Diagnosis and current treatment of nystagmus and other ocular motor disorders

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Disclosures

Michael Strupp, MD, FANA, FEAN, is Joint Chief Editor of the Journal of Neurology, Editor in Chief of Frontiers of Neuro-otology and Section Editor of F1000. He has received speaker's honoraria from Abbott, Actelion, Biogen, Eisai, GSK, Hennig Pharma, Pierre-Fabre, MSD, TEVA, and UCB.

Learning objectives

To correctly diagnose and treat the different forms of

1) nystagmus

- **spontaneous nystagmus**
  - **peripheral vestibular spontaneous nystagmus**
  - **central fixation nystagmus, e.g., downbeat nystagmus**
- **other forms**
  - **gaze-evoked nystagmus**
  - **positioning/positional nystagmus**
  - **head-shaking nystagmus**

2) central ocular disorders

with a correct topographic anatomical diagnosis:

- **brainstem (mesencephalon, pons, medulla)**
- **cerebellum (flocculus, nodulus, vermis, fastigial nucleus)**

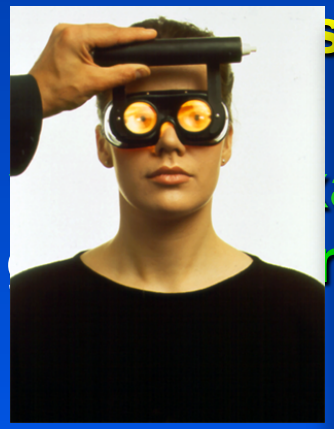
Different types of nystagmus

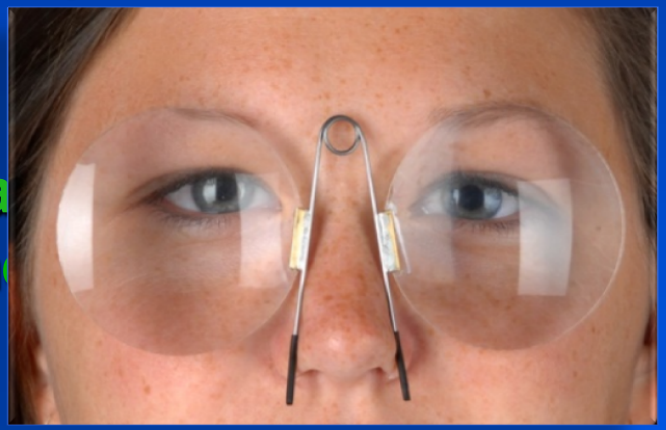
- spontaneous nystagmus
  - peripheral vestibular spontaneous nystagmus
  - central fixation nystagmus, e.g. downbeat nystagmus

- other forms
  - gaze-evoked nystagmus
  - positioning/positional nystagmus
  - e.g., head-shaking, hyperventilation or pressure-induced nystagmus

Nystagmus: clinical examination

Examination	Findings (examples)
1) with fixation: nystagmus:	Central fixation
- gaze straight ahead	Downbeat/upbeat,
acquired nystagmus	pendular, congenital
- to the side, up-, downward	Gaze-evoked
2)	Peripheral vestibular spontaneous nystagmus



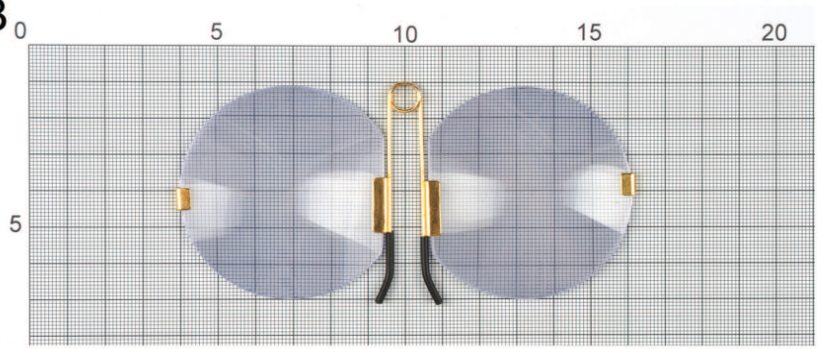


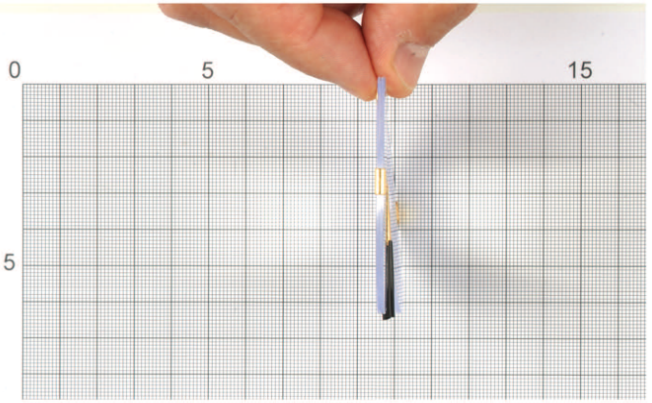
New examination tool for nystagmus:

the take-away "M glasses"

