Maturation and plasticity in biological and artificial networks
October 20-25th 2024

To live and let die: How spontaneous activity controls programmed cell death in the developing cortex

Heiko J. Luhmann
Institute of Physiology
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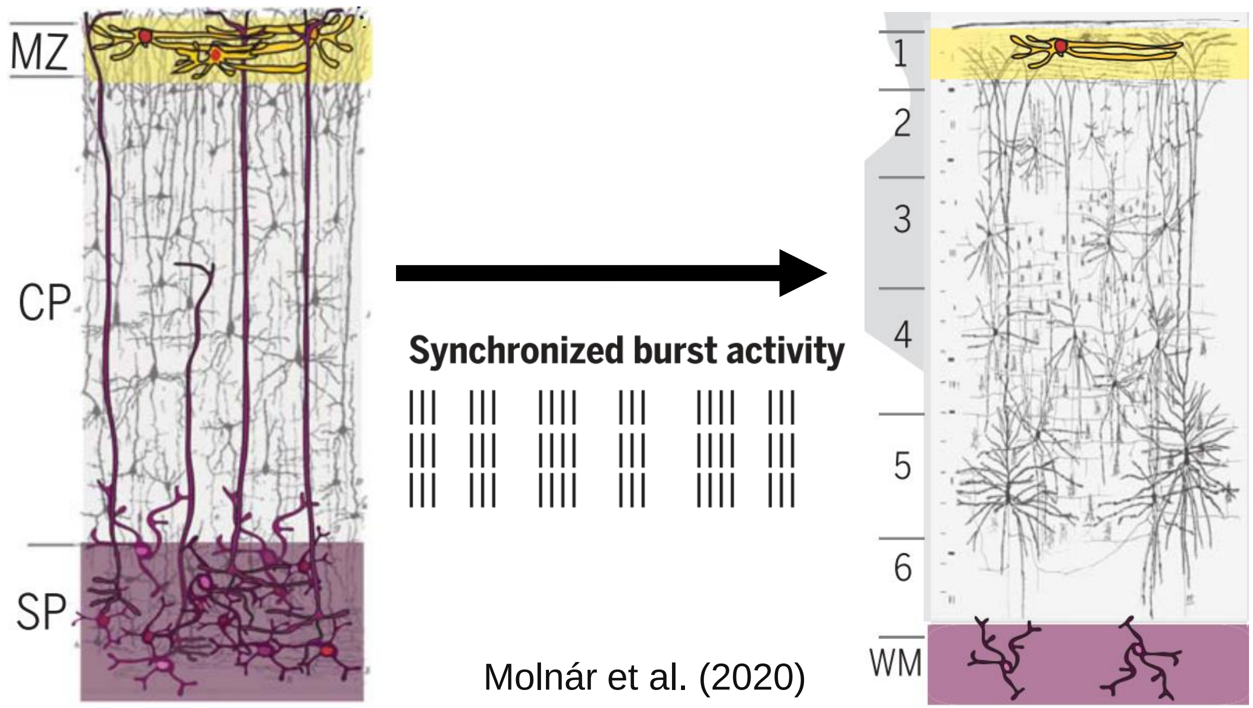


Molnár et al. (2020)

Questions

Q1: What type(s) of physiological spontaneous / ongoing activity can we observe in the very immature (prenatal and early postnatal) cortex?

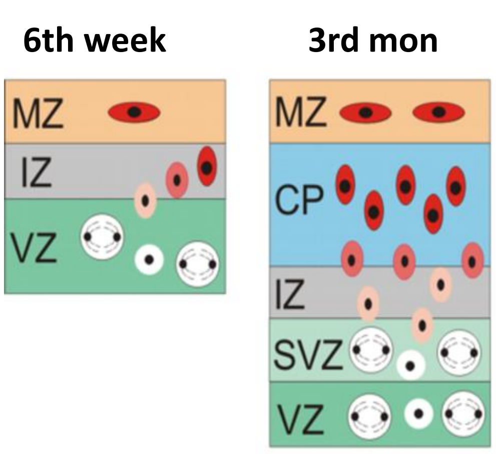
Q2: What are the functional properties of this activity (local, global, wave-like etc.) (in P0-P15 mice in vivo) ?

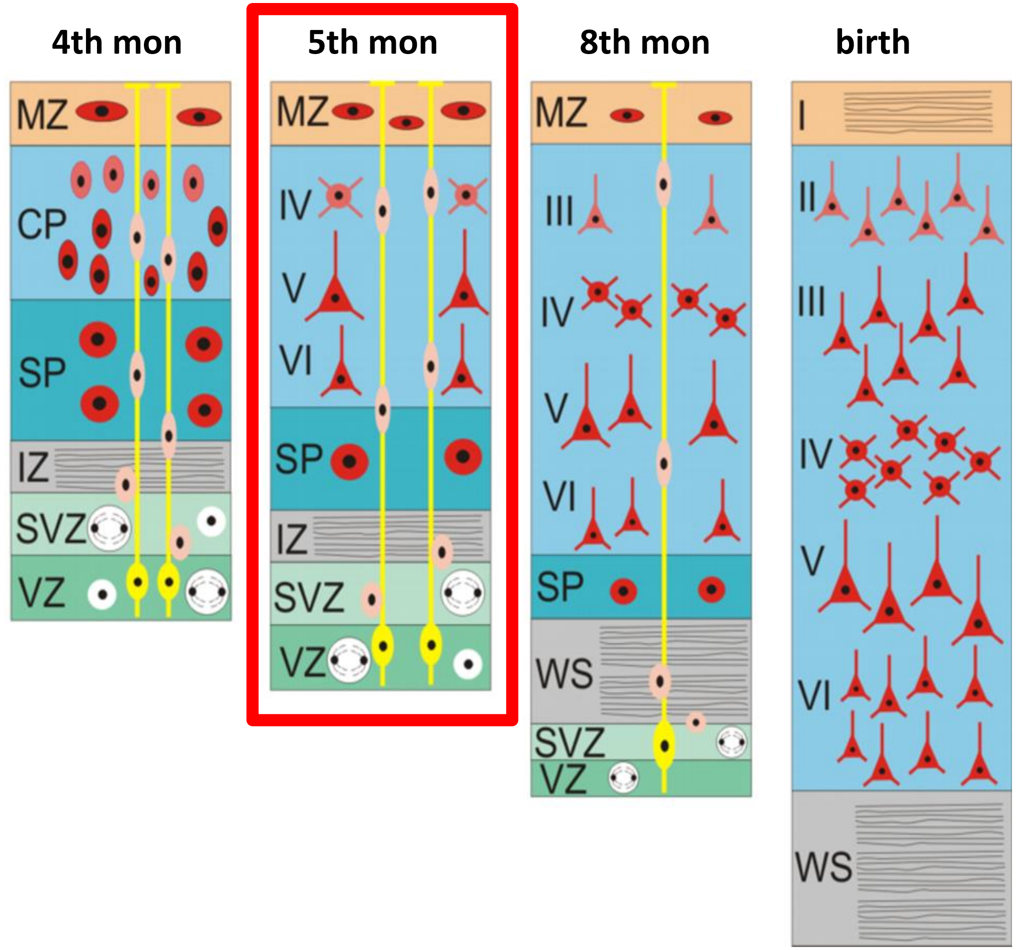
Q3: How is this early activity generated (in newborn rodents) ?

Q4: What is the physiological function of this early activity?

Q5: What are the long-term consequences of disturbances of this activity during early development?

Prenatal development of the human cerebral cortex





Q1: What type(s) of <u>physiological</u> spontaneous activity can we observe in the very immature (prenatal and early postnatal) cortex?

