

Brain Research Institute at University of California, Los Angeles
 Prof. Michele Basso
 2016 November 18th

Brain processes for foveating a visual target here-and-now

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Space and time at the foundation of knowledge (as conditions of its possibility)

“ What then are time and space ?

Are they real beings (existences) ?

Or, are they merely determinations or relations between things ?
 And those relations, are they such that they would remain between things, even though they would never become objects of intuition ?

Or, are they such that **they belong** only to the form of intuition, and consequently **to the subjective constitution of the mind**, without which these predicates of time and space could not be attached to any object ? ”



Immanuel Kant
Critique of pure reason (1781)

Neurobiological foundations of space and time

IF space and time are ***a priori*** and ***necessary*** forms of intuition from which knowledge becomes possible,

THEN one should be able to find some neurobiological substrate for these notions

(and ***THEREAFTER***, eventually appreciate

- the biological nature of knowledge and
- how it is built upon interactions between an organism and its environment).

The orienting reaction (OR) as a probe to search for the neural foundations of "space"

The OR : a set of coordinated and organized muscle contractions / relaxations which lead to orient rapidly one (several) sensory organ(s) toward an object (its location).

1) ORs are relatively accurate

- to the ***physical location*** of an object corresponds the ***flow of neural activity*** from the time when the object is detected to the time when the associated orienting reaction ends.

2) ORs are accurate over a large range of different physical locations

- different locations can be ***ordered*** along dimensions, e.g., the H and V extents. Both H and V dimensions are commonly considered as driven by a topographically-organized map of labeled lines (superior colliculus/optic tectum).
- this map is an inferred entity as ***one single target is aimed at a time***

Morphological & Functional diversity & regularities

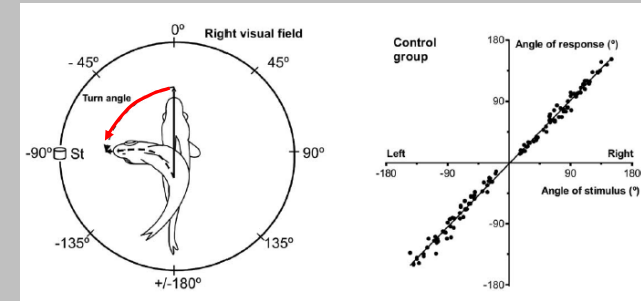
Across living animals, several morphological differences are observed in :
 - the sensory organs (retina, cochlea, olfactory bulb, etc.),
 - the motor plants (extra-ocular and neck muscles, geometry etc.),
 - the neural circuits
 that are involved in transforming a sensory event into an OR.

In spite of this diversity, some *regularities* are found :
 - within a particular animal,
 - within a species and
 - between species.

Temporal regularity : the OR is always extremely rapid (saccadic = ballistic-like), even after a paresis of the oculomotor system (head saccades).

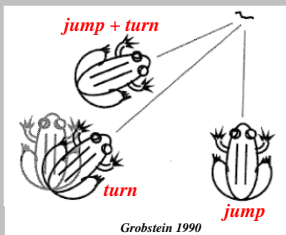
Spatial regularity: the spatial properties of the OR fit with the spatial extent of the environment with a variability that is relatively delimited.

Orienting body movement in the goldfish



Torres et al. Brain Res. Bull. 2005

Orienting body movement in the frog



Result of first reaction :
 orient the gaze
 (field of visuomotor interactions)
 toward the target

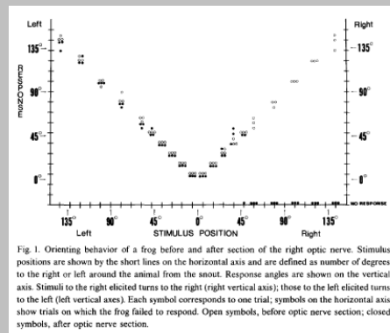


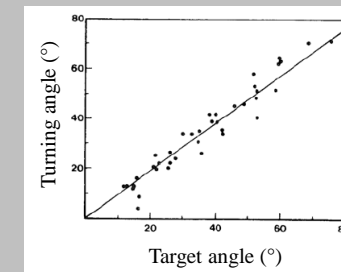
Fig. 1. Orienting behavior of a frog before and after section of the right optic nerve. Stimulus positions are shown by the short lines on the horizontal axis and are defined as number of degrees to the right or left around the animal from the snout. Response angles are shown on the vertical axis. Stimuli to the right elicited turns to the right (right vertical axis); those to the left elicited turns to the left (left vertical axis). Each symbol corresponds to one trial; symbols on the horizontal axis show trials on which the frog failed to respond. Open symbols, before optic nerve section; closed symbols, after optic nerve section.

Kostyk & Grobstein 1982

Orienting head movement in the salamander

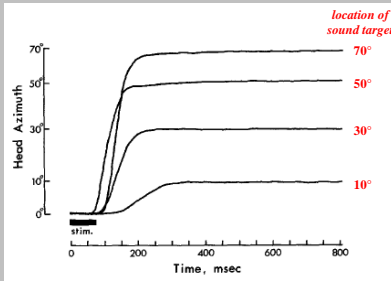


Schüller & Dicke J. Exp Biol 2002



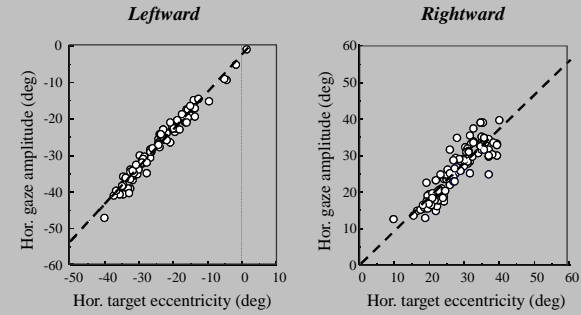
Werner & Himstedt
 Zool. Jb. Physiol. 1985

Orienting head movement in the barn owl



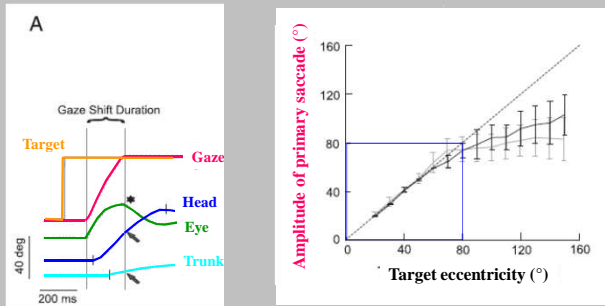
Knudsen, Blasdel & Konishi JCP 1979

Orienting gaze shift in the cat (head free)



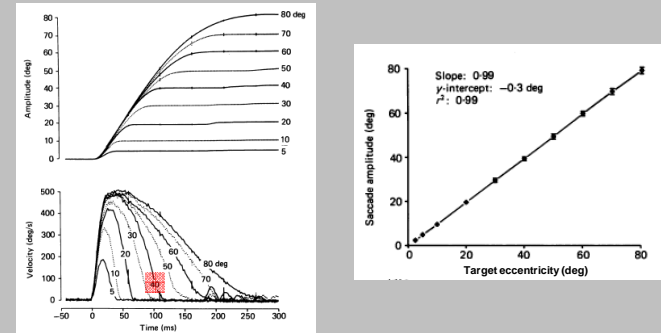
modified from Goffart & Pétiou JNP 1994

Orienting gaze shift in the monkey (head free)



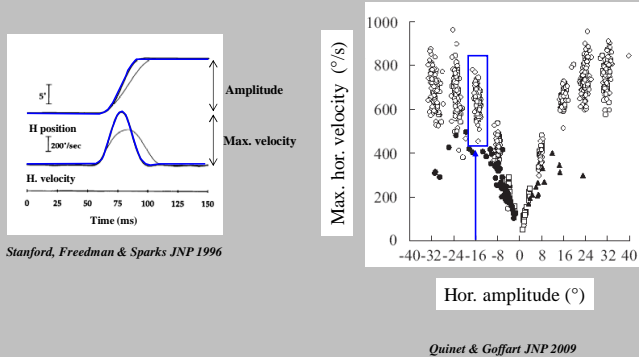
McCluskey & Cullen JNP 2007

Eye saccades in the human subject



Collewijn et al JP 1988

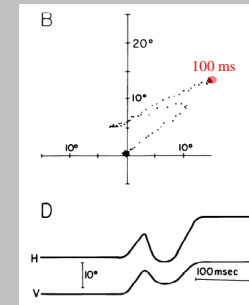
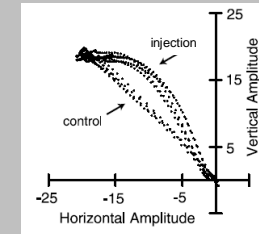
Robustness : spatial accuracy is maintained in spite of variable saccade dynamics



Robustness : spatial accuracy is maintained even after experimental perturbations

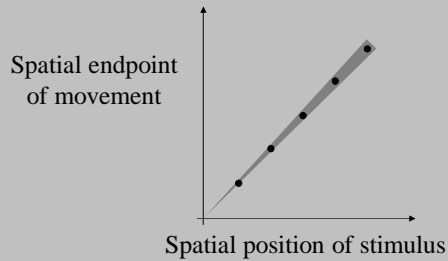
Pharmacological inactivation
(Pontine Reticular Formation)

Brief electrical microstimulation
(deep Superior Colliculus)



Spatial accuracy is robust

In spite of the diversity of sensory organs, motor devices and nervous systems and variable execution (velocity, eye-head-body coupling, perturbation)

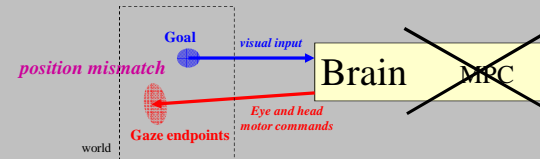


What are the (neuro) biological foundations of this relationship ?