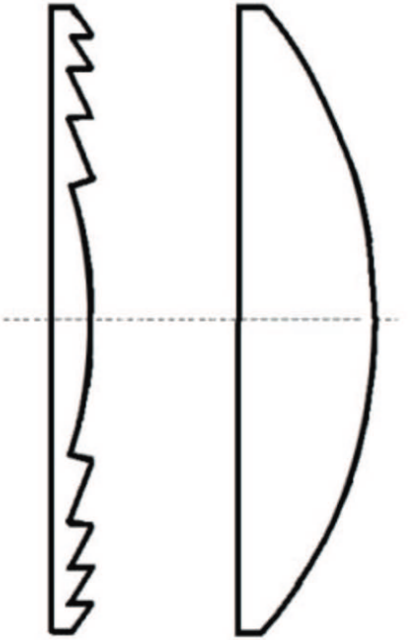
A

B





C



Strupp et al. Neurology (2014)

Relative frequency of different forms of central nystagmus

Type of nystagmus	n
Downbeat nystagmus	**101**
Upbeat nystagmus	**54**
Central positional nystagmus	**26**
Pendular nystagmus	15
Infantile nystagmus	12
Pure torsional nystagmus	12
Seesaw nystagmus	8
Ocular flutter	8
Square wave jerks	7
Opsoclonus	1
Periodic alternating nystagmus	1

Frequency of congenital and/or acquired ocular oscillations in a total of 4854 consecutive patients seen in our neurological dizziness unit. DBN was the most frequent fixation nystagmus (Wagner et al., JNNP, 2008)

Pharmacotherapy of nystagmus

Nystagmus	Therapy
Downbeat nystagmus	4-aminopyridine (4-AP, 3x5 mg/d) (Fampyra 2x10 mg/d) chlorzoxazone
Upbeat nystagmus	4-AP/Baclofen
Central positioning nystagmus	4-AP
Acquired fixation nystagmus	gabapentin/memantine
Infantile nystagmus	gabapentin/memantine
Periodic alternating nystagmus	baclofen

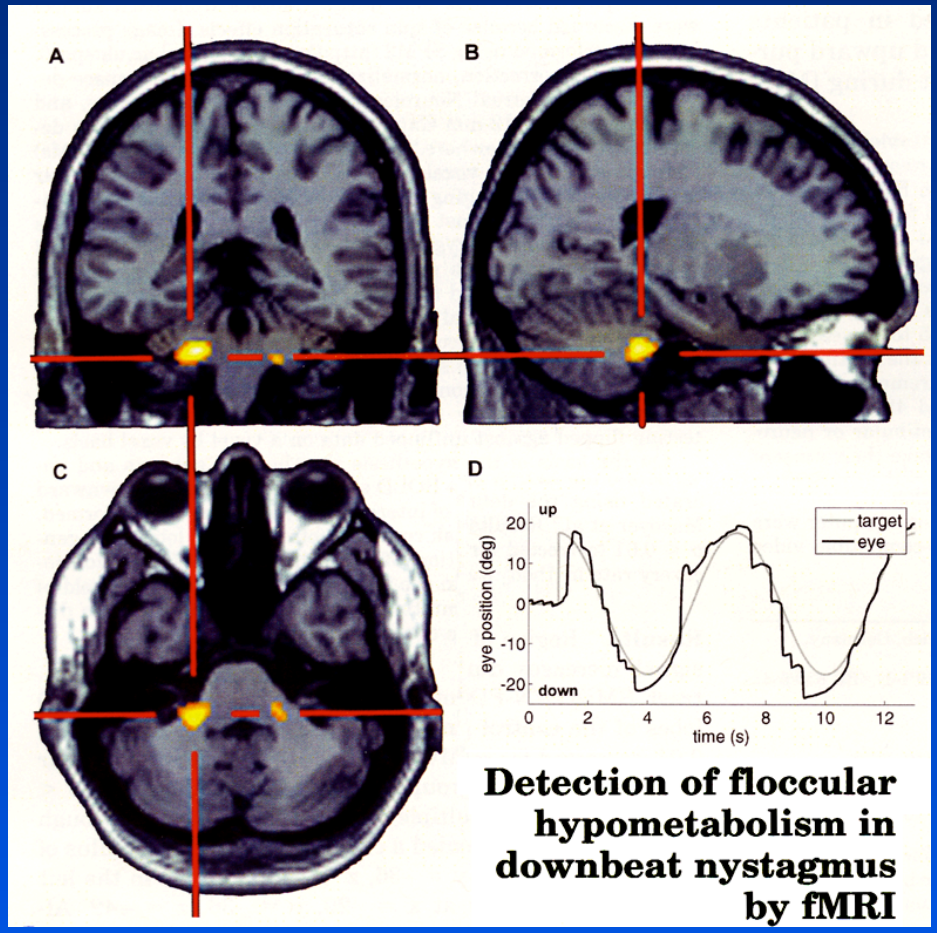
Strupp et al. Pharmacotherapy of vertigo and nystagmus. Seminars in Neurology (2013)

