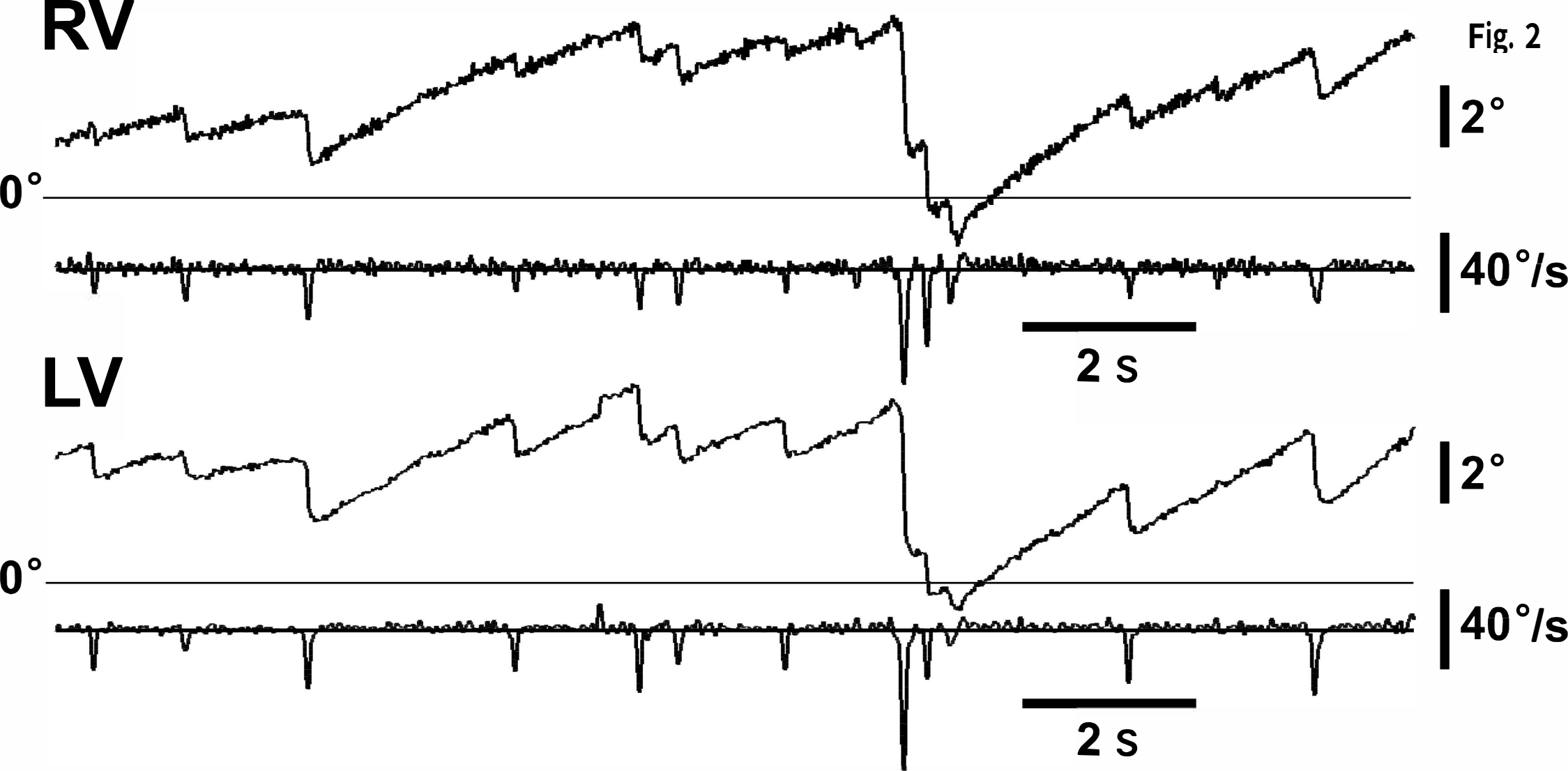
