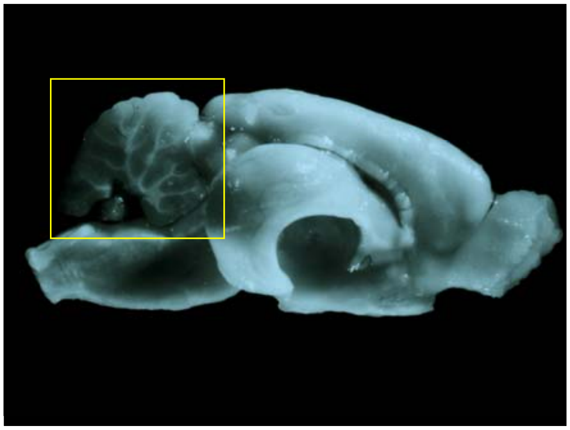


Cerebellum: Origins and Development

- Found in all vertebrates
- Dorsal lip of developing medulla (rhombencephalon)
- Near terminations of vestibular (VIII) and lateral line afferents, which sense fluid displacement
- Also inputs from tectum and spinal cord
- Ancestral role: “representing an image of the relations of the body in space” (Bullock 1969)
- Self vs. non-self?

Deficits associated with the cerebellum

Acute ablation (Rolando, Flourens, Holmes)
exaggerated reflexes, ballistic movements

Congenital reduction
ataxia, but also <u>autism</u> (Courchesne)

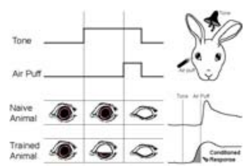
Sensory function may also be an ancestral principle

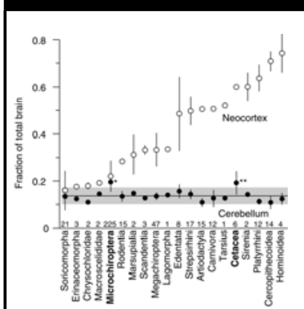
Functional roles for the cerebellum

Sensory surprise / error signals

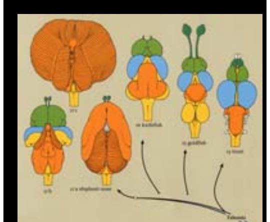
Motor coordination

Sensory teaching signal





Enlargement of the cerebellum for echolocation and electrolocation



Clark *et al.* (2001)

Nieuwenhuys *et al.*

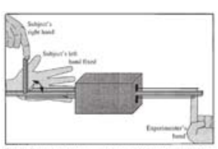
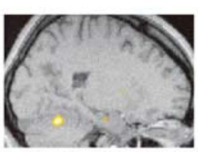


Fig. 1. Diagram of experimental set-up. A tactile stimulus device consisted of a piece of soft foam attached to a plastic rod (length 70 cm), which could pivot about its center. The rotation of the rod was

Central cancellation of self-produced tickle sensation

Sarah J. Blakemore[1,2], Daniel M. Wolpert[2] and Chris D. Frith[1]

nature neuroscience • volume 1 no 7 • november 1998 635



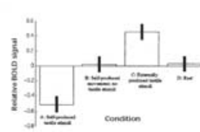


Fig. 5. Significantly decreased activity ($p < 0.05$, corrected for multiple comparisons) in right anterior cerebellar cortex associated with the interaction between the effects of self-generated movement and tactile stimulation. Shown are condition-specific parameter estimates, which reflect the adjusted BOLD contrast signal relative to the fitted mean and are expressed as a percentage of whole brain mean activity. The effects at the voxel 22, -58, -22 are shown, for illustration, for a single subject in the lower panel. Similar parameter estimates were obtained for the remaining subjects in this statistical model. Conditions are labeled as in Table 1. The right anterior cerebellar cortex was the only area of the brain activated in the contrast A–B.

Table 1

Brainstem, limbic and cerebellar abnormalities in autism: autopsy and MR imaging evidence.