Milh, ..., Khazipov (2009) *Cerebral Cortex*

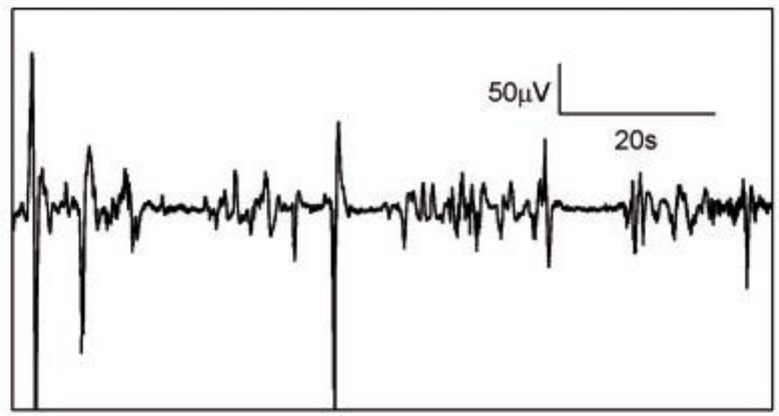
Cortical bursts in EEG are early biomarkers

doi:10.1093/brain/awv129 BRAIN 2015: 138; 2206–2218 | 2206

BRAIN
A JOURNAL OF NEUROLOGY

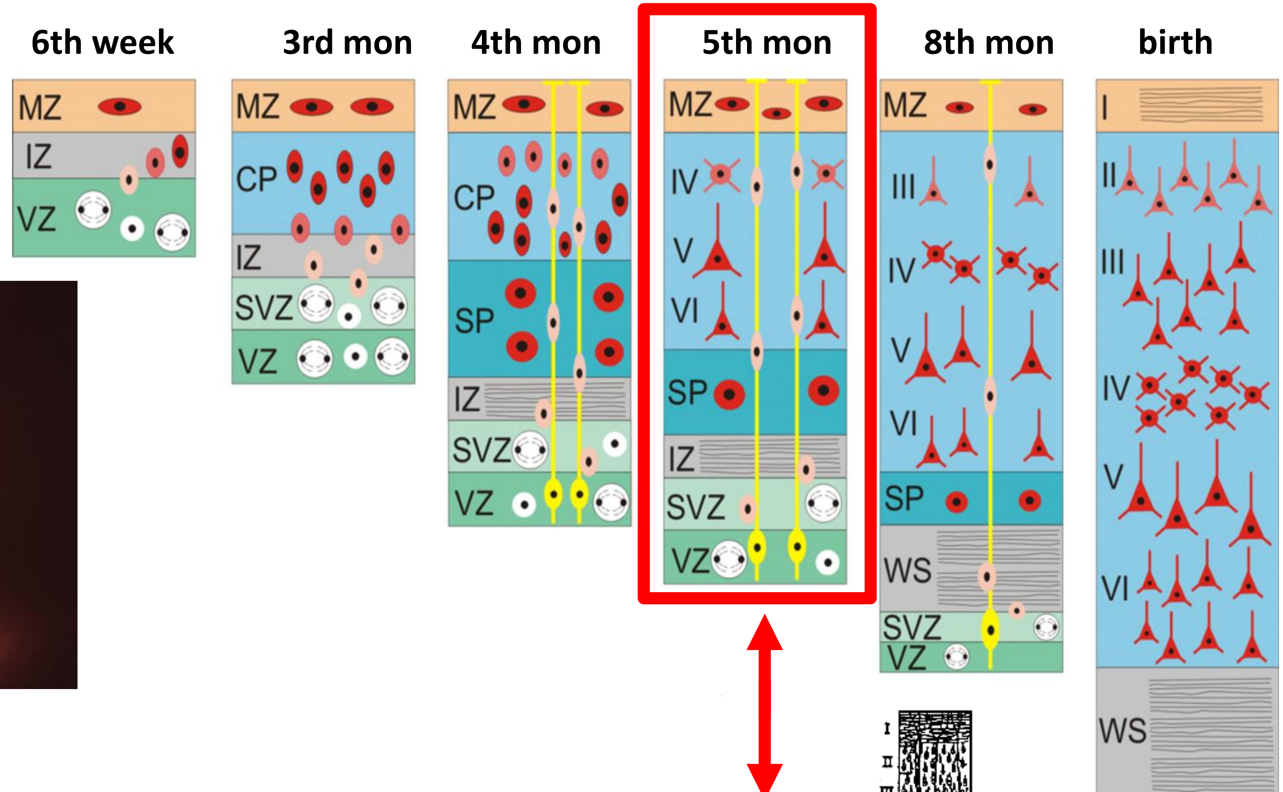
Cortical burst dynamics predict clinical outcome early in extremely preterm infants

Kartik K. Iyer,[1,2] James A. Roberts,[1] Lena Hellström-Westas,[3] Sverre Wikström,[4] Ingrid Hansen Pupp,[5] David Ley,[5] Sampsa Vanhatalo[6,7] and Michael Breakspear[1,8]

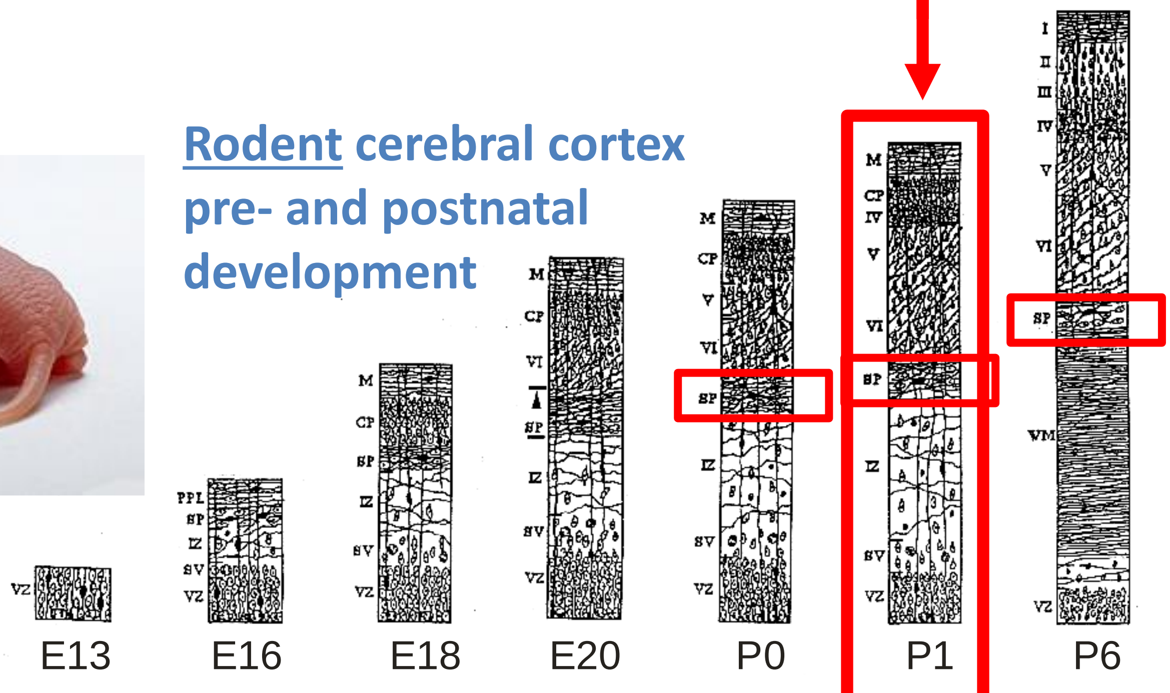


We examined electroencephalographic recordings from 43 extremely preterm infants (gestational age 22–28 weeks) and demonstrated that their cortical bursts exhibit scale-free properties as early as 12 h after birth. The scaling relationships of cortical bursts correlate significantly with later mental development—particularly within the first 12 h of life. These findings show that early preterm brain activity is characterized by scale-free dynamics which carry developmental significance, hence offering novel means for rapid and early clinical prediction of neurodevelopmental outcomes. **over the next 2 years!**