Clinical features of downbeat nystagmus syndrome

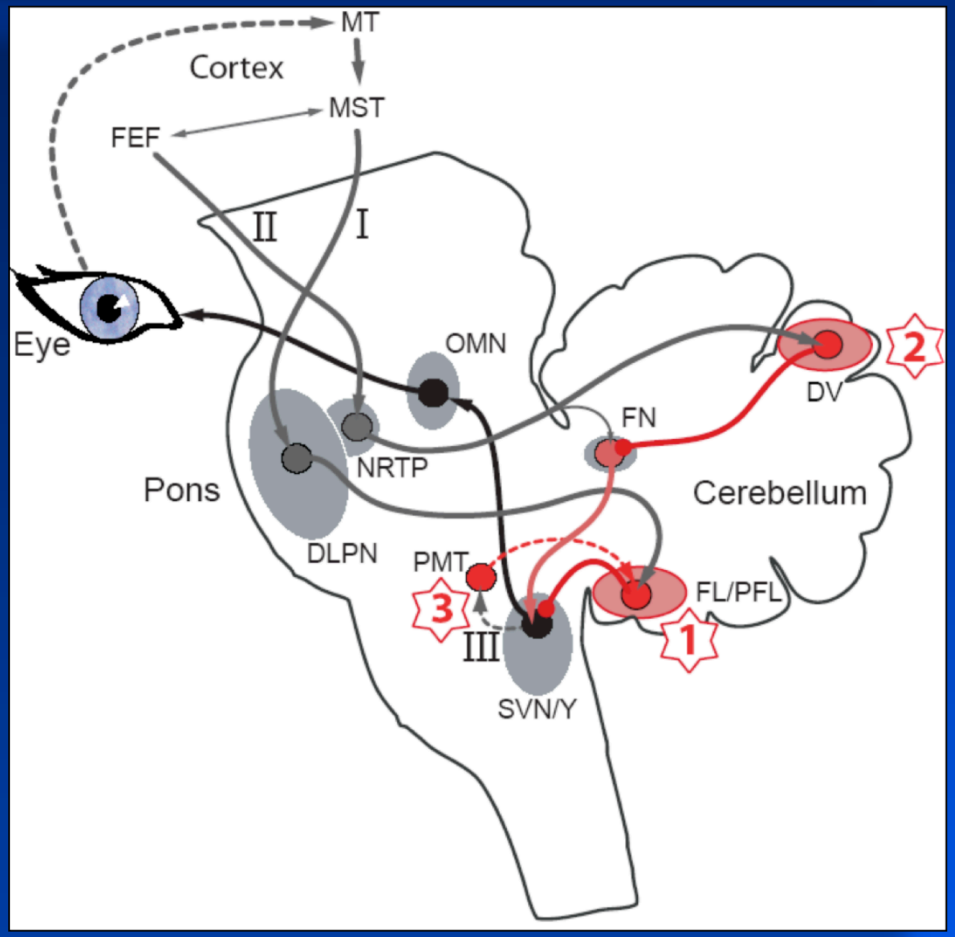
- Most common form of acquired persisting nystagmus
- Leading symptoms: **postural imbalance** (85%) and **oscillopsia** (45%) (Wagner et al., JNNP, 2008)
- **Fixation** nystagmus
- Central spontaneous nystagmus
- Increase of the intensity during **lateral and downward gaze** and when lying prone (nose down)
- Decrease of intensity when lying supine (nose up)
- **Decrease of intensity during daytime** (Spiegel et al. Neurology, 2011)