Brainstem abnormalities	Limbic abnormalities	Cerebellar abnormalities
Autopsy evidence Rodier *et al.* 1996 [4••]	**Autopsy evidence** Bauman and Kemper 1985 [40] Bauman and Kemper 1994 [1] Raymond *et al.* 1996 [8•]	**Autopsy evidence** Williams *et al.* 1980 [2] Bauman and Kemper 1985 [40] Ritvo *et al.* 1986 [13] Bauman and Kemper 1986* Bauman and Kemper 1990† Arin *et al.* 1991‡ Fehlow *et al.* 1993 [14] Bauman and Kemper 1994 [1]
MR imaging evidence Gaffney *et al.* 1988 [18] Hashimoto *et al.* 1995 [17••]	**MR imaging evidence** None	**MR imaging evidence** Courchesne *et al.* 1987 [20] Gaffney *et al.* 1987 [21] Courchesne *et al.* 1988 [23] Murakami *et al.* 1989 [22] Ciesielski *et al.* 1990 [29] Piven *et al.* 1992 [26] Kleiman *et al.* 1992 [24] Courchesne *et al.* 1994 [25,27] Saitoh *et al.* 1995 [19••] Zilbovicius *et al.* 1995§ Hashimoto *et al.* 1995 [17••]

*ML Bauman, TL Kemper, abstract, *Neurology* 1986, 36:190. †ML Bauman, TL Kemper, abstract, *Neurology* 1990, 40:359. ‡DM Arin, ML Bauman, TL Kemper, abstract, *Neurology* 1991, 41:307. §M Zilbovicius *et al.*, abstract, *Neurology* 1995, 45:A162.

Courchesne 1997

Table 2 *Consistent neuropathological findings in autism*

Finding	n	New	MR	E	Results
Increased cell packing density and smaller neurons in the limbic system					
Kemper and Bauman (1993)	6	6	5	4	6 of 6
Guerin et al. (1996)	1	1	1	1	0 of 1
Raymond et al. (1996)	2	2	2	0	2 of 2 (only HBP measured)
Bailey et al. (1998)	6	6	6	3	1 of 5 (only HBP measured)
Total	15	15	14/15	8/15	9 of 14 (64%)
Decreased numbers of/smaller Purkinje cells in CB					
Williams et al. (1980)	4	4	4	2	1 of 4
Ritvo et al. (1986)	4	4	3	0	4 of 4
Fehlow et al. (1993)	1	1	1	0	1 of 1
Kemper and Bauman (1993)	6		5	4	6 of 6
Guerin et al. (1996)	1		1	1	0 of 1
Bailey et al. (1998)	6		6	3	5 of 6 (only the child unaffected)
Fatemi et al. (2002a)	5	5	?	?	2 of 5
Lee et al. (2002)	2		2	1	2 of 2
Total	29	14	22/24	11/24	21 of 29 (72%)
Age changes in CB nuclei and inferior olive					
Bauman (1991)	5		5	4	Large neurons in the 2 children, pale and small neurons in the 3 adults
Total	5	0	5	4	5 of 5 (100%)
Brainstem/olivary dysplasia					
Rodier et al. (1996)	1	1	1	1	1 of 1
Bailey et al. (1998)	5		5	3	3 of 5
Total	6	1	6/6	4/6	4 of 6 (67%)
Alterations in the neocortex					
Coleman et al. (1985)	1	1	1	0	0 of 1
Hof et al. (1991)	1	1	1	0	1 of 1 ↑NFT
Kemper and Bauman (1993)	6		5	4	5 of 6 poorly laminated ACC
Guerin et al. (1996)	1		1	1	0 of 1
Bailey et al. (1998)	6		6	3	4 of 6 abnormal FR neuronal count
Total	15	2	14/15	8/15	6/15 (40%)
Cortical dysgenesis					
Bailey et al. (1998)	6		6	3	4 of 6
Fatemi et al. (2001b)	5	5	3 or >	?	As a group ↓Bcl-2 and ↑p53 PA
Fatemi et al. (2001a)	5		?	?	As a group ↓Bcl-2 and reelin CB
Casanova et al. (2002c)	2AS	2AS	0	?	1 of 2 had smaller minicolumns
Casanova et al. (2002a)	9	9	?	5	As a group smaller minicolumns
Araghi-Niknam and Fatemi (2003)	5		?	?	As a group ↓Bcl-2 and ↑p53 FR
Total	32	14 + 2	16/22	8/15	
Abnormalities in cholinergic system					
Perry et al. (2001)	7	7	?	3 or >	As a group ↓M1 FR; ↓α4 FR + PA; ↑BDNF forebrain
Lee et al. (2002)	8	1	?	5	As a group ↓α3 and α4 and ↑α7 in CB
Total	15	8	14/15	8/15	
Abnormalities in GABAergic system					
Blatt et al. (2001)	4	4	4	2	↓GABAergic system in HBP
Fatemi et al. (2002b)	5		?	?	↓65 and 67 kDA GAD in CB and parietal cortex
Total	9	4	4/9	2/9	

ACC = anterior cingulate cortex; AS = Asperger's syndrome; BDNF = brain-derived neurotrophic factor; CB = cerebellum; E = epilepsy; FR = frontal cortex; GAD = glutamic acid decarboxylase; HBP = hippocampus; MR = mental retardation; n = number of autistic subjects; New = number of brains mentioned for the first time (58 autistic and two Asperger); NFT = neurofibrillary tangles; PA = parietal cortex; ? = not mentioned.