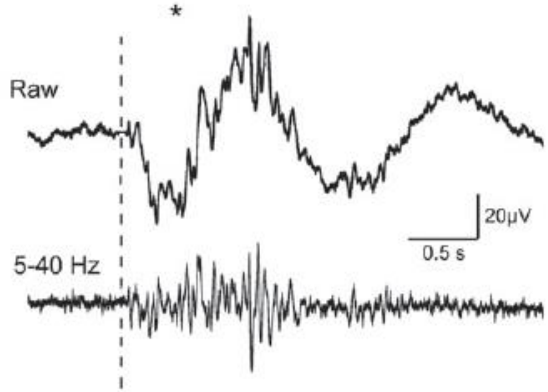
Human cerebral cortex prenatal development

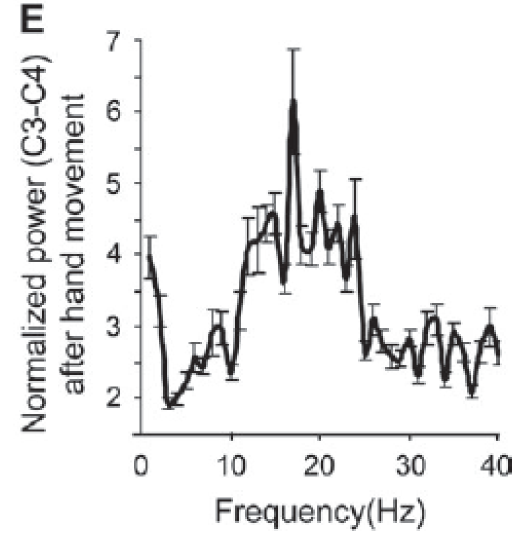


Rodent cerebral cortex pre- and postnatal development



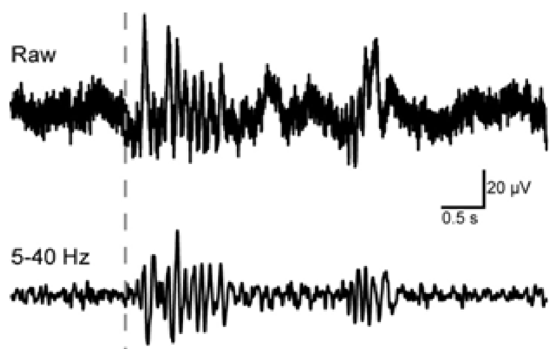
Spontaneous and evoked EEG activity in preterm human baby (*delta brush*)

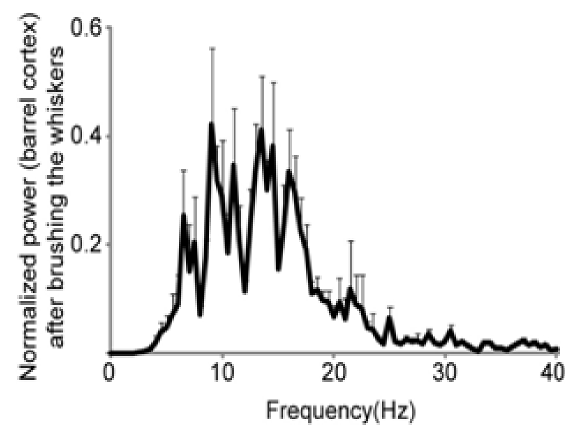




Milh, ..., Khazipov (2009) *Cerebral Cortex*

Spontaneous and evoked EEG activity in newborn rodent (*spindle burst*)





Take home messages

M1: During late prenatal and early postnatal development the cerebral cortex shows spontaneous synchronized burst activity, both in humans (e.g. *delta brush*) and rodents (*spindle bursts*).

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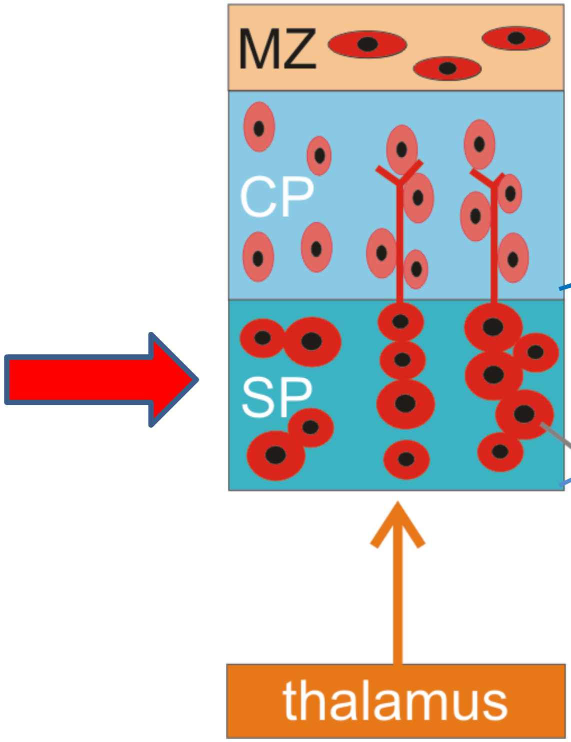
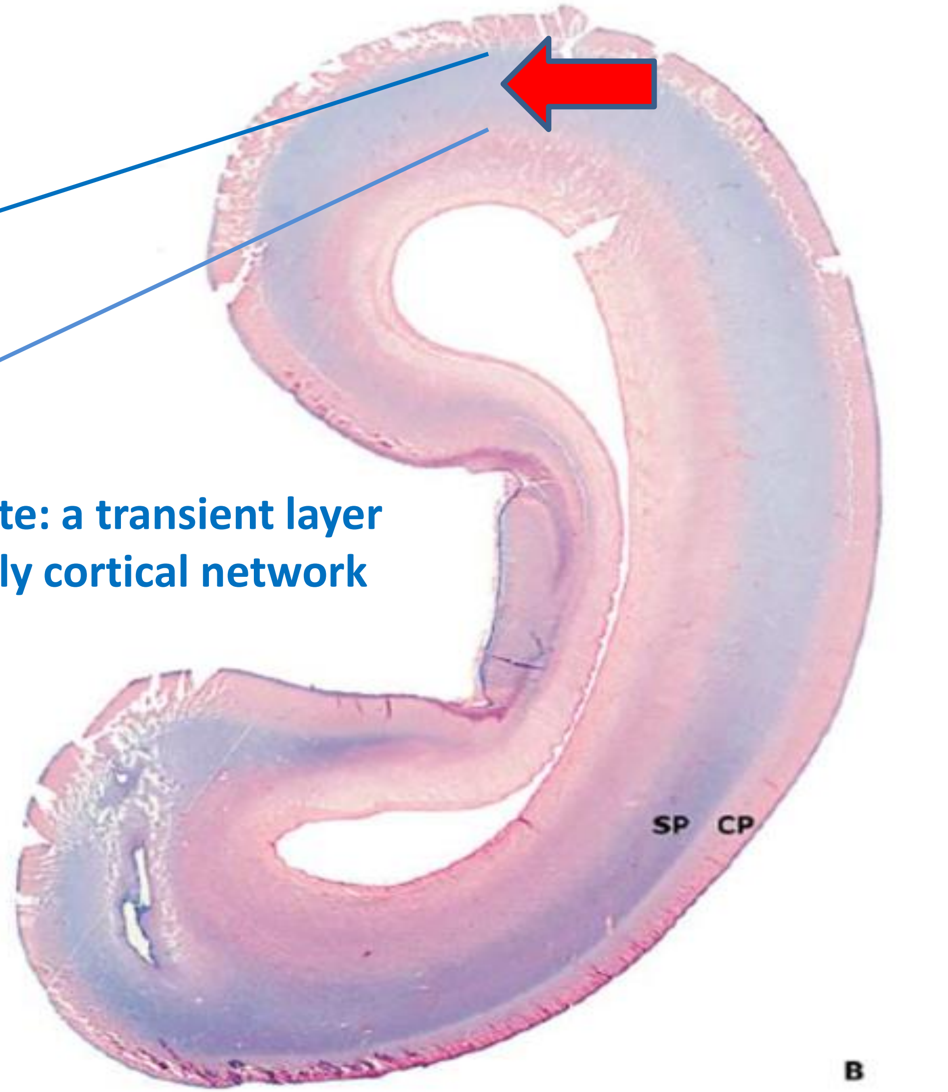
Q3: How is this early activity generated (in newborn rodents) ?