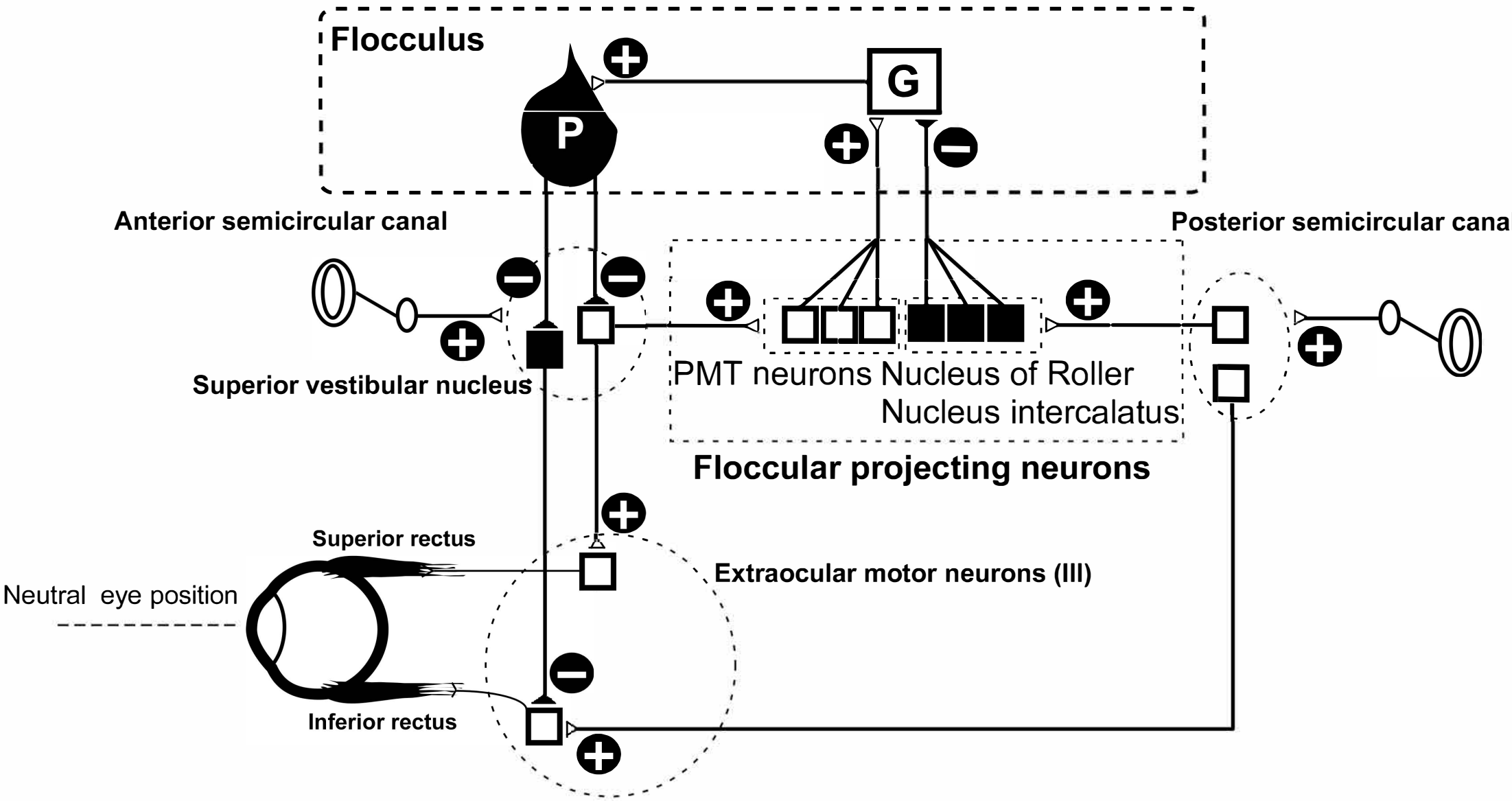