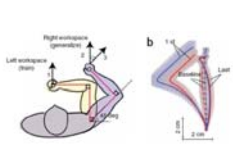
Palmen SJMC *et al.* (2004)
Brain, 127:2572-2583

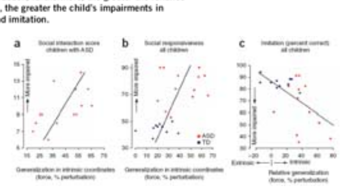
970 VOLUME 12 | NUMBER 8 | AUGUST 2009 NATURE NEUROSCIENCE

Representation of internal models of action in the autistic brain

Courtney C Haswell[1], Jun Izawa[1], Lauren R Dowell[2], Stewart H Mostofsky[2,3] & Reza Shadmehr[1]

Children with autism spectrum disorder (ASD) have deficits in motor control, imitation and social function. Does a dysfunction in the neural basis of representing internal models of action contribute to these problems? We measured patterns of generalization as children learned to control a novel tool and found that the autistic brain built a stronger than normal association between self-generated motor commands and proprioceptive feedback; furthermore, the greater the reliance on proprioception, the greater the child's impairments in social function and imitation.





Timing-based theories

- Eccles' dynamic loop control hypothesis
  - Lead-lag compensator
  - Transforming sensory into muscle space (Pellionisz and Llinas)
  - Modulate, accelerate or synchronize movements (Llinas/Welsh/Bloedel/Thach)
  - "Smith predictor"/inverse dynamics (Miall)

Learning-based theories

- The cerebellum as a site of learning (Marr/Albus/Ito)
  - Vestibulo-ocular reflex gain adaptation (Lisberger/Raymond)
  - Eyeblink conditioning (Thompson/Mauk)
- Sensory expectation subtraction
  - Adaptive learning /inverse dynamics (Miall)
  - Subtraction of sensory expectations (Bell)

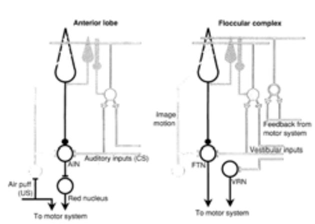


Fig. 2. Simplified circuit diagrams illustrating similarities of the neural pathways that mediate classical conditioning of the eyelid response (left) and motor learning in the VOR (right). The transmission of the air-puff US for eyelid conditioning and the image motion error signal for VOR learning over mossy-fiber pathways are discussed in the text but not shown here. AIN, anterior interpositus nucleus; FTN, floccular target neuron; VRN, vestibular relay neuron; color code as in Fig. 1.

TINS Vol. 21, No. 9, 1998 391

Microcircuitry and function of the inferior olive

Chris I. De Zeeuw, John I. Simpson, Casper C. Hoogenraad, Niels Galjart, S.K.E. Koekkoek and Tom J.H. Ruigrok

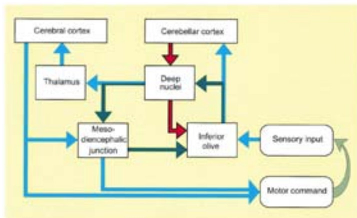
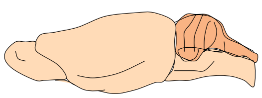
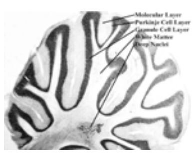


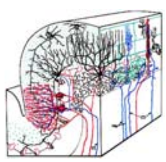
Fig. 1. *The three-element network (dark blue) composed of the mesodiencephalic junction, deep cerebellar nuclei, and inferior olive forms an important loop in sensorimotor control.* Red arrows indicate inhibitory pathways and (light and dark) blue arrows mark excitatory systems.

Cerebellar Structure and Anatomy

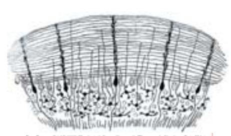




Sagittal cerebellar slice stained with cresyl violet.