The subplate: a transient layer in the early cortical network



B PAS-Alcian blue-stained histochemical preparation of the 18-week-old human fetal telencephalon demonstrating the high content of acid sulphated glycoconjugates within the subplate zone (blue).

Kostovic & Judas (2002)

Progress in Neurobiology xxx (xxxx) xxxx

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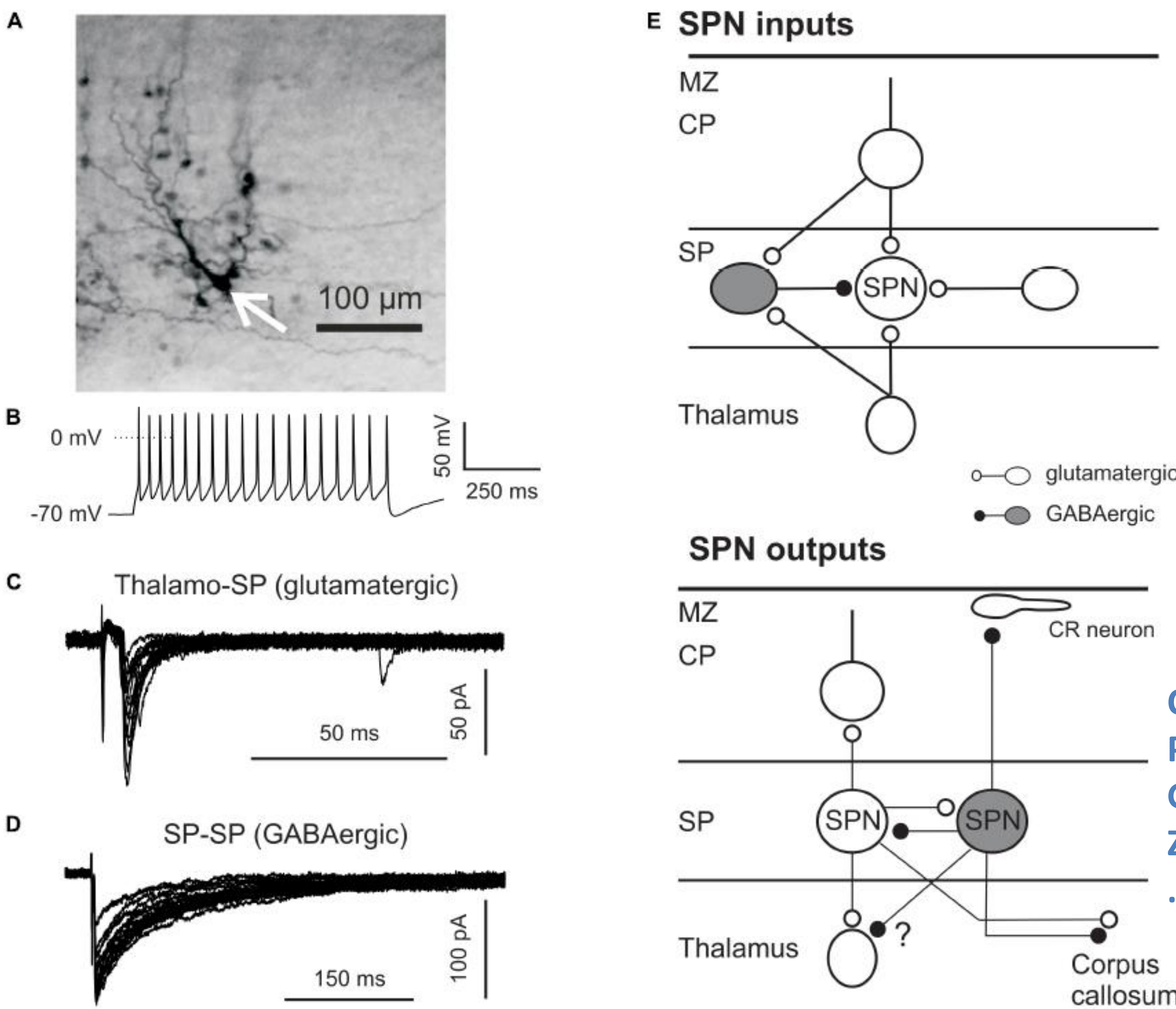
Review article

The enigmatic fetal subplate compartment forms an early tangential cortical nexus and provides the framework for construction of cortical connectivity

Ivica Kostović

Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience, Salata 12, 10000 Zagreb, Croatia

The subplate: a transient hub station in the early cortical network

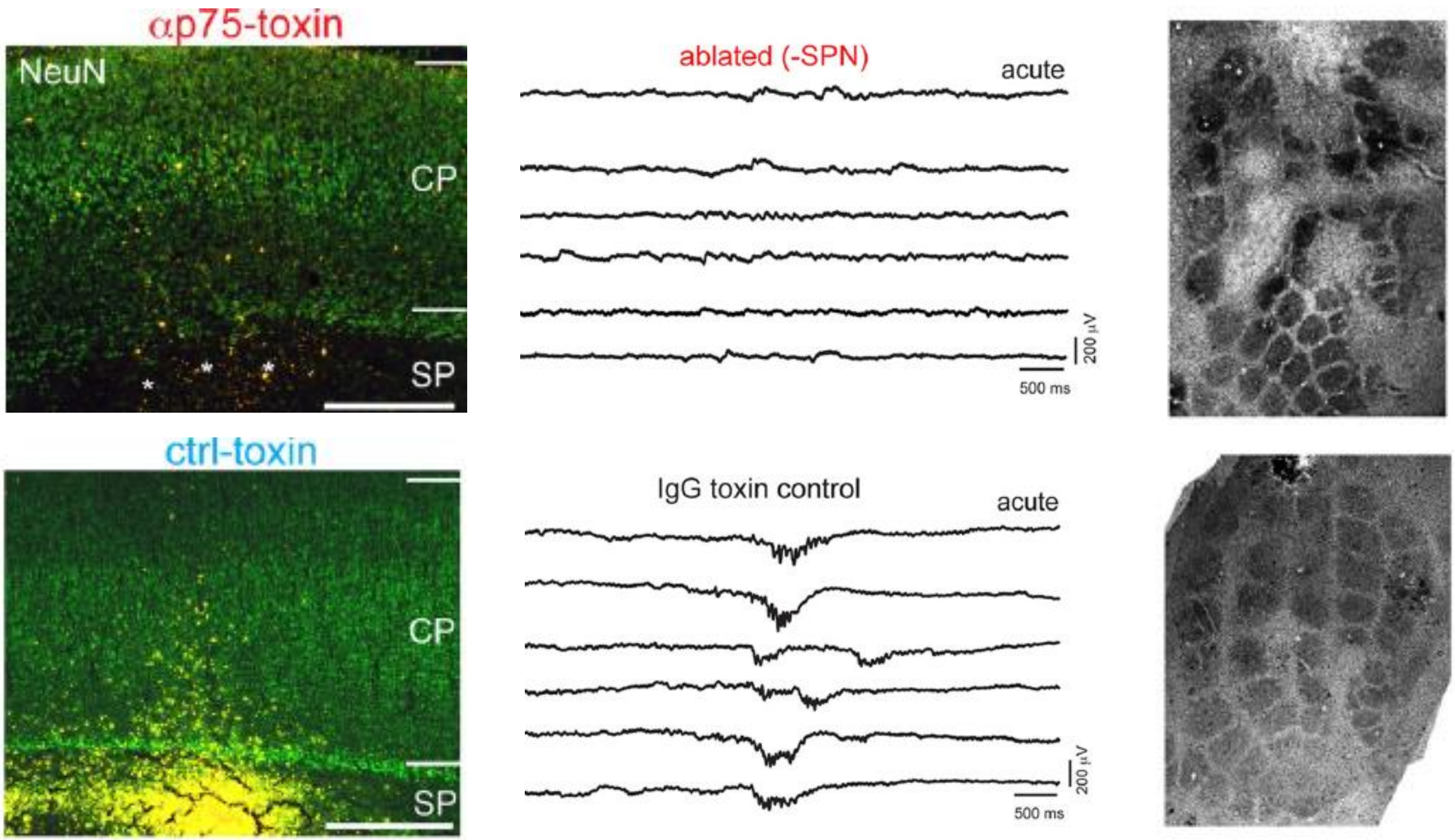


Carla Shatz
Patrick Kanold
Guille López-Bendito
Zoltan Molnar
....