The medio-posterior cerebellum (MPC) and the control of orienting gaze shifts

Dysfunction of MPC leads to gaze **dysmetria** i.e. it alters the spatial congruence between :

- the location of a visual event
- the endpoint of gaze shifts towards it



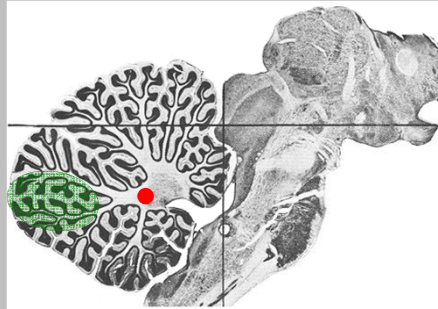
The medio-posterior cerebellum

Lobules VIc-VII

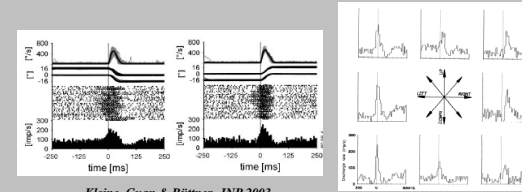


caudal Fastigial Nuclei
(Fastigial Oculomotor Regions)

Saccade-related activity
Pursuit-related activity
Vergence-related activity



Saccade-related activity in the caudal fastigial nucleus (head-restrained monkey)

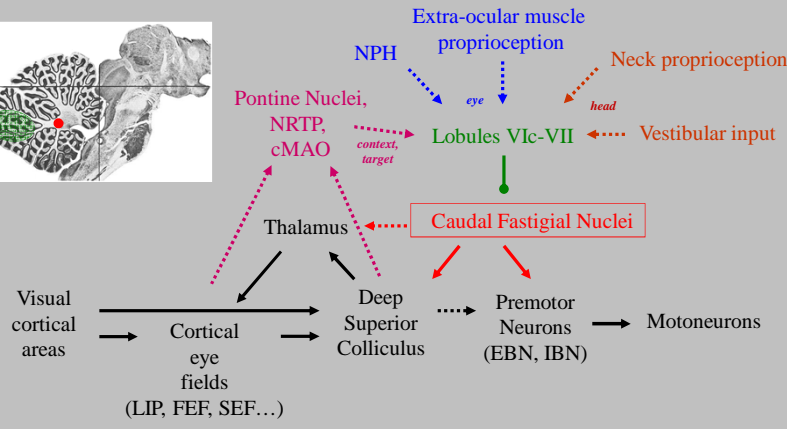
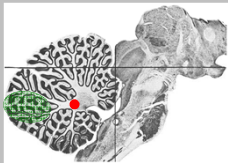


Kleine, Guan & Büttner JNP 2003

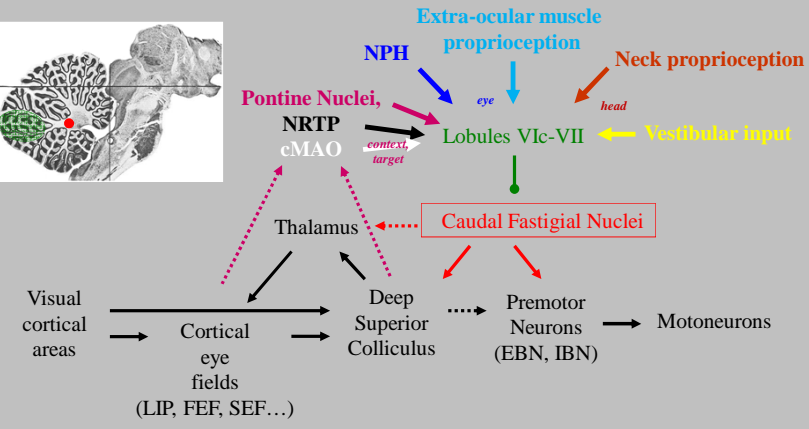
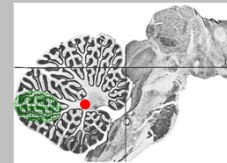
Ohtsuka & Noda JNP 1991

1. Burst of action potentials for all saccades regardless of the amplitude and direction
2. Sustained discharge during inter-saccadic intervals

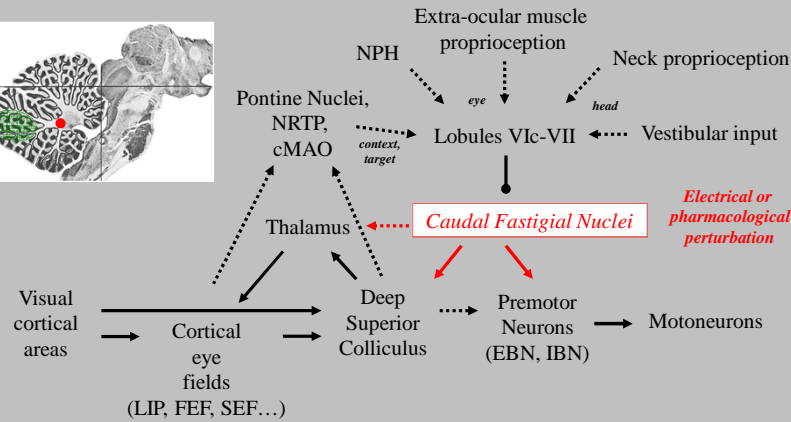
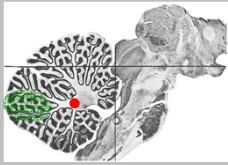
The medio-posterior cerebellum



Inputs with different dynamics (different delays, different dynamics etc...)

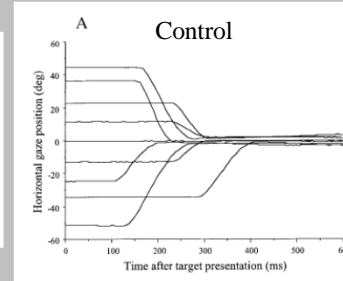
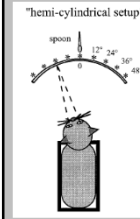


Methodological approach : perturbation (for establishing causal relationships)



Ipsilesional gaze shifts

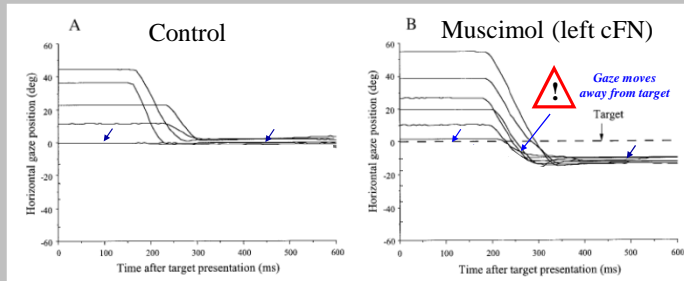
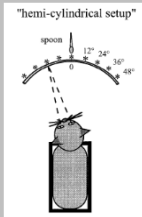
Muscimol injection in the left cFN (0.3 µl; 1µg/µl, cat I)



modified from Goffart & Pélisson JNP 1998

Ipsilesional gaze shifts

Muscimol injection in the left cFN (0.3 µl; 1µg/µl, cat I)

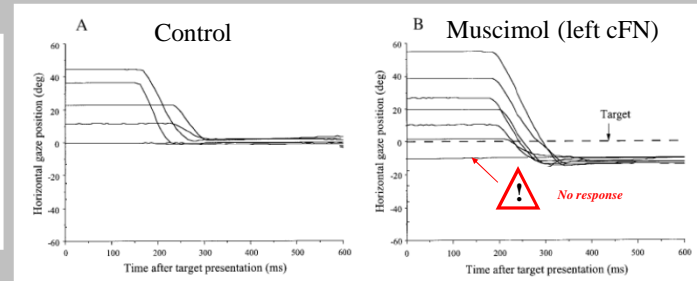
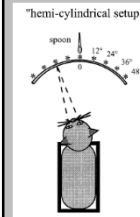


modified from Goffart & Pélisson JNP 1998

Ipsilesional gaze shifts

Muscimol injection in the left cFN (0.3 µl; 1µg/µl, cat I)

Muscimol injection in the left cFN (0.3 µg)

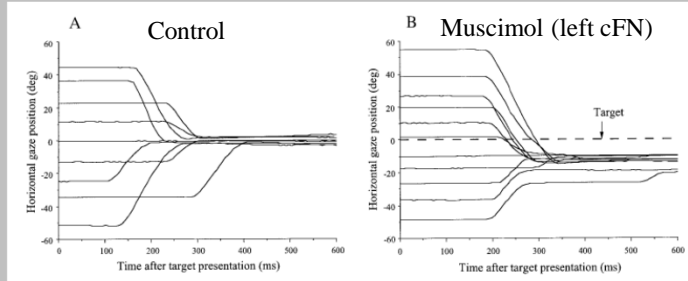
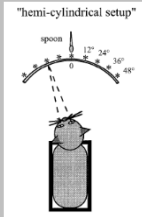


modified from Goffart & Pélisson JNP 1998

Ipsilesional and contralesional gaze shifts

Muscimol injection in the left cFN (0.3 μ l; 1 μ g/ μ l, cat I)