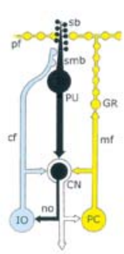


Structure of the cerebellar cortex.
Mossy fiber & climbing fiber afferents: BLUE
Granule cells & parallel fibers: GREEN
Purkinje cells: RED
Inhibitory interneurons: BLACK



Common features of all cerebella

1. Cerebellar cortex
Purkinje neurons, the sole output: <u>inhibitory</u>
2. Inputs:
Mossy fibers>>granule cells>parallel fibers
The inferior olive>climbing fibers
3. Output: The vestibular nuclei and deep nuclei
4. A few local inhibitory neurons: stellate and Golgi neurons



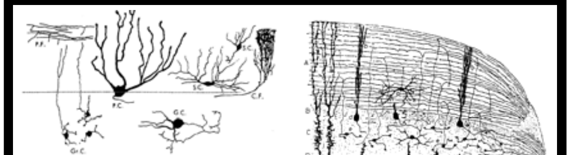


Fig. 5. Neural elements of the dogfish cerebellum. These drawings of Golgi preparations are reproduced from figures prepared by SCHAPER (1898 [25]), by HOUSER (1901 [12]) and by ARIENS KAPPERS, HUBER, and CROSBY (1936 [1]). The broken line represents the plane of the Purkyně cell bodies and separates the molecular layer from the granular layer. Full description in text

Fig. 6. Drawing of a longitudinal section along the transverse folium of a lizard cerebellum. *A*, *B*, *C* and *D* show respectively the molecular, Purkyně, granular and ependymal layers and *E* is the peduncle. Glia cells are shown in *j*. Full description in text [24]

JC Eccles (1969) *Naturwissenschaften* 56:525-534

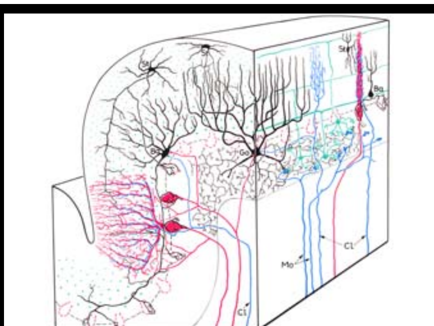
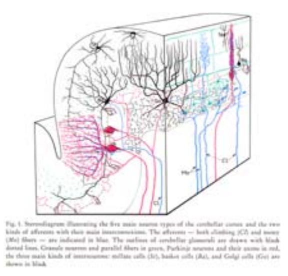


Fig. 1. Stereodiagram illustrating the five main neuron types of the cerebellar cortex and the two kinds of afferents with their main interconnexions. The afferents — both climbing (*Cl*) and mossy (*Mo*) fibers — are indicated in blue. The outlines of cerebellar glomeruli are drawn with black dotted lines. Granule neurons and parallel fibers in green, Purkinje neurons and their axons in red, the three main kinds of interneurons: stellate cells (*St*), basket cells (*Ba*), and Golgi cells (*Go*) are shown in black

Innovations during cerebellar evolution

1. *Increasing divergence of the mossy fiber pathway*
2. *Proliferation of inhibitory neurons:*
   Golgi neurons (not quite the same in dogfish), basket cells (birds and mammals)

3. Lugaro cells, unipolar brush cells

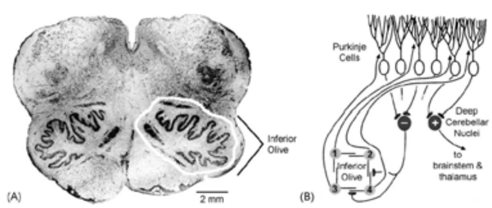


Median cell counts in vertebrate cerebellar structures

	Purkinje cells (10^3)	Granule cells (10^6)	Inferior olive (10^3)	Deep nuclei (10^3)	*Purkinje:deep n. cell ratio*	*Olive:deep n. cell ratio*
human	16,500	54,000	1,030	620[*]	*26*	*1.7*
monkey	3,600	3,500	-	260[*]	*14*	-
cat	1,500	2,200	140	46[*,†]	*33*	*3.0*
rat	400	120	50[*]	78[*]	*5*	*0.6*
mouse	200	41	30	19	*11*	*1.6*
dogfish	35	11	-	1.1[*]	*33*	-
					20 ± 12	**1.7 ± 1.0**

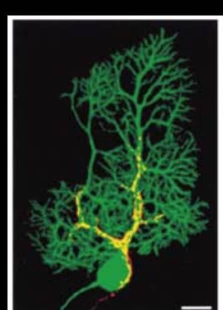
[*]n=1.
[†]Deiters' nucleus excluded.