Pathophysiology of DBN

bilateral hypofunction of the flocculus



Kalla, Glasauer, Brandt, Strupp. Neurology, 2006



Hüfner, Glasauer, Kalla, Brandt, Strupp. Neurology, 2007

The aminopyridine story …

CME

VIDEO

Treatment of downbeat nystagmus with 3,4-diaminopyridine

A placebo-controlled study

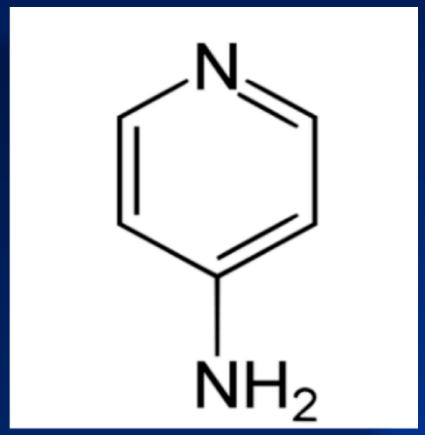
M. Strupp, MD; O. Schüler, MD; S. Krafczyk, PhD; K. Jahn, MD; F. Schautzer, MD; U. Büttner, MD; and T. Brandt, MD, FRCP

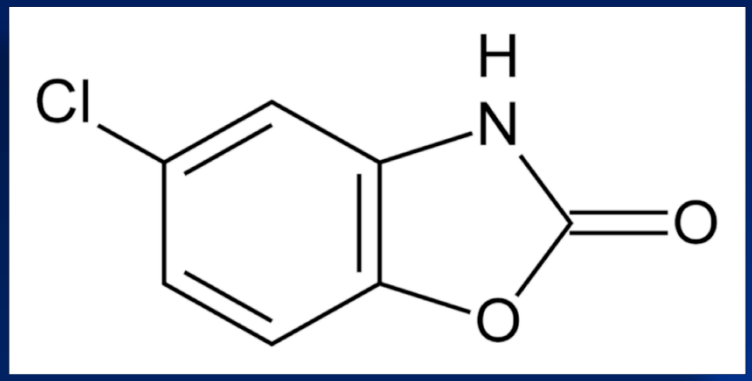
NEUROLOGY 2003;61:165–170

Treatment of episodic ataxia type 2 with the potassium channel blocker 4-aminopyridine

M. Strupp, MD; R. Kalla, MD; M. Dichgans, MD; T. Freilinger, MD; S. Glasauer, PhD; and T. Brandt, MD, FRCP

NEUROLOGY 2004;62:1623–1625





4-Aminopyridine

Downbeat nystagmus (DBN)
Upbeat nystagmus
Central postioning nystagmus
Episodic ataxia type 2 (EA 2)
Cerebellar ataxia

K^+_V channel blocker
Purkinje cells

Chlorzoxazone

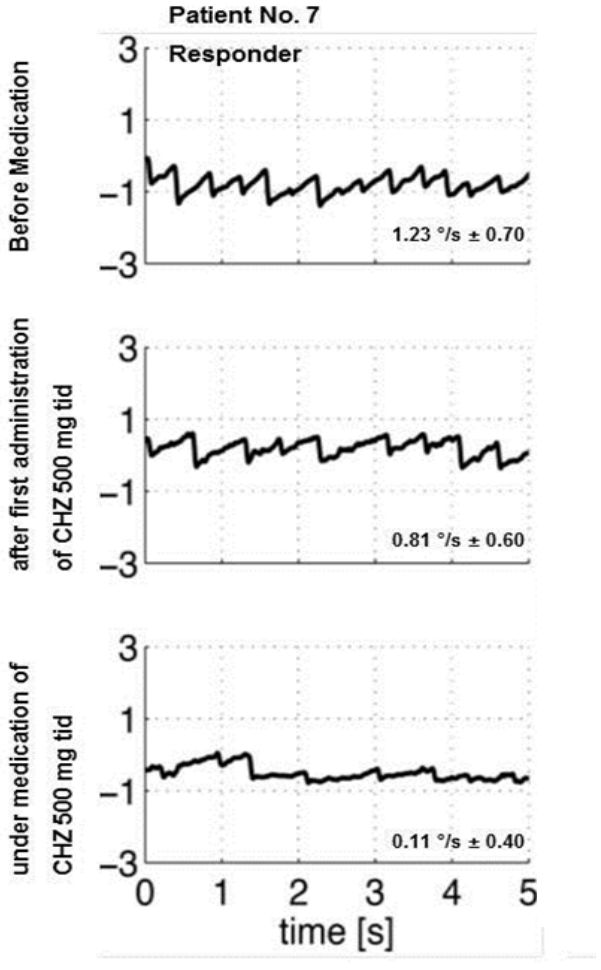
DBN

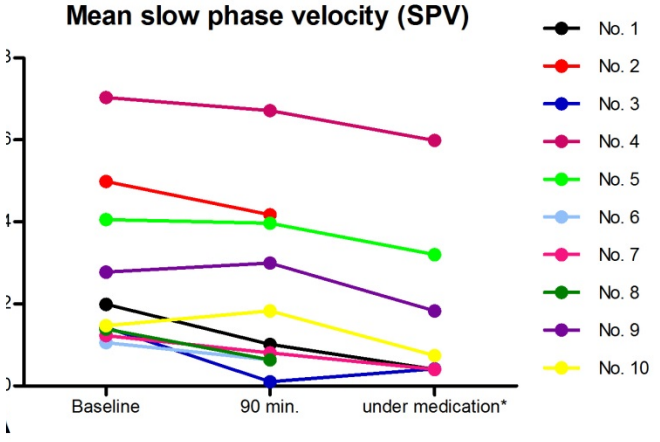
activator of small
Ca^{2+}-activated
K^+ channels