Muscimol injection in the left cFN (0.3 μ g)

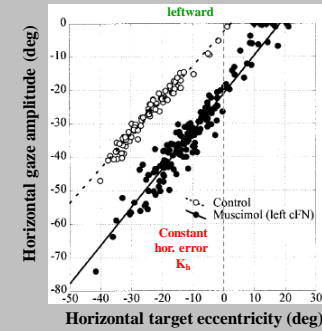


modified from Goffart & Pélisson JNP 1998

Gaze dysmetria

Muscimol injection in the left cFN (0.3 μ l; 1 μ g/ μ l, cat G)

Ipsilesional movements

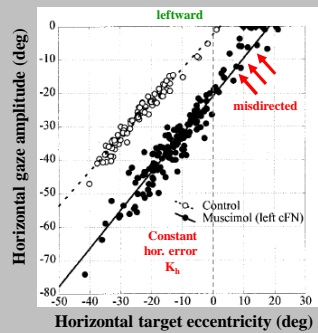


modified from Goffart & Pélisson JNP 1998

Gaze dysmetria

Muscimol injection in the left cFN (0.3 μ l; 1 μ g/ μ l, cat G)

Ipsilesional movements

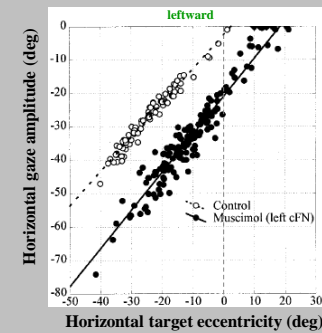


modified from Goffart & Pélisson JNP 1998

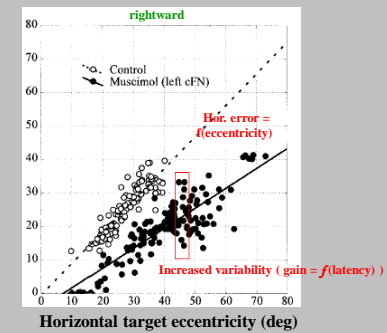
Gaze dysmetria

Muscimol injection in the left cFN (0.3 μ l; 1 μ g/ μ l, cat G)

Ipsilesional movements



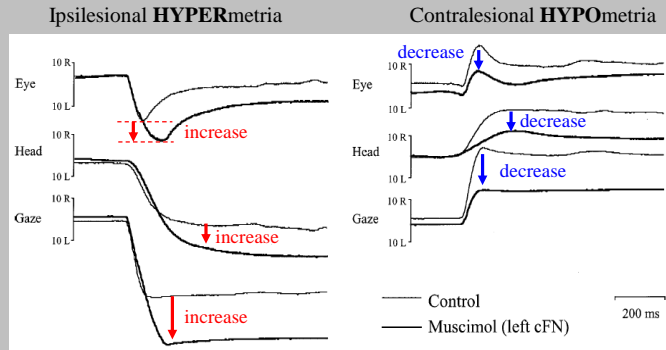
Contralesional movements



modified from Goffart & Pélisson JNP 1998
(see also Goffart & Pélisson JP 1997)

Dysmetria affects eye and head movements

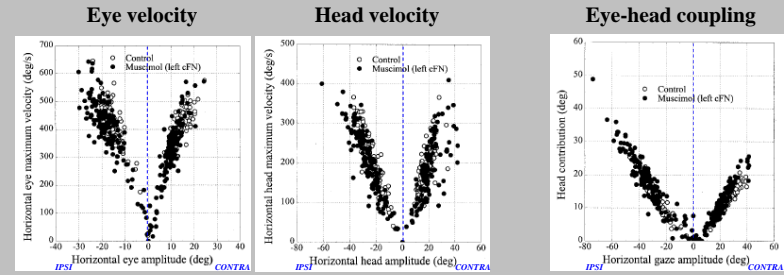
Muscimol injection in the left cFN (0.3 μ l; 1 μ g/ μ l, cat G)



modified from Goffart, Pélisson & Guillaume JNP 1998

No sign of movement execution disorder

Muscimol injection in the left cFN (0.3 μ l; 1 μ g/ μ l, cat G)



modified from Goffart, Pélisson & Guillaume JNP 1998

Control (pre-injection)

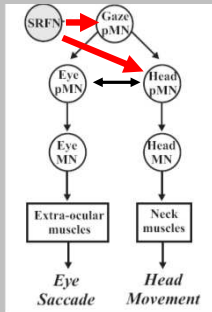


Deficit in head orientation

Muscimol (right cFN)



Cat

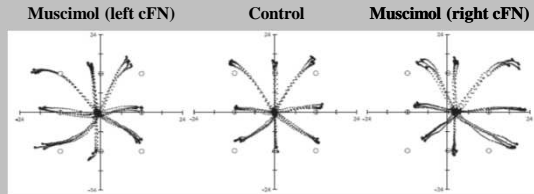


- Gaze dysmetria due to dysmetric eye + head
- Eye/head velocity **unchanged**
- Eye/head coupling **unchanged**

Goffart & Pétilson JP London 1997
 Goffart & Pétilson JNP 1994, 1998
 Goffart et al. JNP 1998a,b

Observations in the head-fixed monkey

target LEDs @ 145 cm : 0.25° visual angle, mesopic conditions, 0.4 μl (1μg/μl)



Goffart, Chen & Sparks, JNP 2004

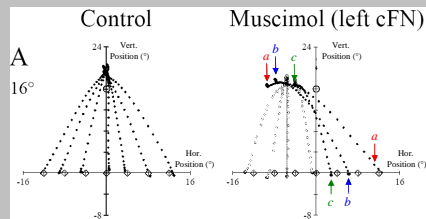
Ipsilesional saccades : horizontal component is **hypermetric**

Contralesional saccades : horizontal component is **hypometric**

like in the head-unrestrained cat

Horizontal error is not constant

unlike the head-unrestrained cat

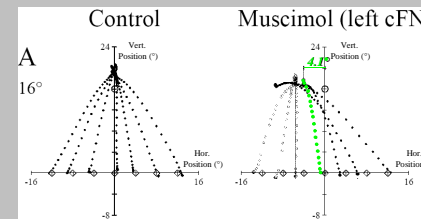


modified from Goffart, Chen & Sparks JNP 2004

Hor. Error *saccade a* > Hor. Error *saccade b* > Hor. Error *saccade c*

Horizontal error is not constant

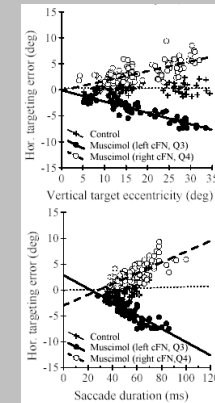
unlike the head-unrestrained cat



modified from Goffart, Chen & Sparks JNP 2004

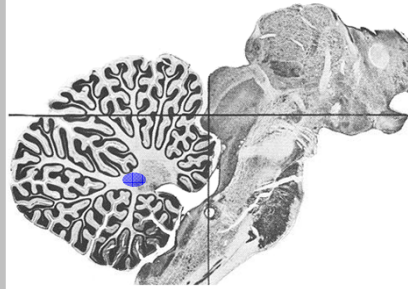
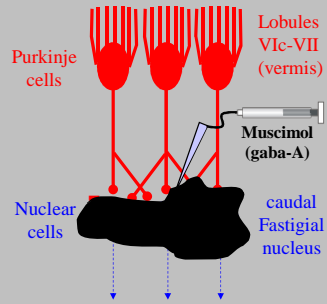
Hor. error. = $f(\text{target eccentricity})$
 $f(\text{saccade duration})$

Vertical saccades



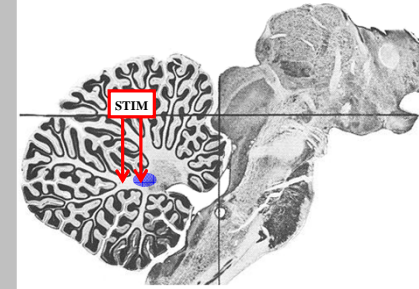
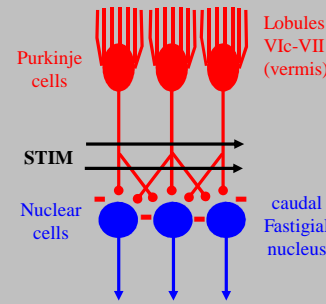
Impaired planning or execution ?

(pre- or intra-saccadic disorder ?)



Duration of inactivation ~ 2-3 hours :
 This long-lasting perturbation does not allow deficits that are pre-saccadic to be distinguished from those occurring during saccade execution

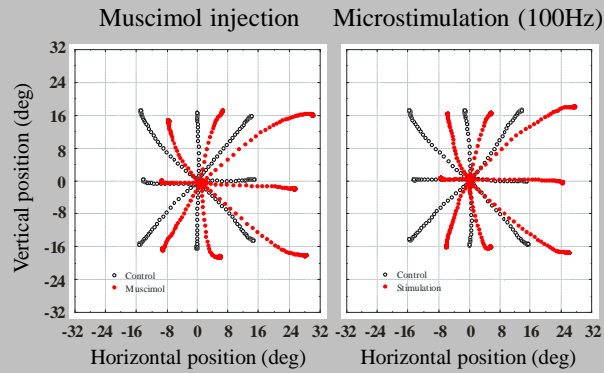
Inhibition of cFN activity with electrical microstimulation



Purkinje cells inhibit cFN neurons with Gaba-A as a neurotransmitter.
 By stimulating their axons, one should be able to mimics, with a microstimulation train, the effects of muscimol on saccade accuracy.