Fig. 2

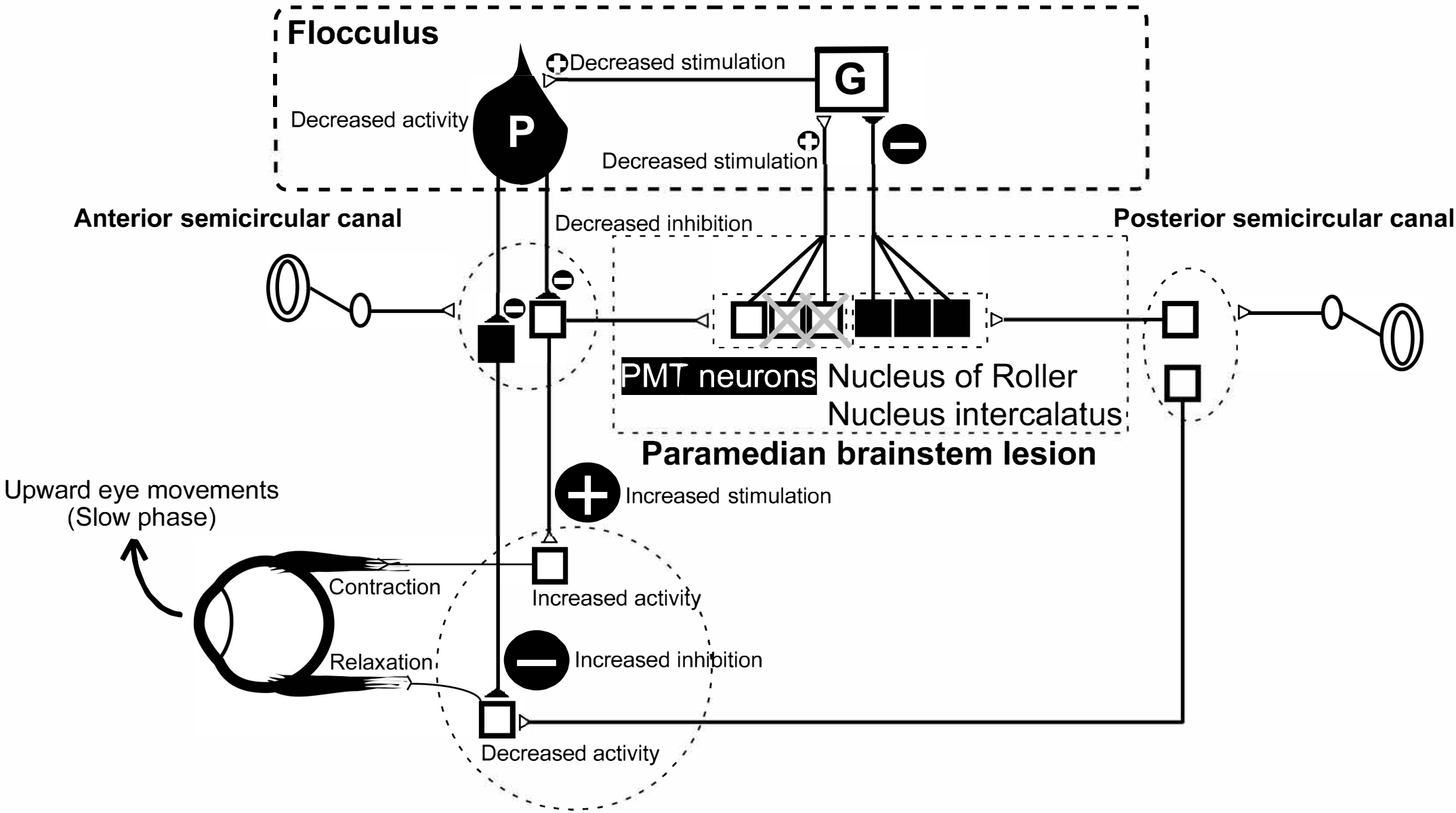
Fig. 3

A


Flocculus
P
G
Anterior semicircular canal
Posterior semicircular canal
Superior vestibular nucleus
PMT neurons Nucleus of Roller
Nucleus intercalatus
Floccular projecting neurons
Superior rectus
Extraocular motor neurons (III)
Neutral eye position
Inferior rectus