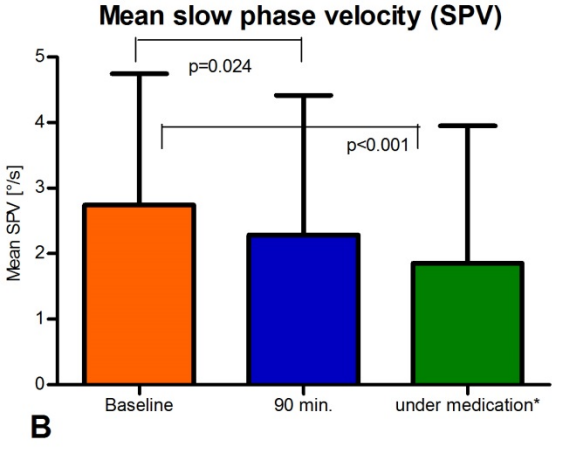
NEUROLOGY (2013)

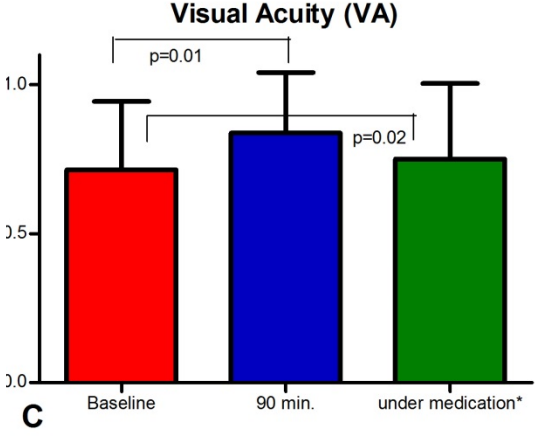
Effect of chlorzoxazone in patients with downbeat nystagmus: a pilot-trial

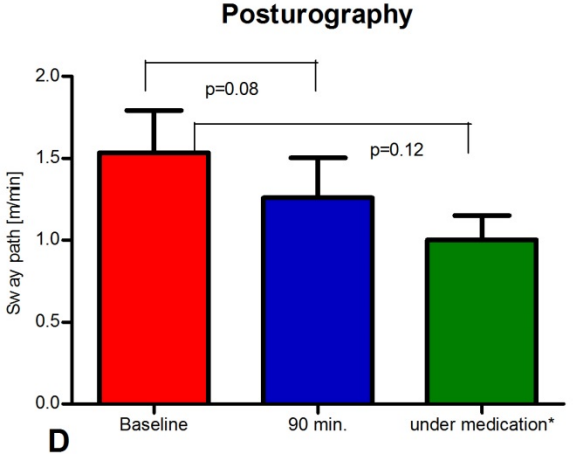
K. Feil, J. Claaßen, S. Bardins, J. Teufel, S. Krafczyk, E. Schneider, R . Schniepp, K. Jahn, R. Kalla, M. Strupp