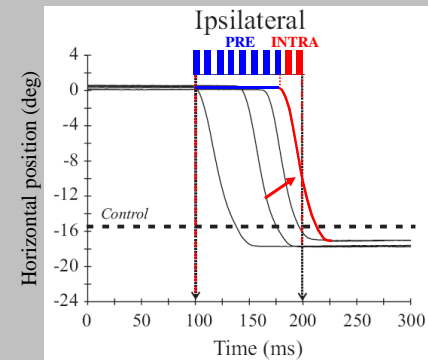
Inhibition of cFN

Right cFN (rebound saccades removed)



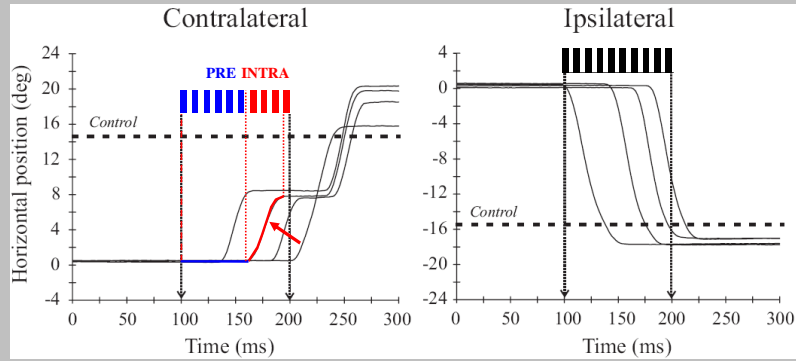
Time window of the perturbation

left caudal Fastigial Nucleus



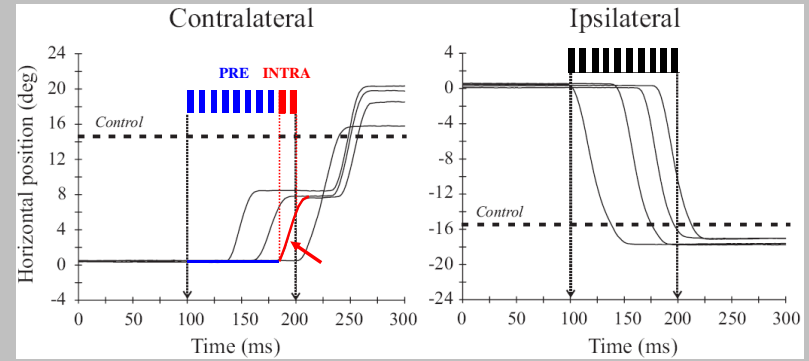
Increasing the number of pre-saccadic pulses does not change the magnitude of hypermetria

Time window of the perturbation left caudal Fastigial Nucleus



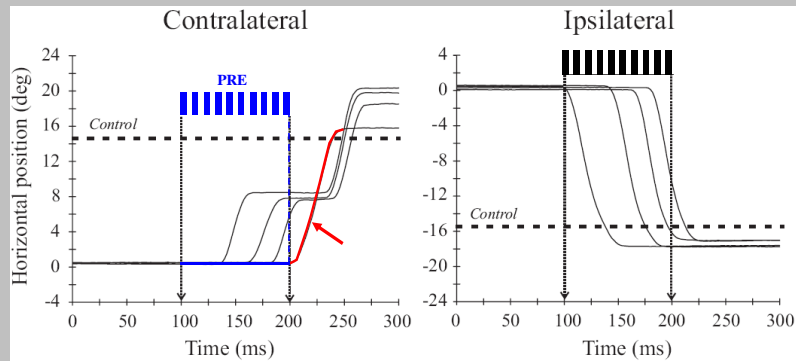
Goffart & Quinet in preparation

Time window of the perturbation left caudal Fastigial Nucleus



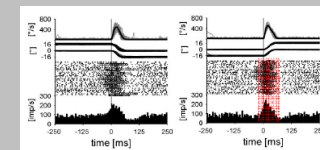
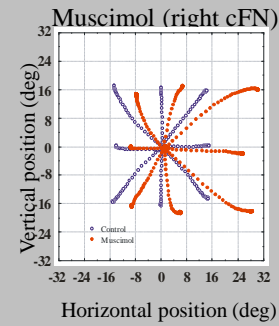
Goffart & Quinet in preparation

Time window of the perturbation left caudal Fastigial Nucleus



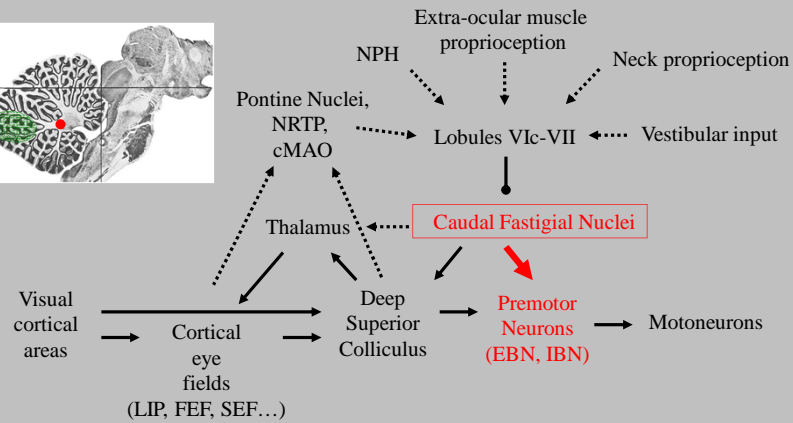
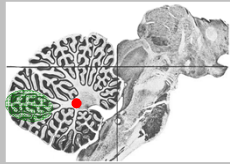
Goffart & Quinet in preparation

Horizontal dysmetria is due to the unilateral suppression of saccade-related bursts



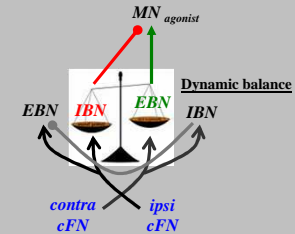
modified from Kleine, Guan & Büttner JNP 2003

Fastigio-reticular projections and the cerebellar control of saccade amplitude



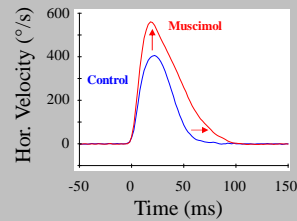
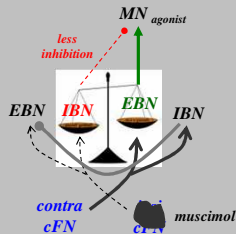
Bilateral hypothesis

For every saccade (horizontal, oblique or vertical), the left and right cFN regulates the balance of activity between excitatory input (EBNs) and inhibitory input (IBNs)



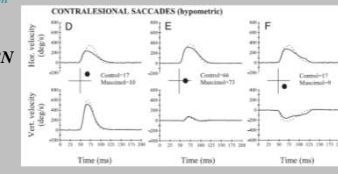
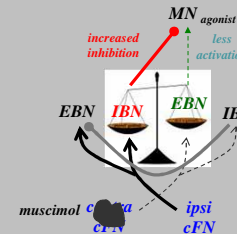
Bilateral hypothesis

Ipsilesional hypermetria



Bilateral hypothesis

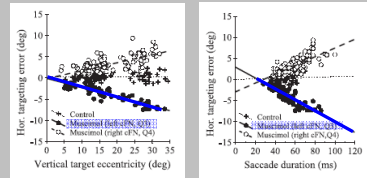
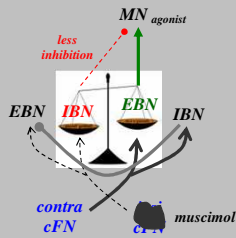
Contralesional hypometria



modified from Goffart, Chen & Sparks JNP 2004

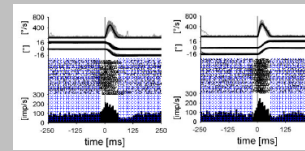
Bilateral hypothesis

Ipsipulsion of vertical saccades

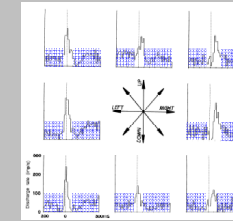


modified from Goffart, Chen & Sparks JNP 2004

What about the sustained activity in cFN ?