From data summarized in KWT Caddy and TJ Biscoe (1978) *Phil Trans Roy Soc Lond Ser B* 287:167-201, with additional measurements from BB Gould and P Rakic (1981) *Exp Brain Res* 44:195-206, R Alvarez and R Anadón (1987) *J Hirnforsch* 28:133-137, RJ Harvey and RMA Napper(1991) Prog Neurobiol 36:437-463, JA Heckroth (1994) *J Comp Neurol* 343:173-182, and R Alvarez-Otero et al (1996) *J Comp Neurol* 368:487-502.



Climbing fibers

- Powerful input causing massive dendritic spike
- More focused in their branching than mossy fibers
- Instructive signal conveying errors or other sensory events (Marr, Albus, Ito)
- Regulation of Purkinje cell excitability:
  Synchronize sodium spike activity of Purkinje cells (Llinás, Welsh)
  Fire together to accelerate movement (Bloedel)



Kreitzer *et al.* 2000

Functions of climbing fiber firing and complex spikes

- Sensory events such as error signals (Simpson *et al* 1996 *Behav Brain Sci*)
- Instructive signal for learning (Raymond *et al* 1996 *Science*)
- Synchronization guides timing and activity (Welsh 2002 *NYAS*)

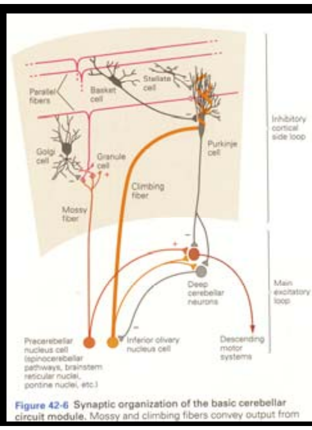
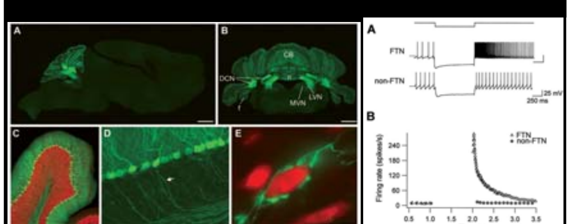


Figure 42-6 Synaptic organization of the basic cerebellar circuit module. Mossy and climbing fibers convey output from

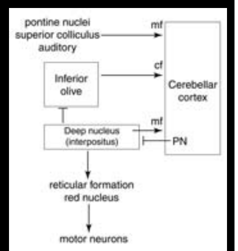
Floccular target neurons in the medial vestibular nucleus: deep-nuclear homologs



C Sekirnjak *et al.* (2003) *J. Neurosci.* 23:6392-639

Deep nuclei

- Output relay of cerebellum; target of Purkinje cell axon output
- Inhibit inferior olive and send mossy fibers back into cerebellum
- Possible site of learning
- Reverberating activity?
  …a black box.



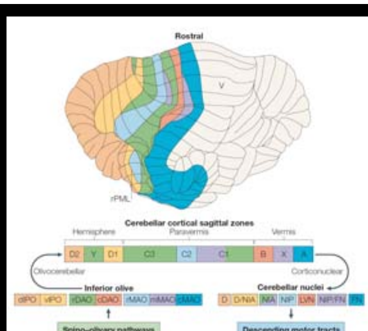
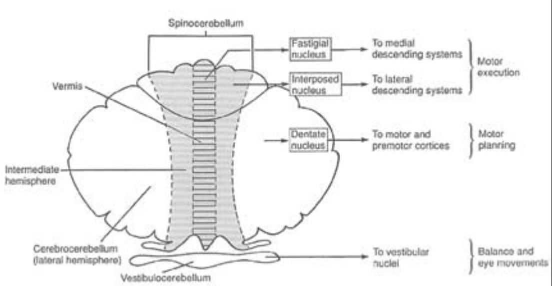
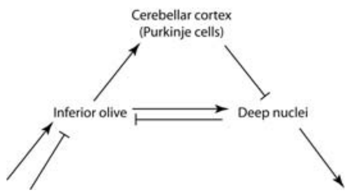


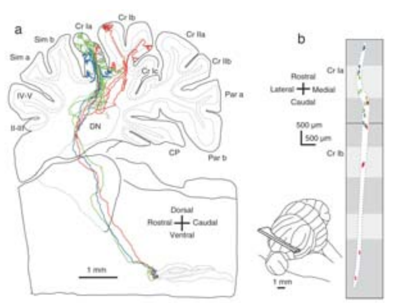
Figure 2 | **Connectivity of the cerebellum.** The top panel shows a dorsal view of the cat cerebellum, indicating the approximate location of different sagittal zones on the cerebellar surface. In the simplified block diagrams below, matching colours show, for individual cerebellar cortical zones, the sites of origin of climbing fibres in the contralateral inferior olive, and the corresponding corticonuclear output targets in the ipsilateral cerebellar nuclei. Different regions of the inferior olive