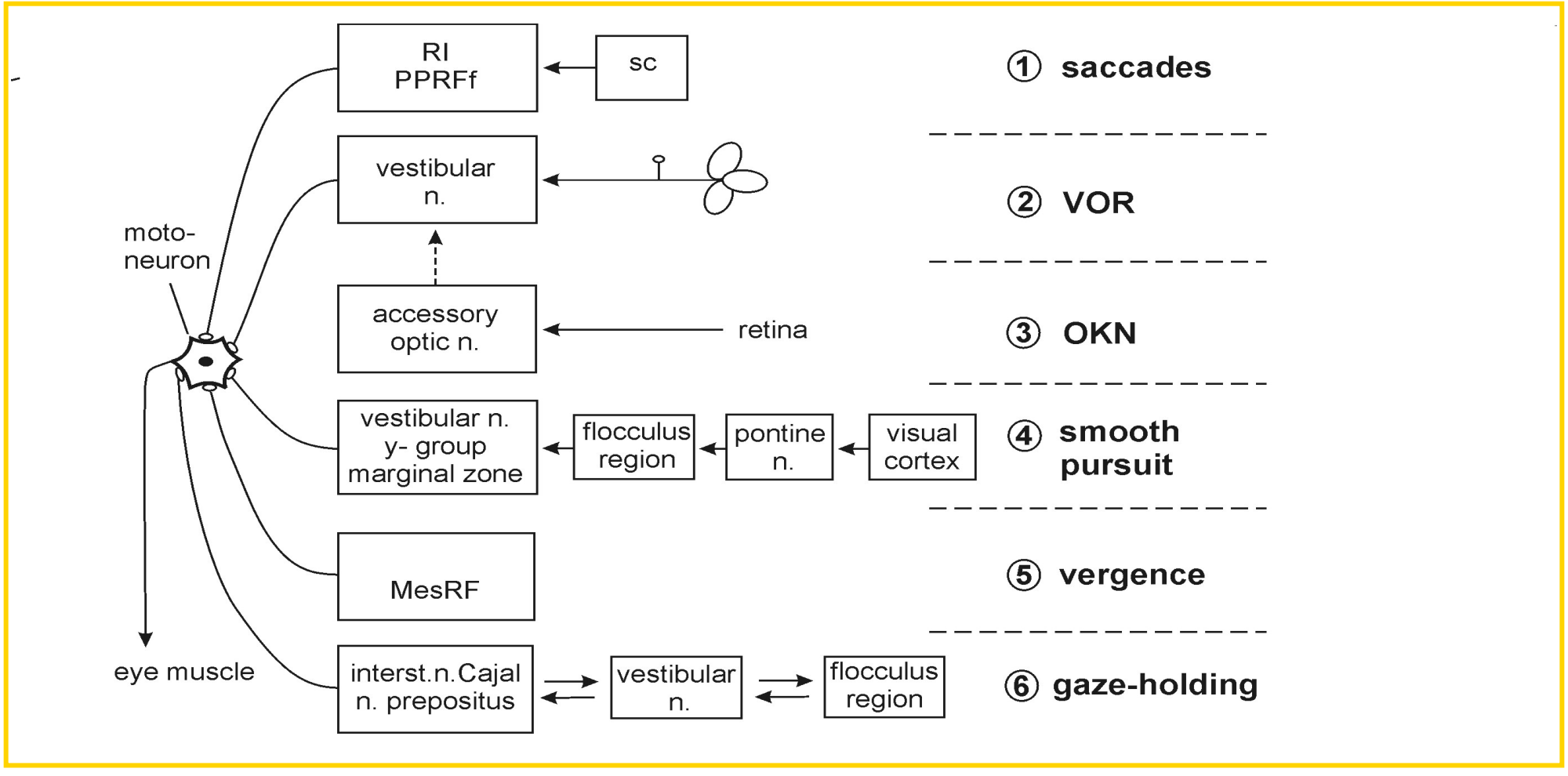




A “new” therapeutic principle - aminopyridines for the treatment of

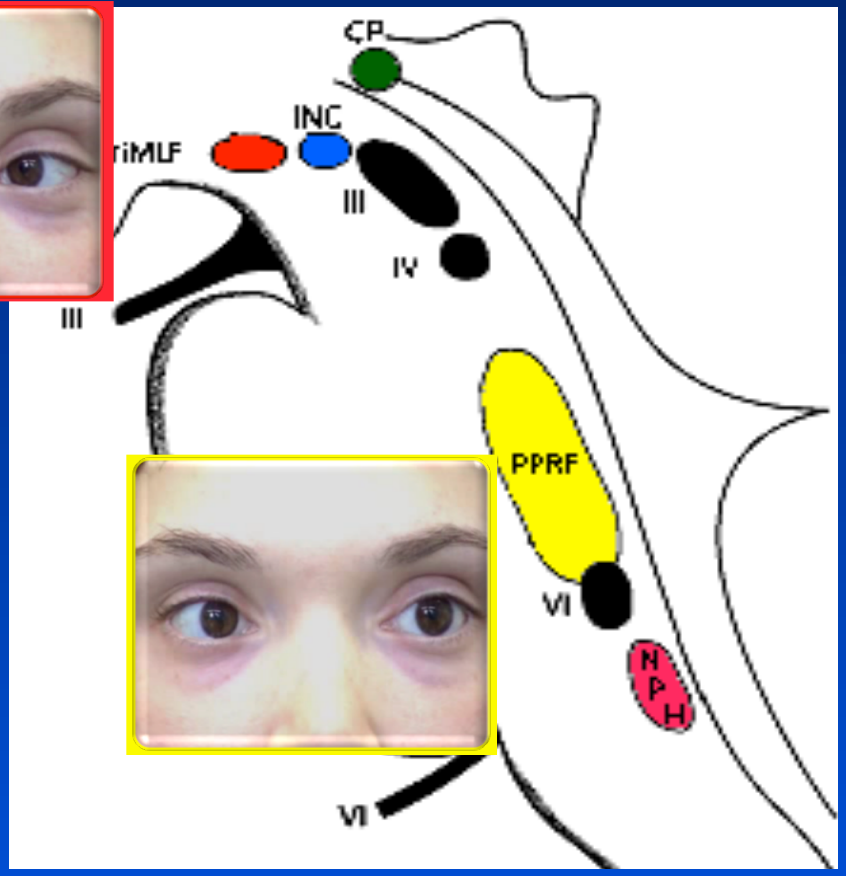
1. **Downbeat nystagmus**
   3,4-diaminopyridine: 10 mg tid (Strupp et al. (2003) Neurology)
   4-aminopyridine: 5 to 10 mg tid (Kalla et al. (2004) Neurology, Kalla et al. (2007) Brain, Claassen et al. (2013) JNNP)
   Fampiridine: (Claassen et al. (2013) J Neurol 2013)
2. **Upbeat nystagmus** (Glasauer et al. (2005) JNNP)
3. **Episodic ataxia type 2** (Strupp et al. (2004, 2011) Neurology)
   Fampiridine: (Claassen et al. (2013) J Neurol)
4. **Gait ataxia in cerebellar ataxias** (Schniepp et al. (2012) J Neurol)
5. **Positioning nystagmus** (Kremmyda et al. (2013) J Neurol)
6. **Acute vertigo** (Zwergal et al.)
7. **More …**