Kleine, Guan & Büttner JNP 2003

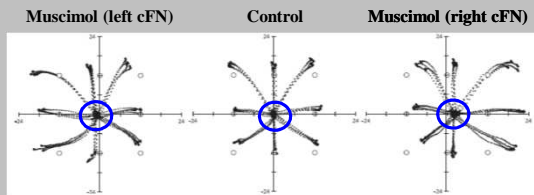


Ohtsuka & Noda JNP 1991

Ipsilesional fixation offset

like in the head-unrestrained cat

target LEDs @ 145 cm : 0.25° visual angle, mesopic conditions

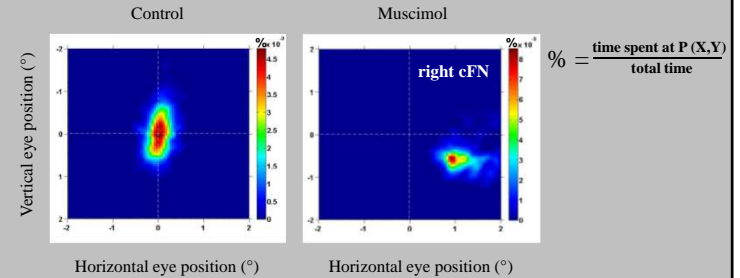


Goffart, Chen & Sparks, JNP 2004

Fixation offset : shift in the scatter of eye positions during fixation

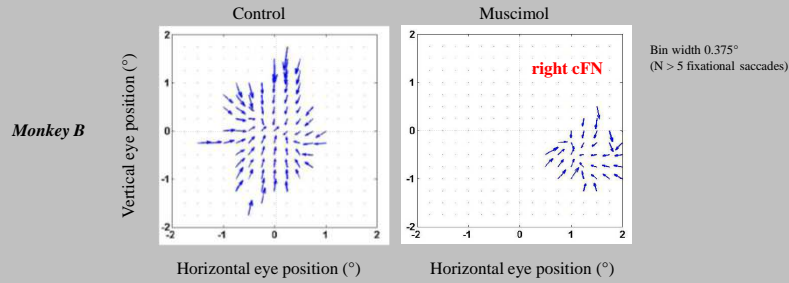
Fixation offset : spatio-temporal map

Monkey B

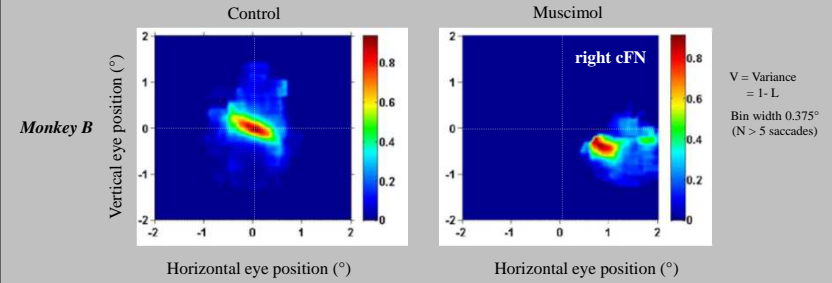


$$\% = \frac{\text{time spent at } P(X,Y)}{\text{total time}}$$

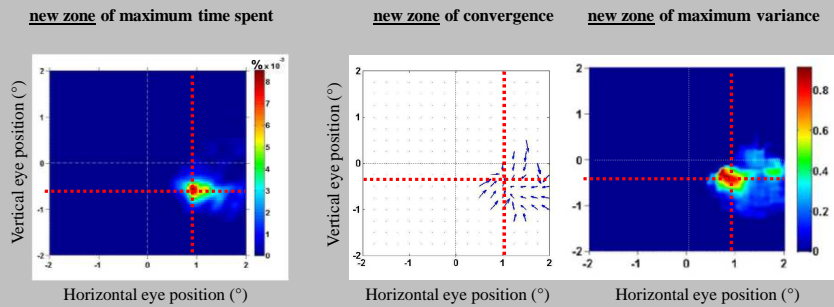
Directional field of fixational saccades



Directional field : zone of maximum variance



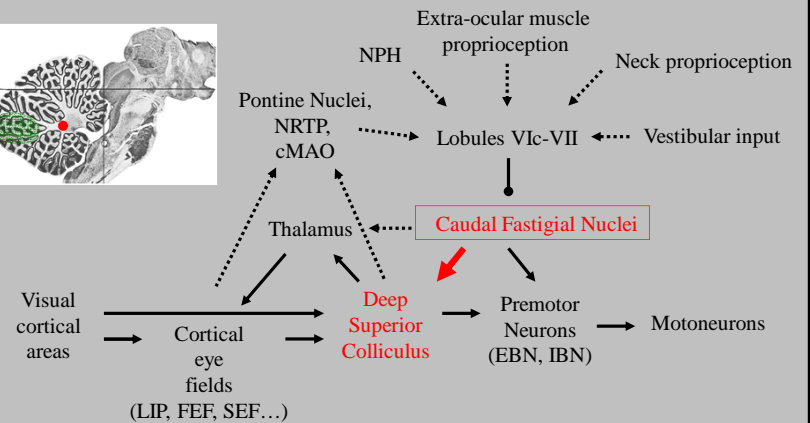
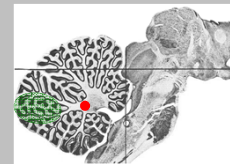
Change in the oculomotor encoding of a foveal target ?



J Neurophysiol 103: 1988–2001, 2010.
 First published February 3, 2010; doi:10.1152/jn.00771.2009.

Fastigial Oculomotor Region and the Control of Foveation During Fixation

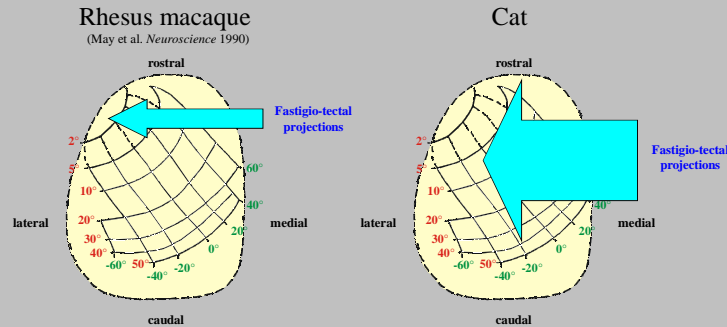
Lorenzo Guerrasio,¹ Julie Quinet,² Ulrich Büttner,¹ and Laurent Goffart³



Behavior and neuroanatomy

In the monkey, a spatial deficit similar to that observed in the cat, is observed when one considers the microsaccades generated when a visual target is being fixated.

The difference between the feline and primate disorders could result from differences in the extent of fastigio-tectal projections.



If the fixation offset corresponds to an altered encoding of foveal target, what is visual fixation ?

Fixation is classically considered as a state where "gaze" and "target" position / displacement -related signals match (zero motor error)

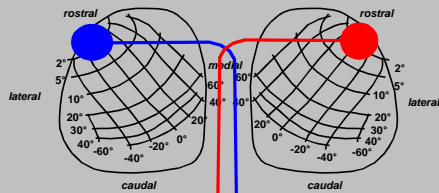
→ this line of thinking assumes an encoding of magnitudes such as position / displacement or error (signals of a spatial kind)

→ it does not explain what "zero motor error" means, neurophysiologically speaking

Visual Fixation as Equilibrium: Evidence from Superior Colliculus Inactivation

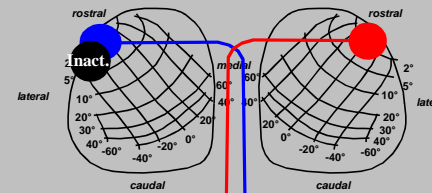
Laurent Goffart,¹ Ziad M. Hafed,² and Richard J. Krauzlis^{3,4}
¹Institut de Neurosciences de la Timone, UMR 7289, Centre National de la Recherche Scientifique, Aix-Marseille Universit s, 13385 Marseille, France; ²Werner Reichardt Centre for Integrative Neuroscience, 72076 T ubingen, Germany; ³Systems Neurobiology Laboratory, Salk Institute for Biological Studies, La Jolla, California 92037; and ⁴Laboratory of Sensorimotor Research, National Eye Institute, National Institutes of Health, Bethesda, Maryland, 20892

Journal of Neuroscience 2012



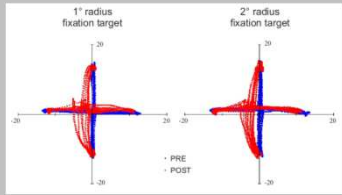
Equilibrium requires symmetry :
 The symmetry could be achieved by modulations exerted by projections from the cFN to the brainstem

Experimental prediction after muscimol injection in the rostral SC

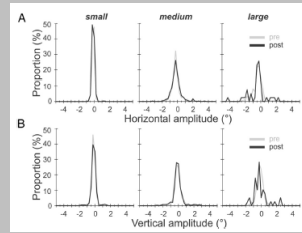


Equilibrium requires symmetry :
 The symmetry could be achieved by modulations exerted by projections from the cFN to the brainstem

Experimental prediction : fixation offset after muscimol injection in the **rostral SC**



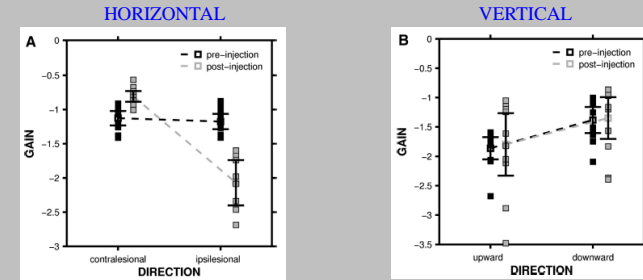
Ipsilesional fixation offset
Saccades to peripheral targets are accurate



No asymmetry in the H or V amplitude of fixational saccades

Goffart, Hafed & Krauzlis JN 2012

Asymmetry in the hor. ampl. of fixational saccades after muscimol injection in the **caudal FN**

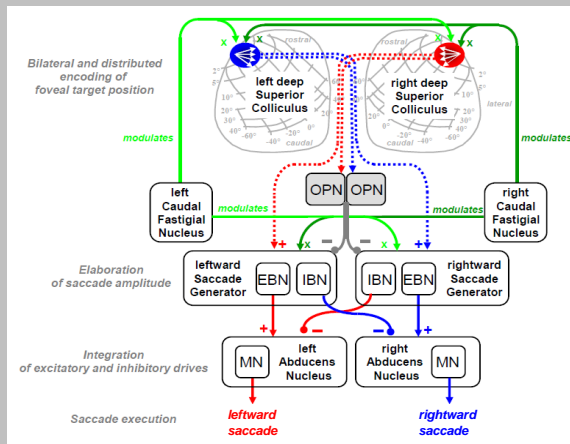


J Neurophysiol 103: 1988–2001, 2010.
First published February 3, 2010; doi:10.1152/jn.00771.2009.