Apps and Garwicz (2005) *Nat Rev Neurosci* 6:297-311



Kandel et al. 1991 / Barlow





Sugihara I, Wu H-S, Shinoda Y (2001) *J. Neurosci.* 21:7715-7723

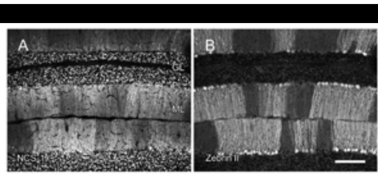
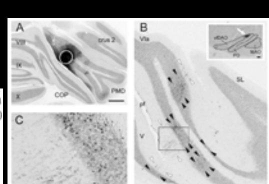


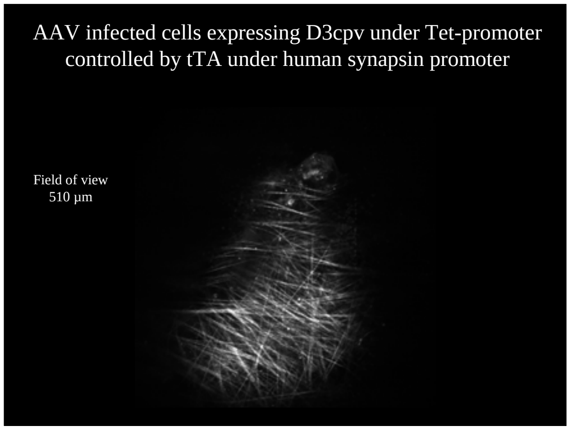
Figure 3
Immunofluorescent double-labeled images for NCS-1 (A) and zebrin II (B) in the vermis of posterior lobules. The boundaries of NCS-1 immunostained bands are comparable to those defined by zebrin II. GL, granule cell layer; ML, molecular layer; PL, Purkinje cell layer. Scale bar in B = 200 µm (applies to A and B).

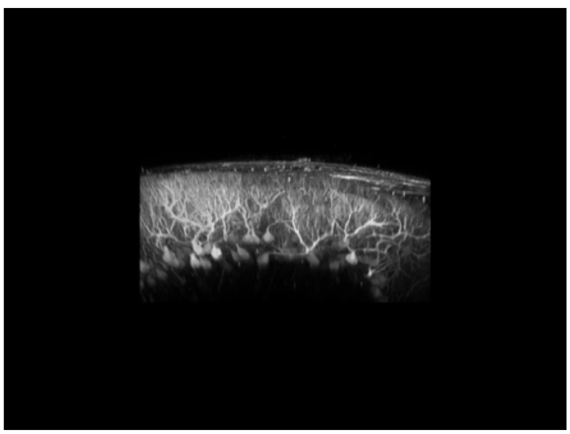
Jinno, Jeromin, and Kosaka (2004) *Cerebellum* 3:83-88

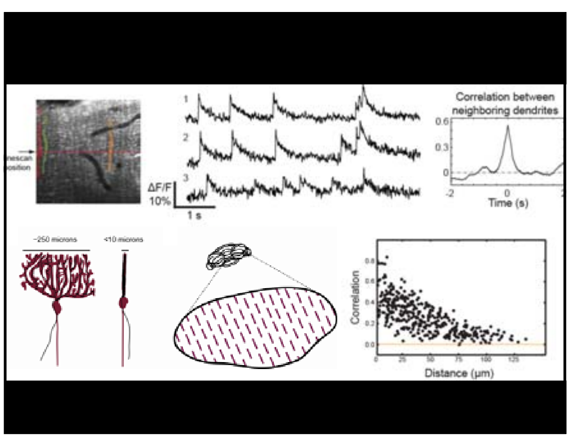
Pijpers et al. • Congruence in Mossy and Climbing Fiber Organization
J. Neurosci., November 15, 2006 • 26(46):12067–12080

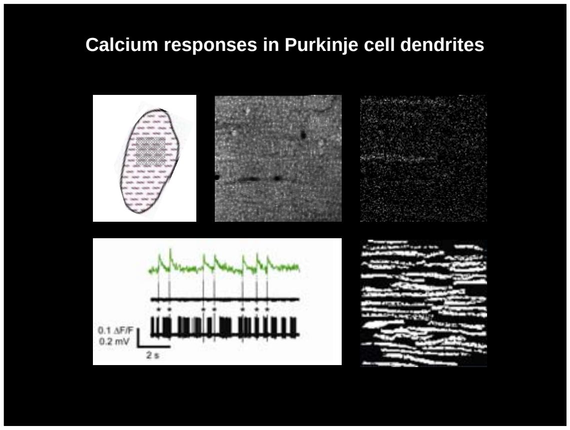
Terminal arborizations of labeled climbing fiber collaterals were confined ipsilaterally within the molecular layer of both the anterior and posterior cerebellum, usually in rostrocaudally oriented strips that were usually a few and up to ~10 Purkinje cells wide (Fig. 1*B–D*).