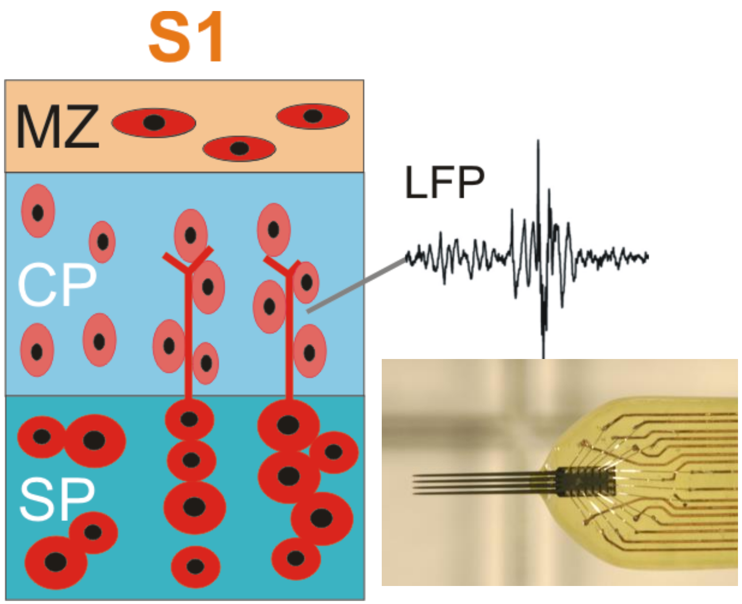
Subplate Neurons Promote Spindle Bursts and Thalamocortical Patterning in the Neonatal Rat Somatosensory Cortex

The Journal of Neuroscience, January 11, 2012 • 32(2):692–702

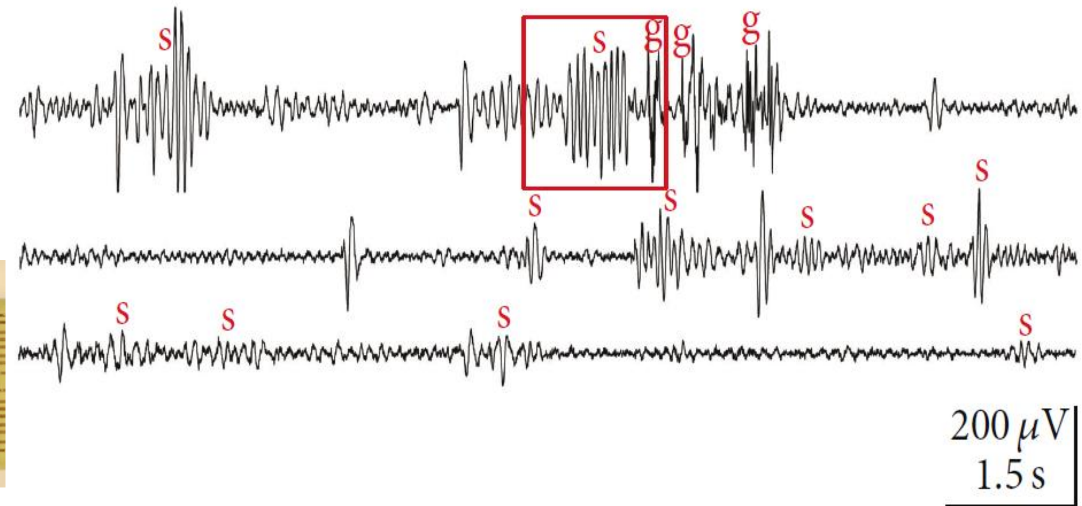
Else A. Tolner,[1,2]* Aminah Sheikh,[3]* Alexey Y. Yukin,[1] Kai Kaila,[1,2] and Patrick O. Kanold[3]

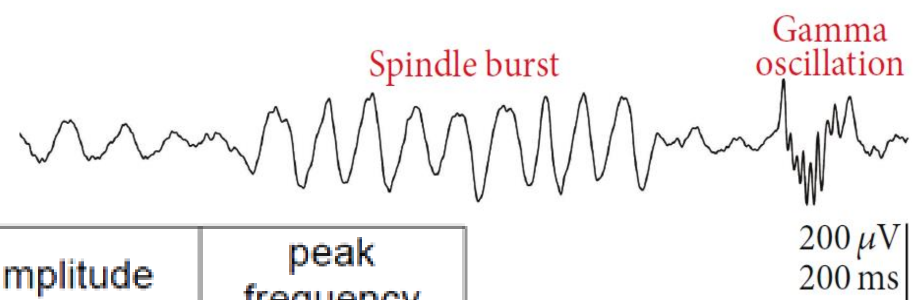


Intracortical local field potential (LFP) recordings in urethane-anesthetized and awake <u>newborn</u> rodents *in vivo*: On-going activity !



~10 Hz spindle bursts (s) and ~40 Hz gamma bursts (g)