Fastigial Oculomotor Region and the Control of Foveation During Fixation

Lorenzo Guerrasio,¹ Julie Quinet,² Ulrich Büttner,¹ and Laurent Goffart³

Fastigial control of brainstem equilibria



Some evidences against a collicular origin of the dysmetria of gaze shifts

Quinet & Goffart JNP 2005

J Neurophysiol 93: 2343–2349, 2005.
First published November 24, 2004; doi:10.1152/jn.00705.2004.

Report

Saccade Dysmetria in Head-Unrestrained Gaze Shifts After Muscimol Inactivation of the Caudal Fastigial Nucleus in the Monkey

Quinet & Goffart JNP 2007

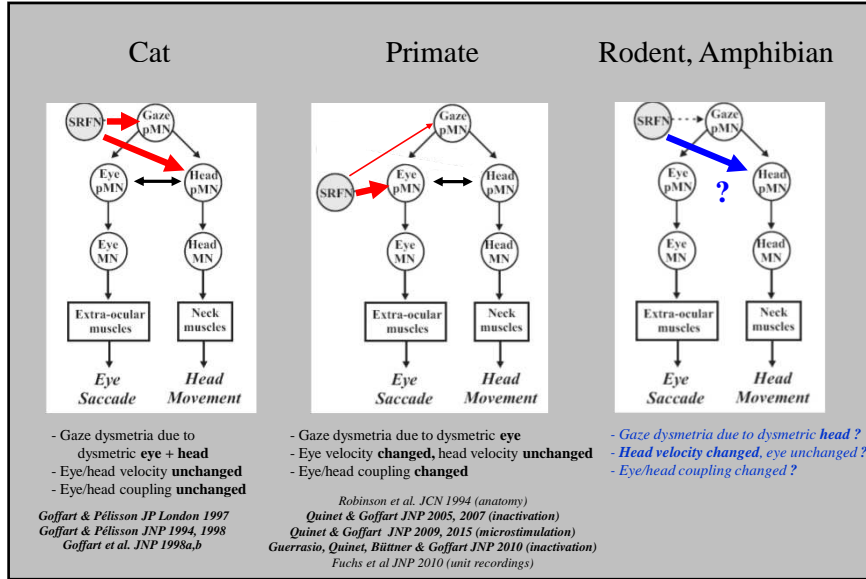
J Neurophysiol 98: 3269–3283, 2007.
First published October 10, 2007; doi:10.1152/jn.00741.2007.

Head-Unrestrained Gaze Shifts After Muscimol Injection in the Caudal Fastigial Nucleus of the Monkey

Quinet & Goffart JNP 2009

J Neurophysiol 102: 320–336, 2009.
First published May 13, 2009; doi:10.1152/jn.90716.2008.

Electrical Microstimulation of the Fastigial Oculomotor Region in the Head-Unrestrained Monkey



“The cerebellum is specifically involved in monitoring and adjusting the acquisition of most of the sensory data on which the rest of the nervous system depends.”
James M. Bower *International Review of Neurobiology* 41: 489-513, 1997

Adapted to our paradigm :

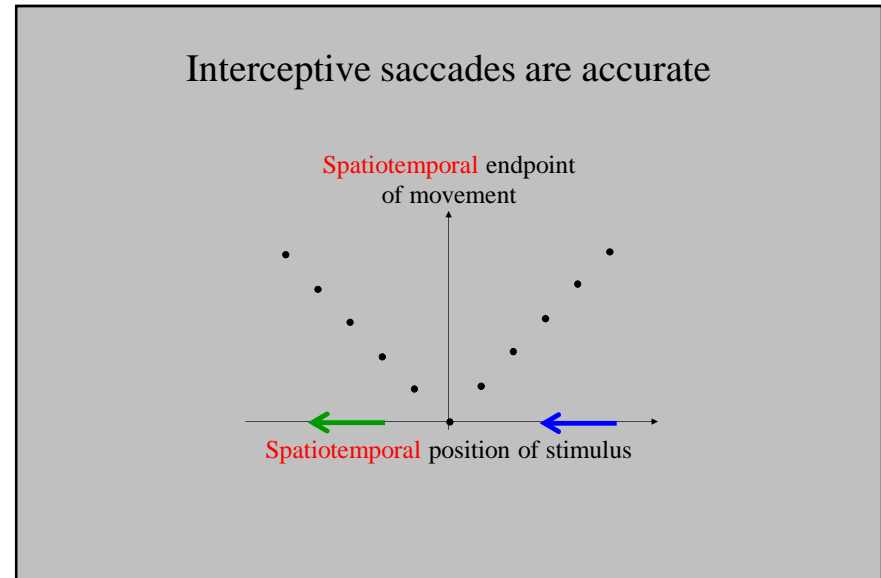
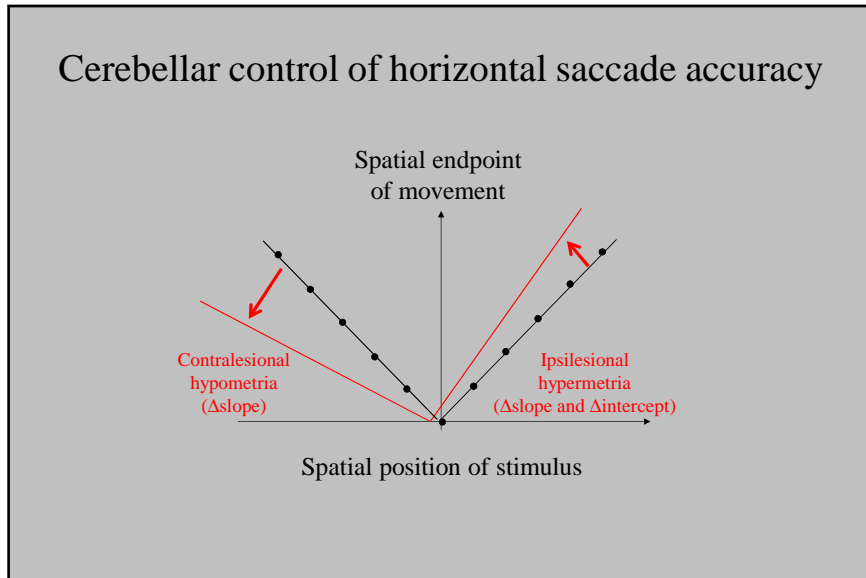
The medio-posterior cerebellum (MPC) is involved in orienting the *primary sensory apparatus*.

More specifically, the MPC would **compensate for intra- and inter-specific morphological variability**

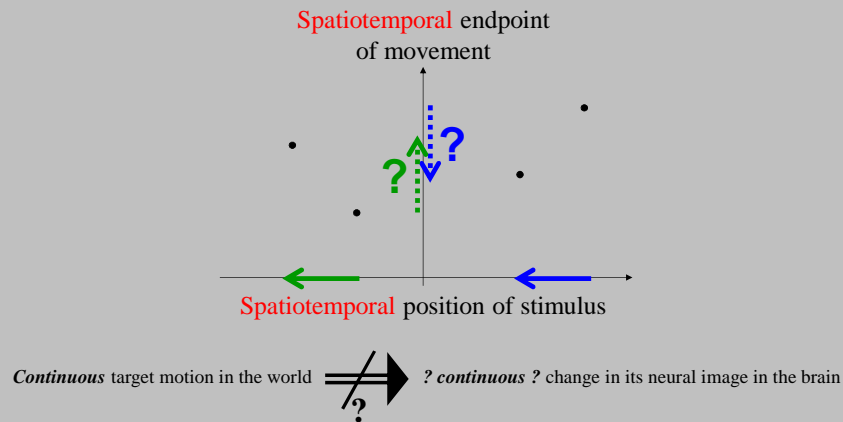
- in the *sensory organs used for detecting events (afferents)* and
- in the *motor plants (efferents) used for orienting toward them.*

Experimental prediction :

Dysfunction of MPC in species where the primary sensory apparatus is transported by the head (e.g., Salamander, Mice etc) would lead to a deficit in orienting the head toward a target (no eye dysmetria).



Interceptive saccades are accurate

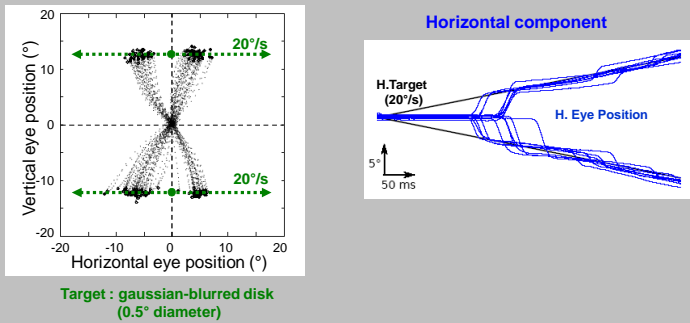


The here-and-now aspect of saccade endpoints

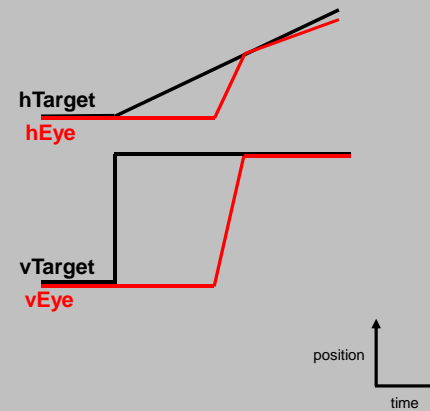
Animals can make saccadic eye movements to visually intercept the location of a moving object and foveate it *at the right place and time*, and initiate its pursuit.