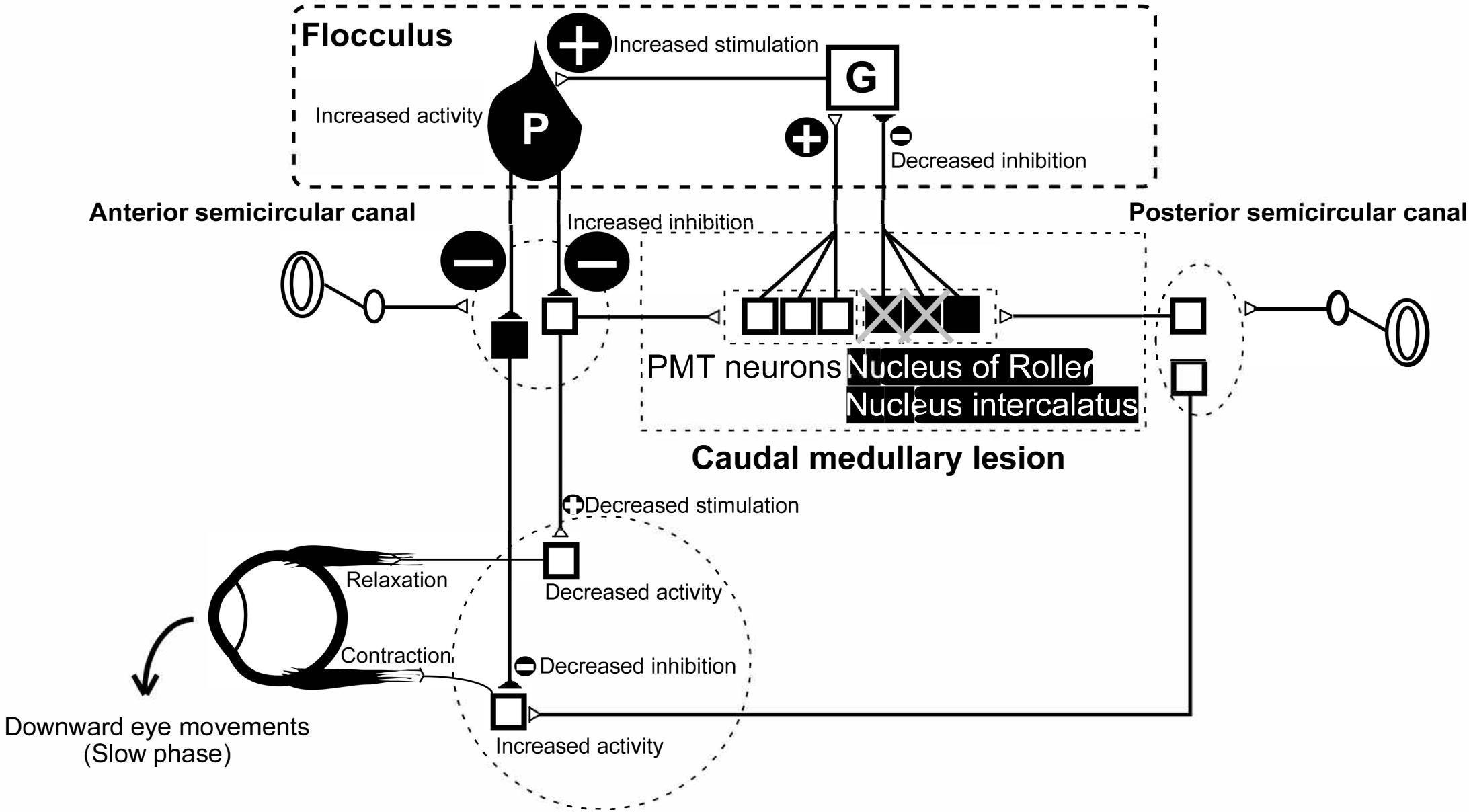
B

Fig. 3


Flocculus
Decreased stimulation
G
Decreased activity
P
Decreased stimulation
Anterior semicircular canal
Decreased inhibition
Posterior semicircular canal
PMT neurons
Nucleus of Roller
Nucleus intercalatus
Paramedian brainstem lesion
Upward eye movements
(Slow phase)
Increased stimulation
Contraction
Increased activity
Relaxation
Increased inhibition
Decreased activity

C

Fig. 3


Flocculus
Increased stimulation
G
Increased activity
P
Decreased inhibition
Anterior semicircular canal
Increased inhibition
Posterior semicircular canal
PMT neurons
Nucleus of Roller
Nucleus intercalatus
Caudal medullary lesion
Decreased stimulation
Relaxation
Decreased activity
Contraction
Decreased inhibition
Increased activity
Downward eye movements
(Slow phase)