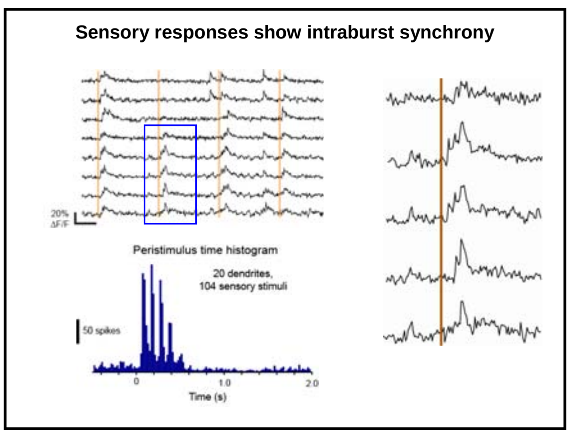


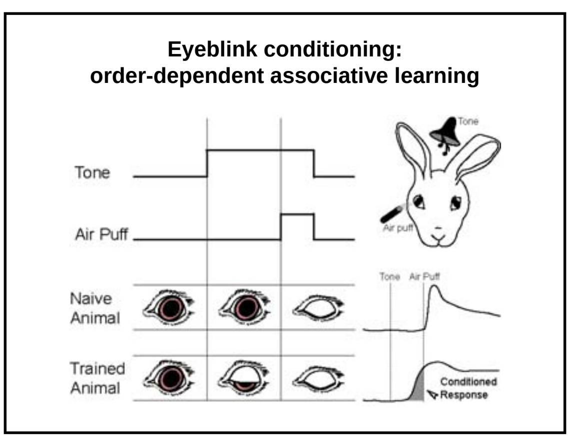

AAV infected cells expressing D3cpv under Tet-promoter controlled by tTA under human synapsin promoter
Field of view
510 µm



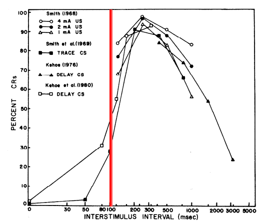

Correlation between neighboring dendrites
Time (s)
ΔF/F
10%
1 s
Correlation
Distance (µm)


Calcium responses in Purkinje cell dendrites
0.1 ΔF/F
0.2 mV
2 s


Sensory responses show intraburst synchrony
20% ΔF/F
Peristimulus time histogram
20 dendrites,
104 sensory stimuli
50 spikes
0
1.0
2.0
Time (s)


Eyeblink conditioning:
order-dependent associative learning
Tone
Air Puff
Naive Animal
Trained Animal
Tone
Air puff
Tone
Air Puff
Conditioned Response

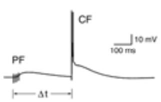
Timing-dependence of eyeblink conditioning *in vivo*

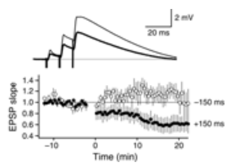


In eyeblink conditioning, tone must precede airpuff by >80 msec

I. Goremezano, E.J. Kehoe, and B.S. Marshall (1983)
Prog. Psychobiol. and Physiol. Psych., 10:197-275

Cerebellar long-term depression is order-dependent





Wang, Denk and Hausser (2000)
Nature Neuroscience 3:1266

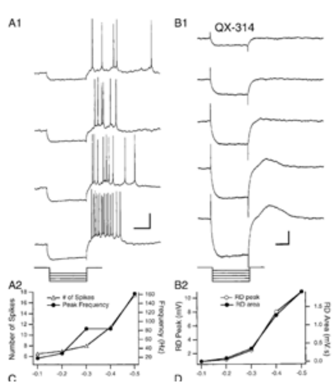
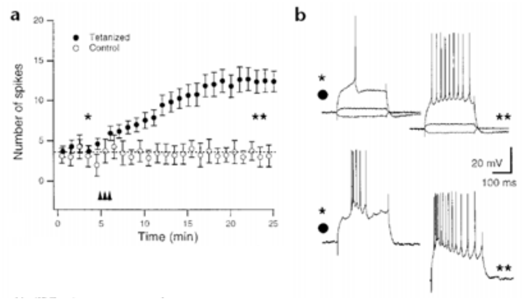