Different types of eye movements



J. Büttner-Ennever

Anatomy of the supranuclear ocular motor centers



riMLF = Rostral interstitial nucleus of the medial longitudinal fascicle

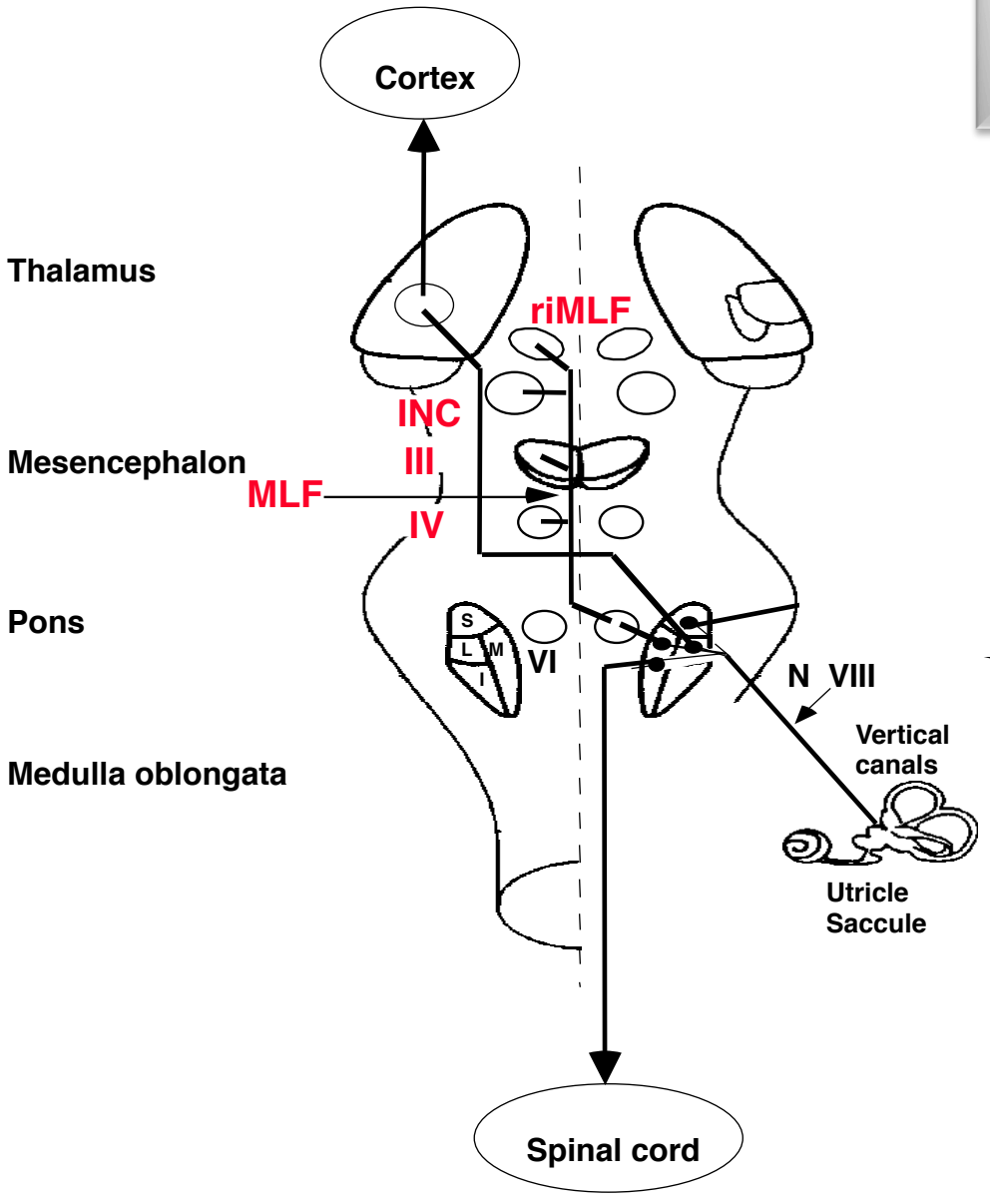
INC = Interstitial nucleus of Cajal

CP = Posterior commissure

PPRF = Paramedian pontine reticular formation

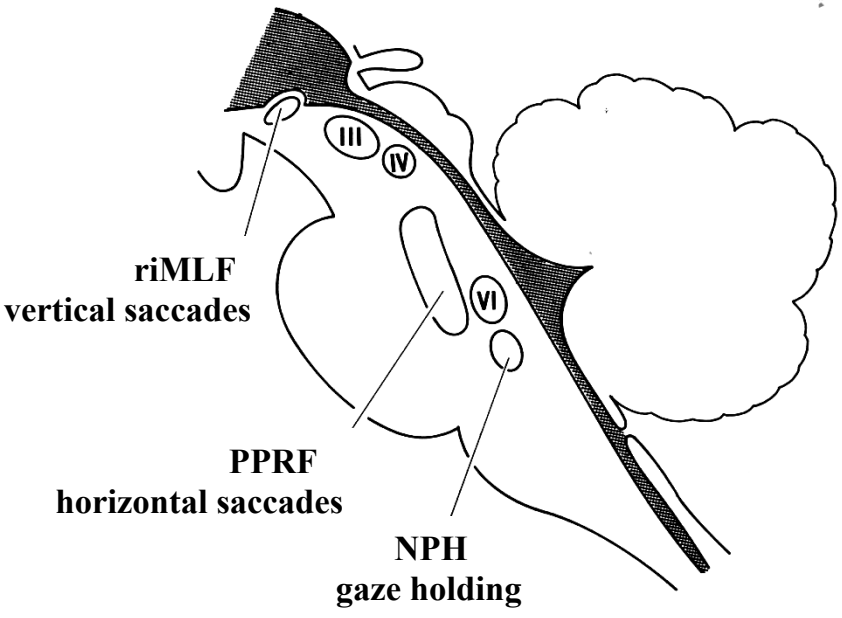
NPH = Nucleus praepositus hypoglossi

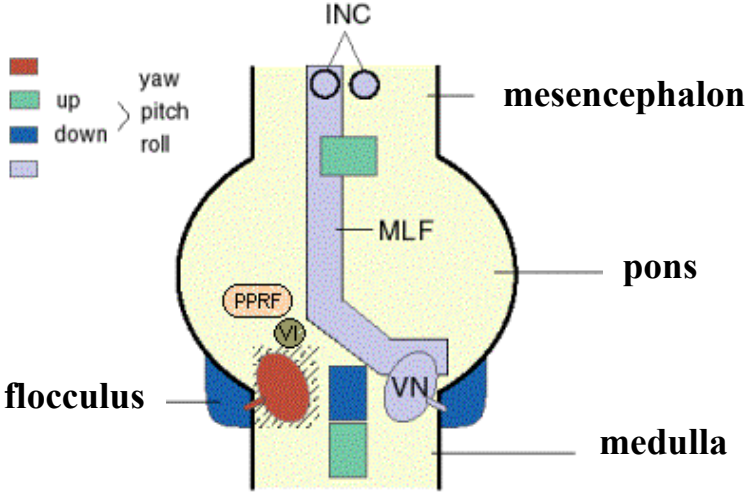
Pathological anatomy of the upper brainstem



- **riMLF lesion:** vertical gaze palsy
- **INC lesion:** vertical gaze-evoked nystagmus
- **Posterior commissural pathway:** convergence-retraction nystagmus
- **MLF lesion:** INO

Pathological anatomy of the lower brainstem





- **MLF lesion = INO**
- **PPRF** (paramedian pontine reticular formation): supranuclear center for horizontal saccades
  Lesion: impaired horizontal saccades
- **NPH** (Nucleus praepositus hypoglossi) gaze-holding function
  Lesion: horizontal gaze-evoked nystagmus