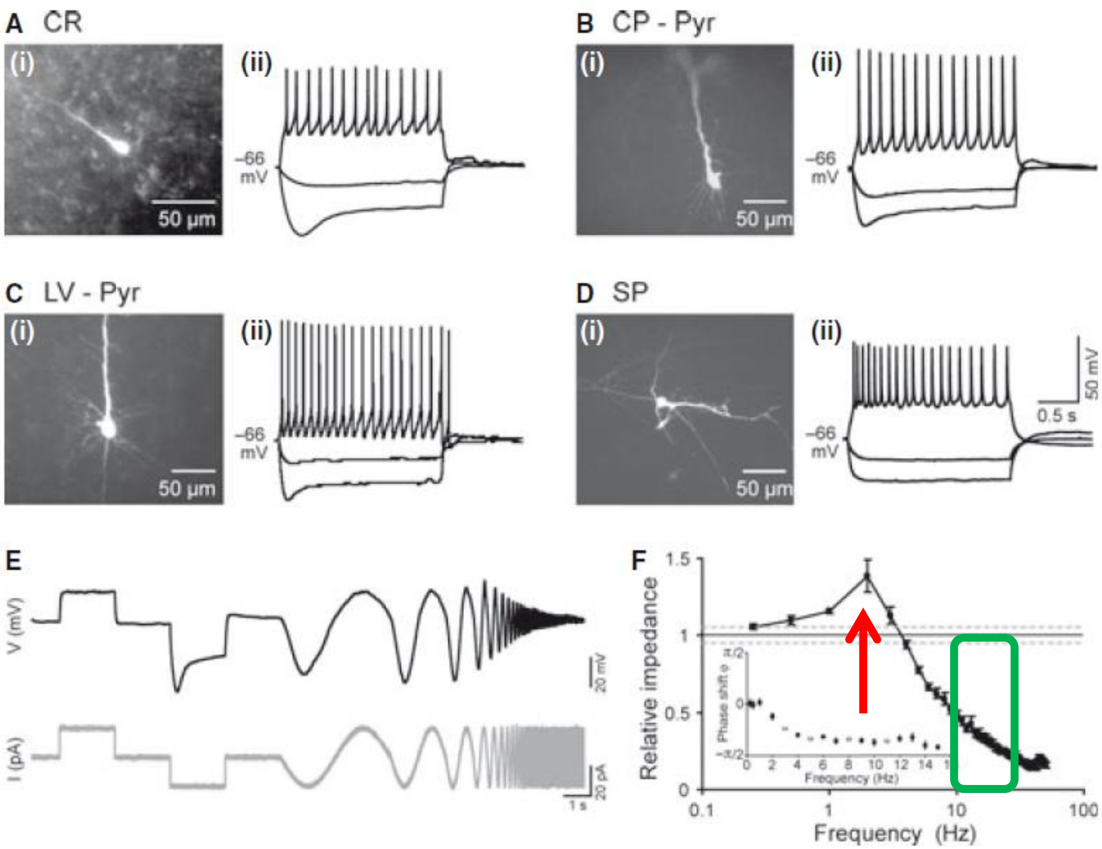


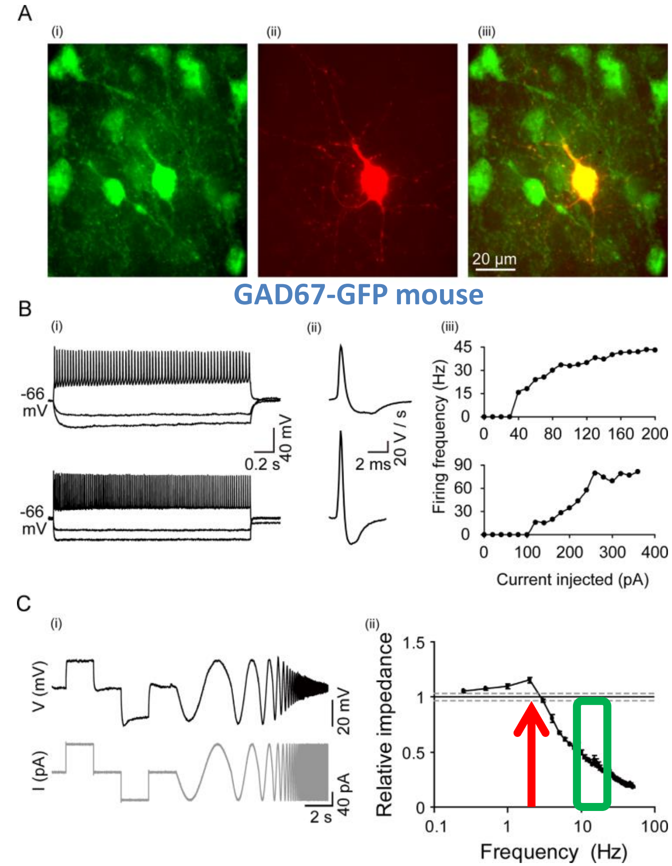


	occurrence	duration	amplitude	peak frequency
spindle bursts	every ~10 s	1-2 s	~ 250 µV	~10 Hz
gamma oscillations	every 10-30 s	~200 ms	~150 µV	30-40 Hz

How is the spindle and gamma burst activity generated?

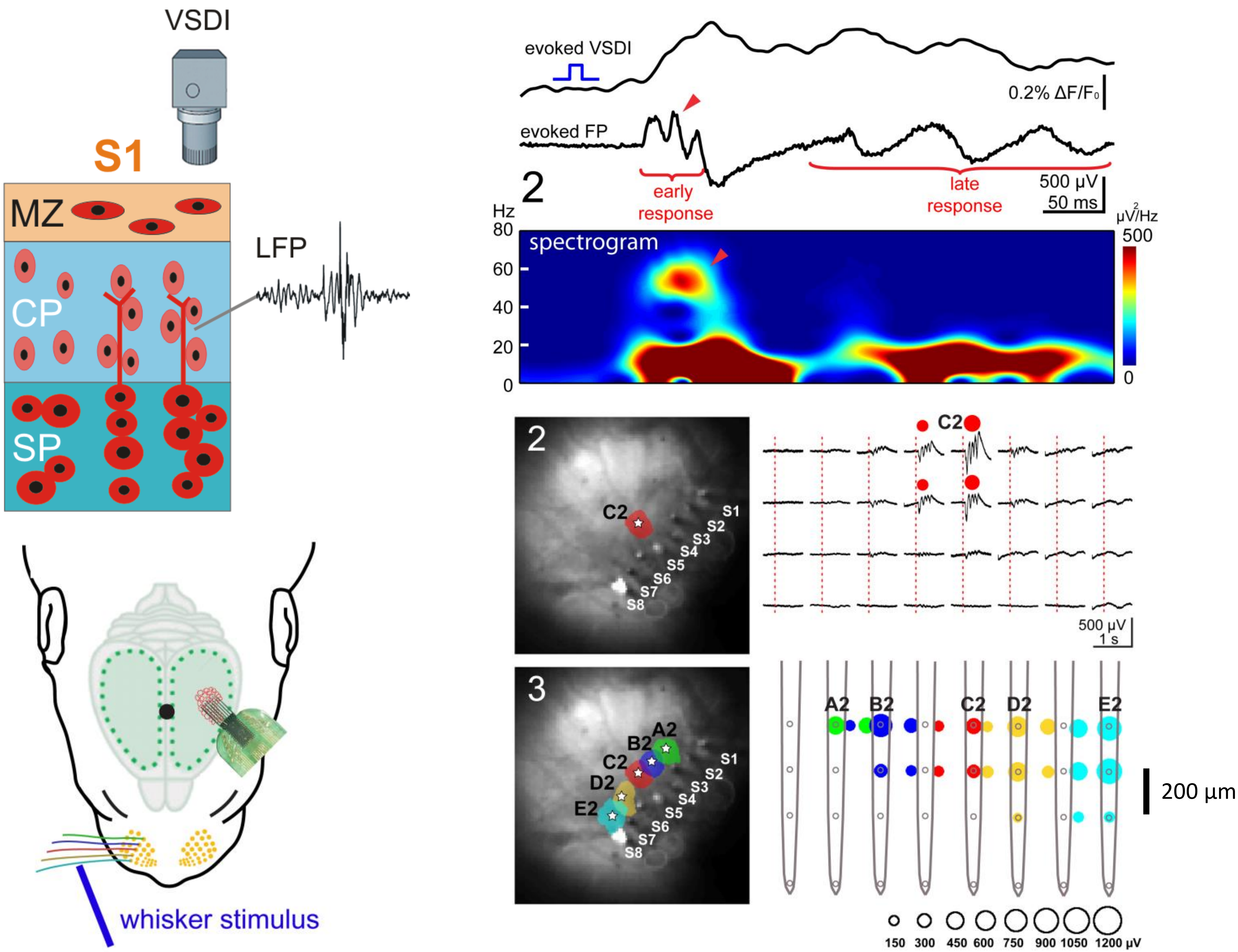
Patch-clamp recordings from identified, biocytin-filled neocortical neurons in slices of newborn mice