FIG. 3. RD induction is dependent on the amplitude of the hyperpolarizing pulse. *A1*: sample traces of RDs and associated spike bursts evoked by hyperpolarizing pulses with amplitudes ranging from −0.2 to −0.5 nA in a cell held at −65 mV. *A2*: plot of number of RD-evoked spikes (△) and peak spiking frequency (●) as a function of hyperpolarizing pulse amplitude. *B1*: sample traces of RDs in a QX-314-filled cell held at −55 mV, evoked by hyperpolarizing pulses with amplitudes ranging from −0.1 to −0.5 nA. *B2*: RD area (●) and peak amplitude (○) plotted as a function of pulse amplitude. *C* and *D*: corresponding aver-

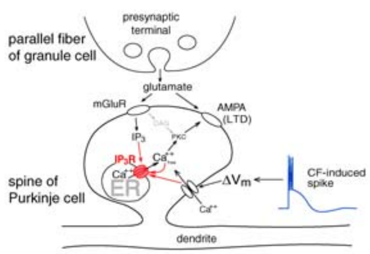
Rapid, synaptically driven increases in the intrinsic excitability of cerebellar deep nuclear neurons

Carlos D. Aizenman and David J. Linden

nature neuroscience • volume 3 no 2 • february 2000 109



The IP_3 receptor: a synaptic coincidence detector



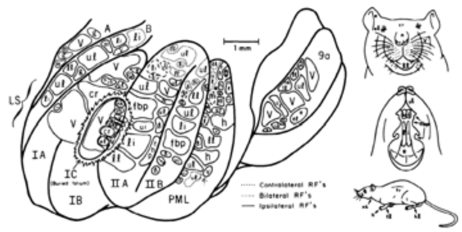
Parallel fiber (IP_3) and climbing fiber (Ca^{++} entry) activity co-activate calcium release

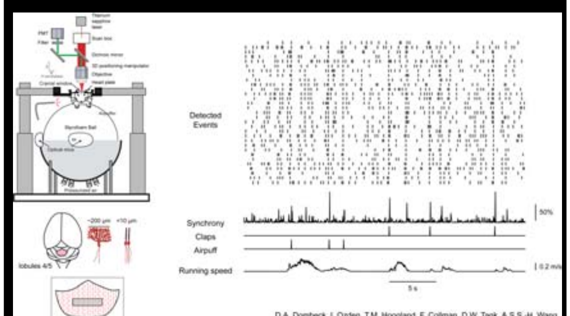
Functions of the olivary system

- Cerebellar cortex: local chemical signaling
- Inferior olive: local and regional synchrony
- Deep nuclei: coincidence-based readout mechanism

Congruence of Spatial Organization of Tactile Projections to Granule Cell and Purkinje Cell Layers of Cerebellar Hemispheres of the Albino Rat: Vertical Organization of Cerebellar Cortex

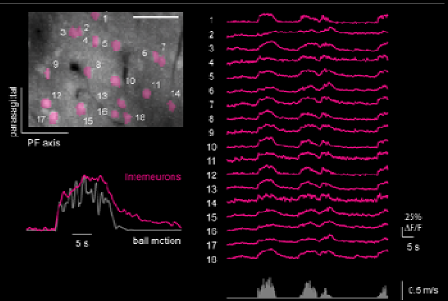
Bower JM and Woolston DC (1983) J. Neurophysiol. 49:745-766





Interneuron activation in a running mouse

Interneuron activation in a running mouse



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Microcircuitry and function of the inferior olive

Chris I. De Zeeuw, John I. Simpson, Casper C. Hoogenraad, Niels Galjart, S.K.E. Koekkoek and Tom J.H. Ruigrok

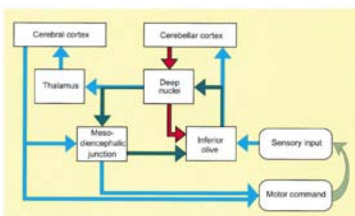

Fig. 1. *The three-element network (dark blue) composed of the mesodiencephalic junction, deep cerebellar nuclei, and inferior olive forms an important loop in sensorimotor control.* Red arrows indicate inhibitory pathways and (light and dark) blue arrows mark excitatory systems.