Such interceptive saccades indicate that, in spite of variable sensorimotor delays, the brain activity is able to estimate the **here-and-now** location of a target, at least at the time of saccade landing.

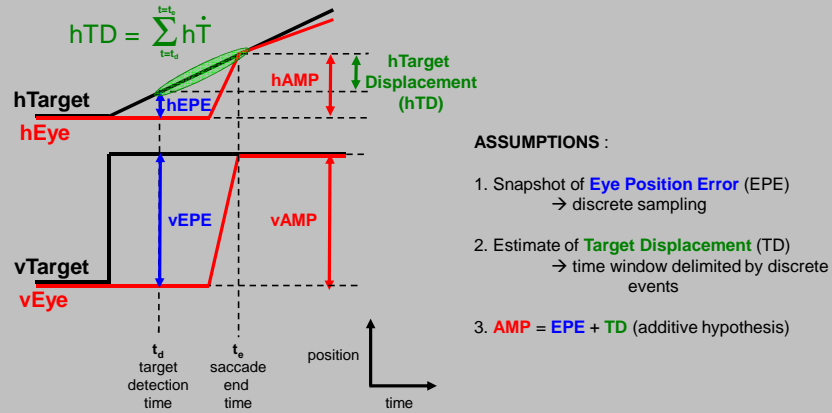
Saccades toward a moving target



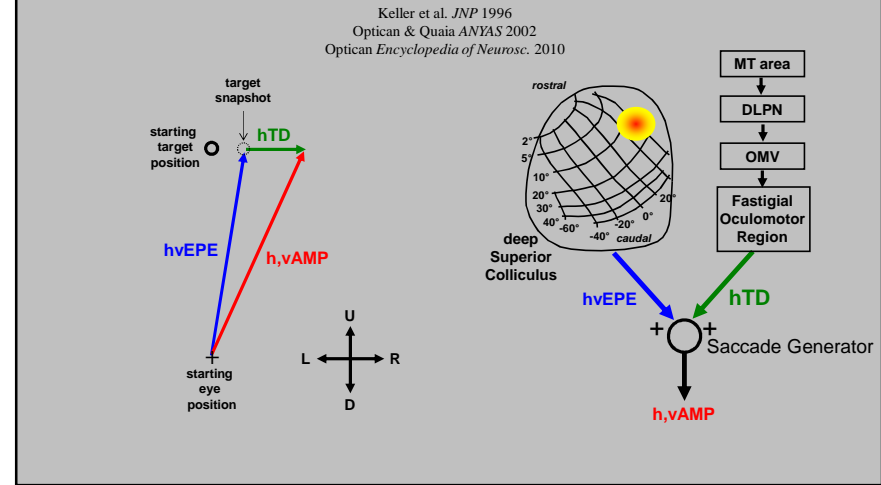
From the behavior to its neural substrate



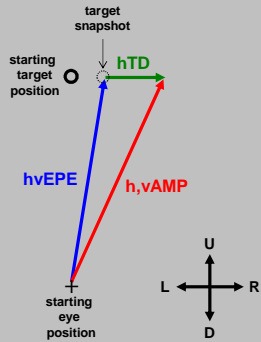
The dual-drive hypothesis



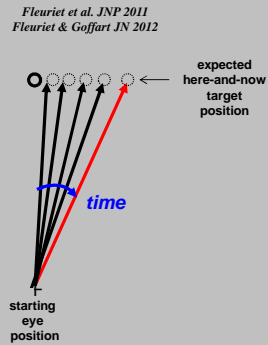
The dual-drive hypothesis



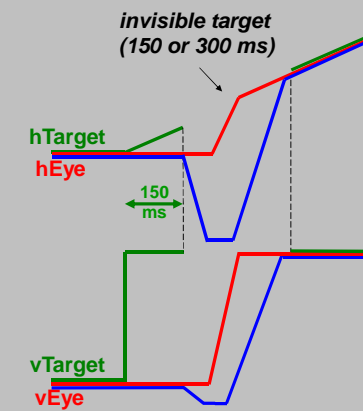
The 'dual drive' hypothesis



The 'dynamic remapping' or 'here-and-now' hypothesis

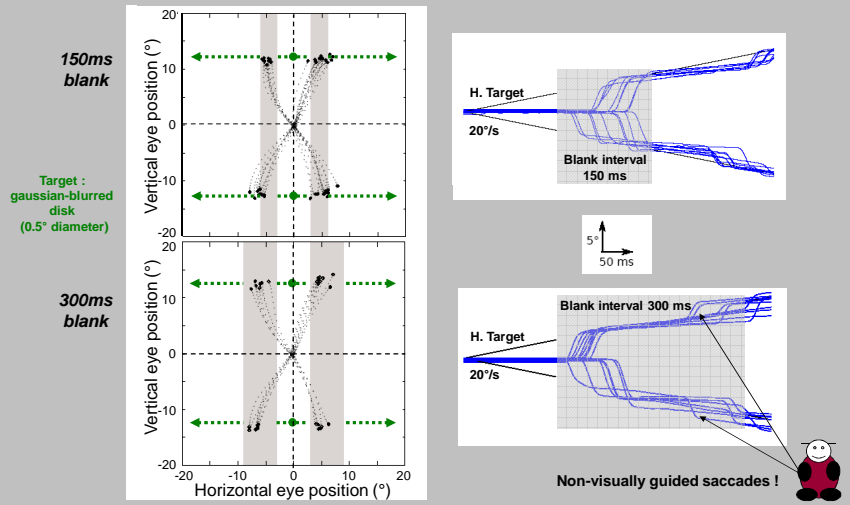


Visual feedback is removed



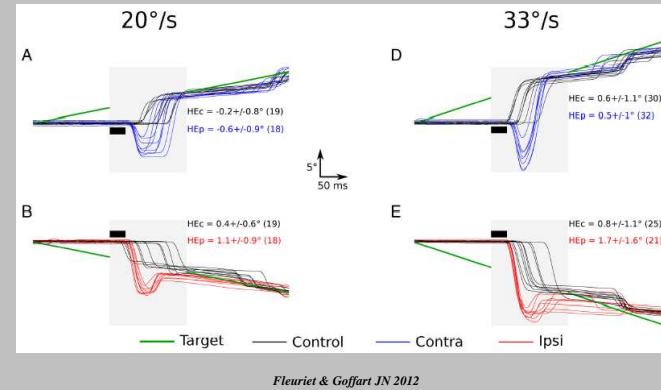
IF the saccade goal = here-and-now target position
THEN change in eye position and added delay should be taken into account (accurate saccades)

Saccadic interception of an occluded target



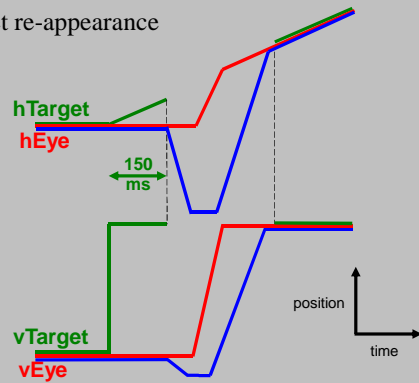
Perturbation of interceptive saccades

Microstimulation in the right deep Superior Colliculus (30ms 400Hz 12µA)