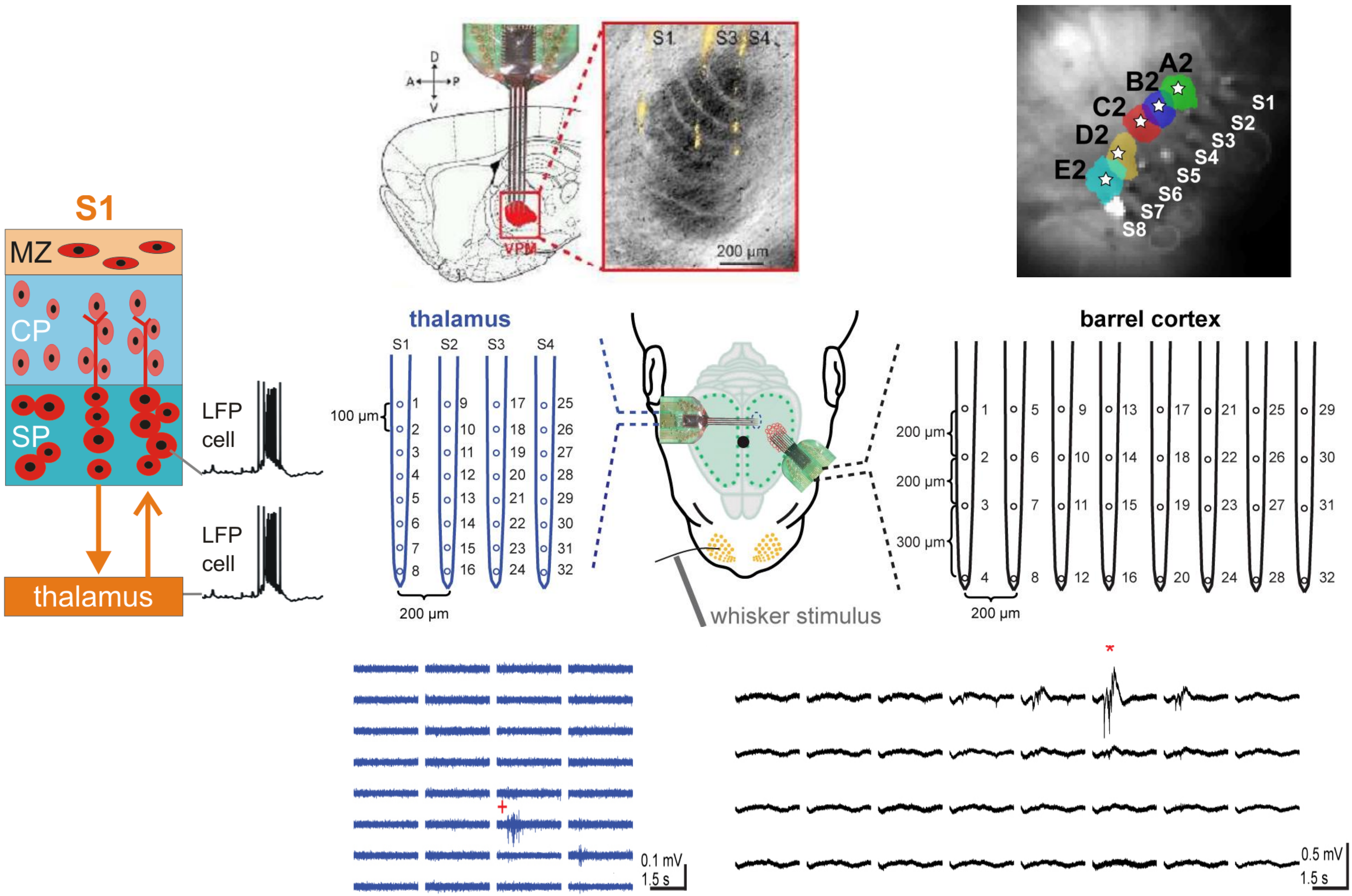


No evidence for <u>intrinsic</u> membrane resonance properties in frequency range of spindle and gamma burst!

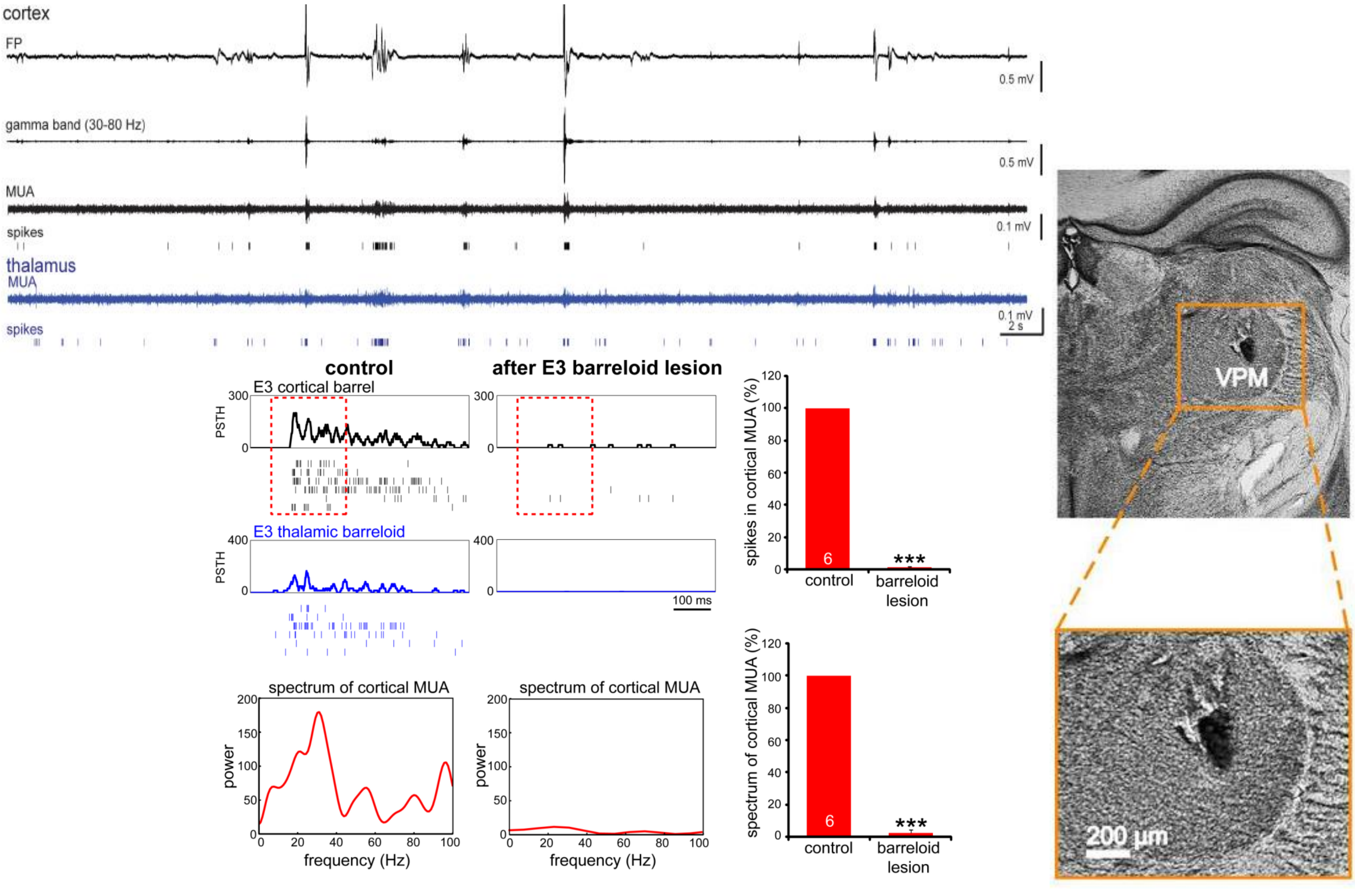
Voltage-sensitive dye imaging (VSDI with RH1691) and simultaneous 32-channel LFP recording in P0 rat barrel cortex *in vivo*: sensory evoked activity