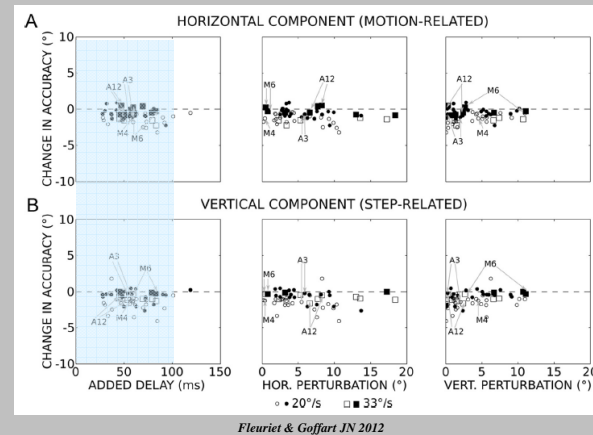


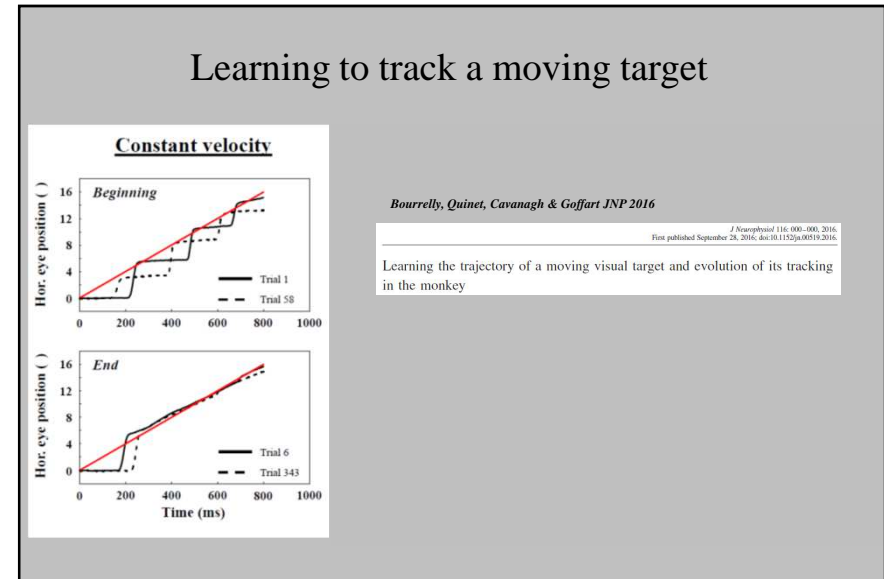
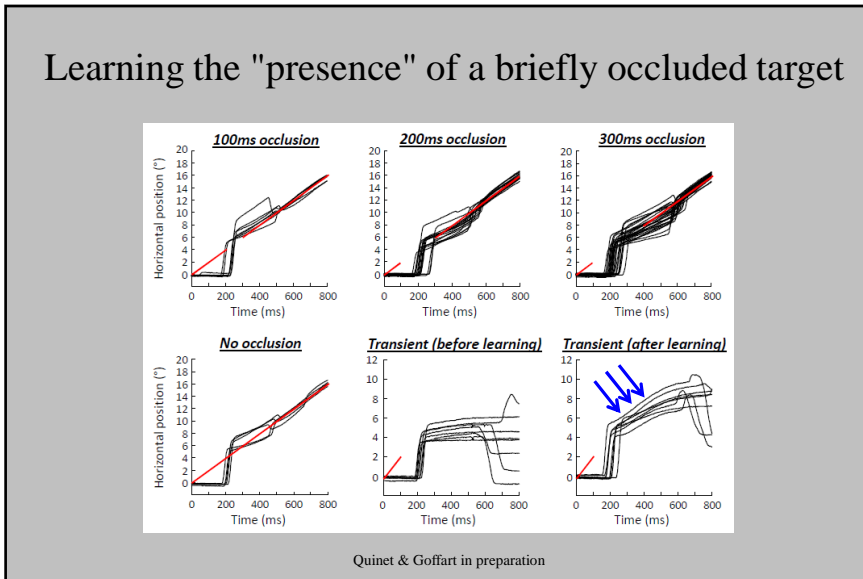
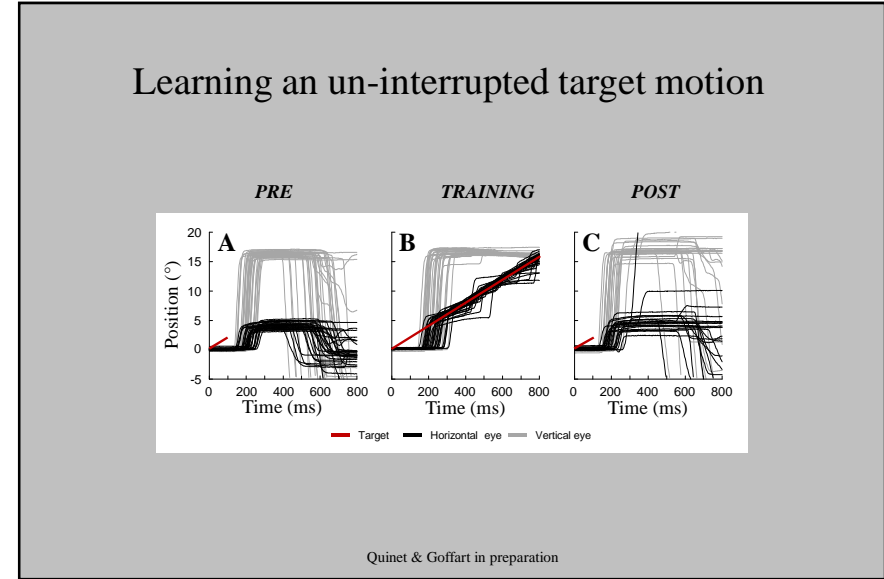
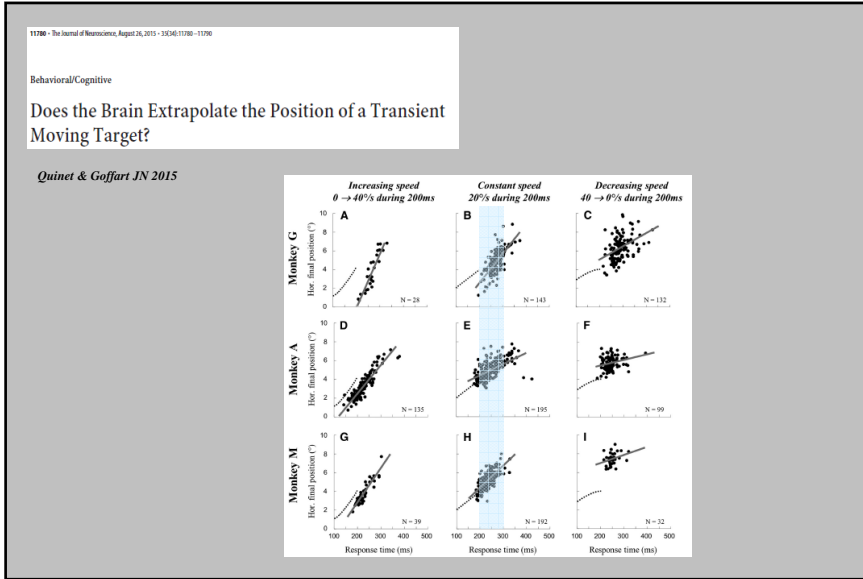
What signals drive the saccade during the occlusion ?

1. Extrapolation based upon pre-occlusion signals
2. Expectation of target re-appearance

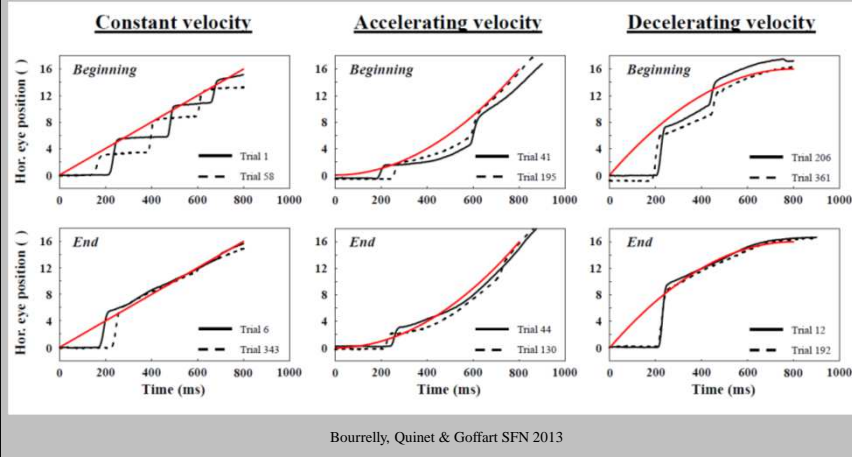


Interception time of perturbed saccades delayed by <150 ms





Learning to track a moving target



J Neurophysiol 116: 000-000, 2016.
First published September 28, 2016; doi:10.1152/jn.00519.2016.

Learning the trajectory of a moving visual target and evolution of its tracking in the monkey

Bourrelly, Quinet, Cavanagh & Goffart JNP 2016

What is learning the trajectory of a moving visual target ?

→ Is it building up an "internal model" of its trajectory ?

→ What then would be the neural representation of a target trajectory ?

How would a trajectory (spatiotemporal phenomenon) be represented in the brain activity ?
Should we presume a brain hyperspace within which the neural image of the target would move ? → complicated hypothesis

→ Alternative hypothesis :

Increase in the size of active population in foveal brain regions (e.g. rostral SC)

→ i) larger target size increases the pursuit gain

→ ii) larger target size is associated with a larger active population in the rostral SC

Conclusions

Space and time : *a priori* and necessary forms of intuition (Kant) or concepts (Poincaré) ?



"The properties of time are only those of clocks, like the properties of space are only those of measuring instruments"

"In fact, it [space] is amorphous, it is a flabby form, with no rigidity, that can be applied to anything; it has no intrinsic properties; doing geometry is studying the properties of our instruments"

Henri Poincaré
Dernières pensées (1917)

If space is a concept, searching for its neurobiological substrate is as meaningful as searching for the neurophysiological implementation of any other conventional notion.

The work that I presented indicates that space and spatial-related notions are not necessary notions for explaining the brain processes involved in foveating a visual target.

Acknowledgments

Experiments in the caudal Fastigial Nucleus

Head-free cat Denis Pélisson, PhD Alain Guillaume, PhD	Head-restrained monkey David L. Sparks, PhD Longtang L. Chen, PhD	Head-free monkey Lorenzo Guerrasio, PhD Ulrich Büttner, MD PhD Julie Quinet, PhD
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Experiments in the deep Superior Colliculus (monkey)

Ziad M. Hafed, PhD
Richard J. Krauzlis, PhD
Jérôme Fleuriet, PhD

Behavioral experiments

Sandrine Hugues, PhD
Julie Quinet, PhD
Clara Bourrelly, MS
Patrick Cavanagh, PhD