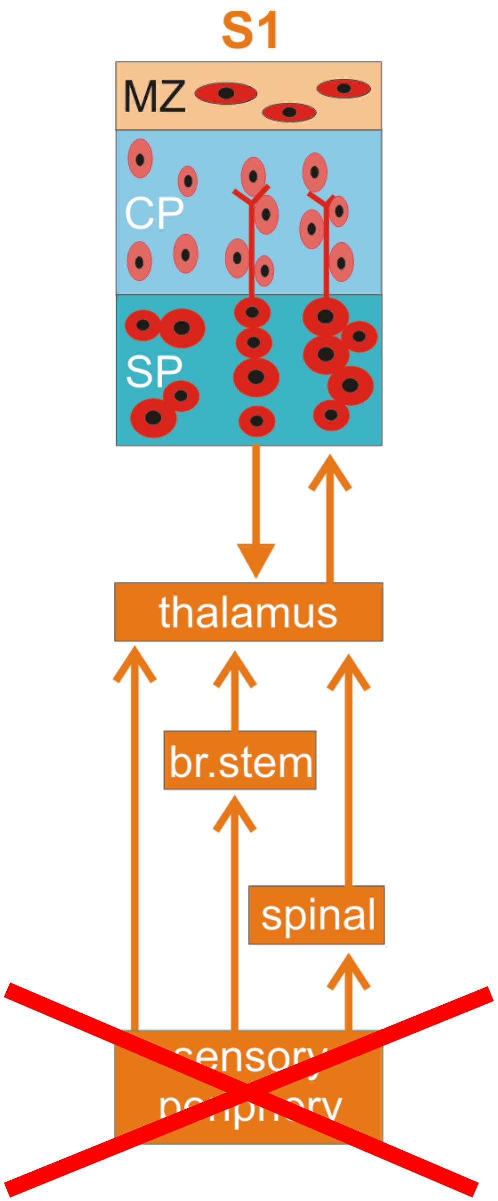
Simultaneous 32-channel recordings in VPM and barrel cortex in P0-P1 rat barrel cortex *in vivo*

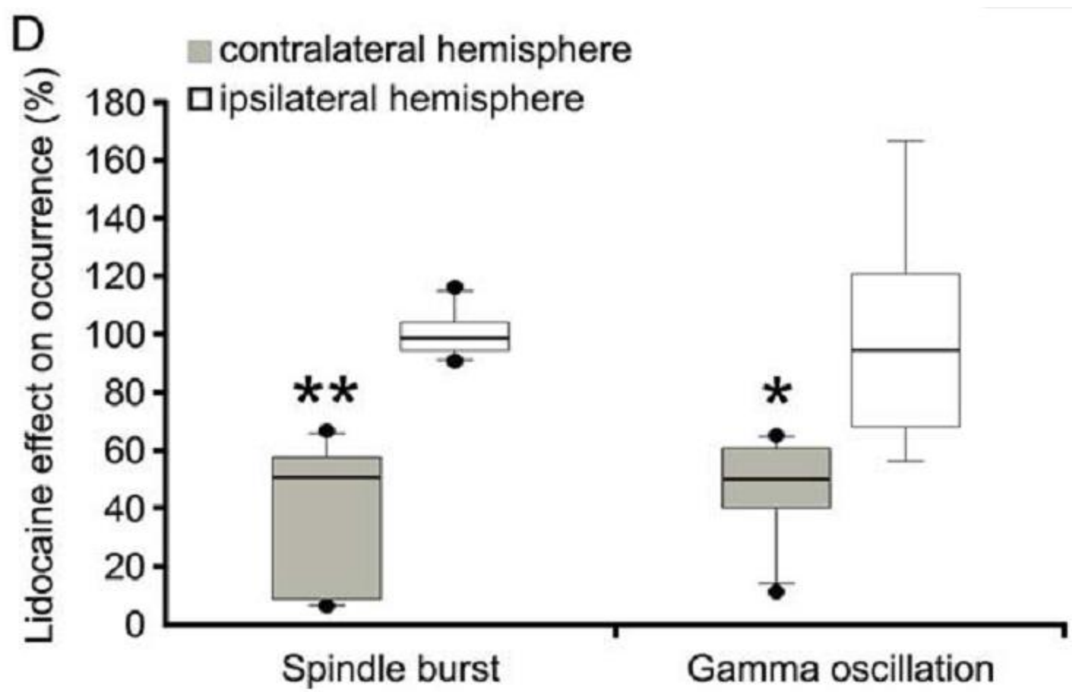


Spontaneous activity in the *in vivo* P0-P1 rat barrel cortex is blocked by local electrolytic lesion in the thalamus



Injection of lidocaine into the whisker pad reduces spontaneous cortical spindle bursts and gamma oscillations by ca. 50%



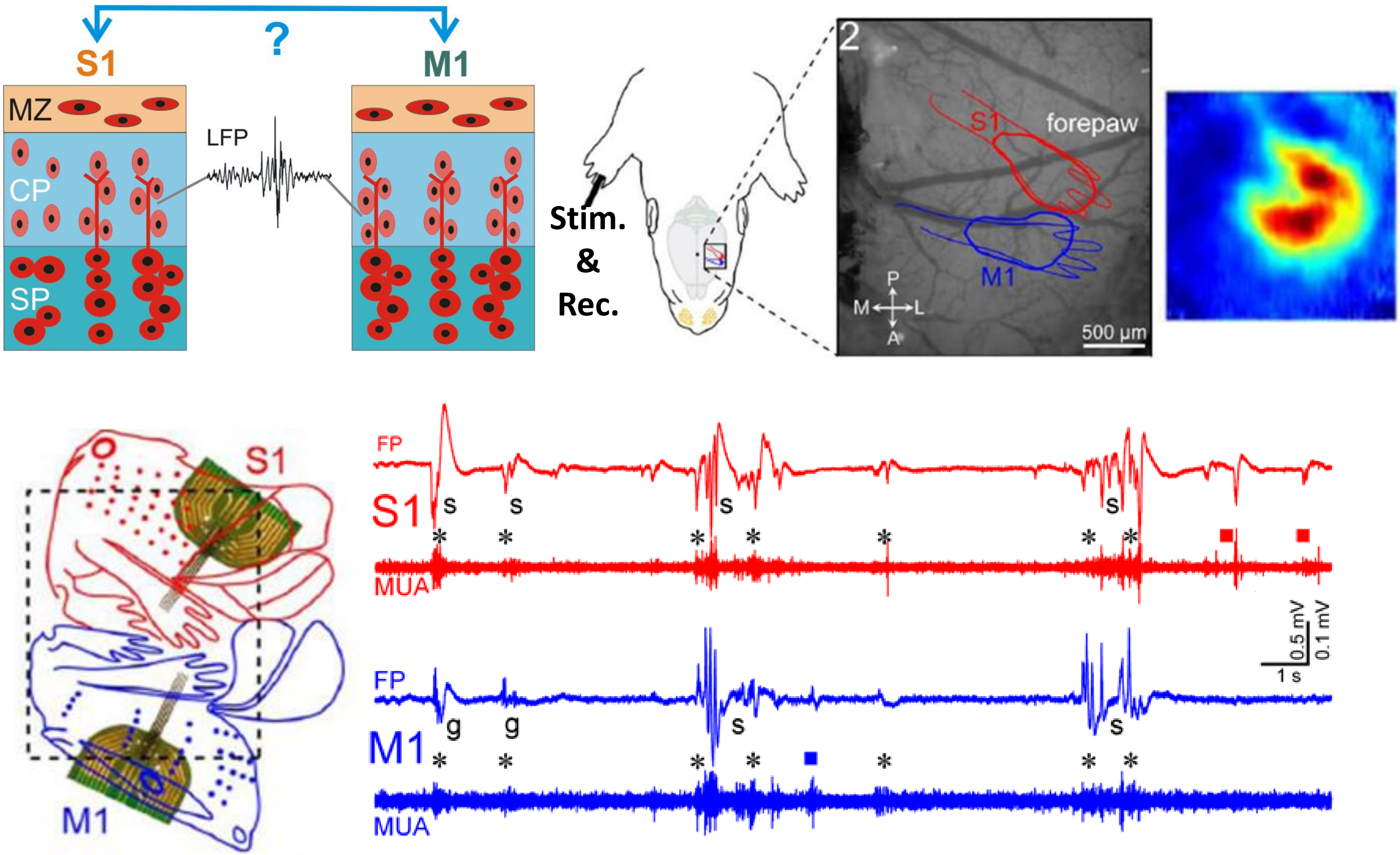


Where is the other 50% of spontaneous activity coming from?

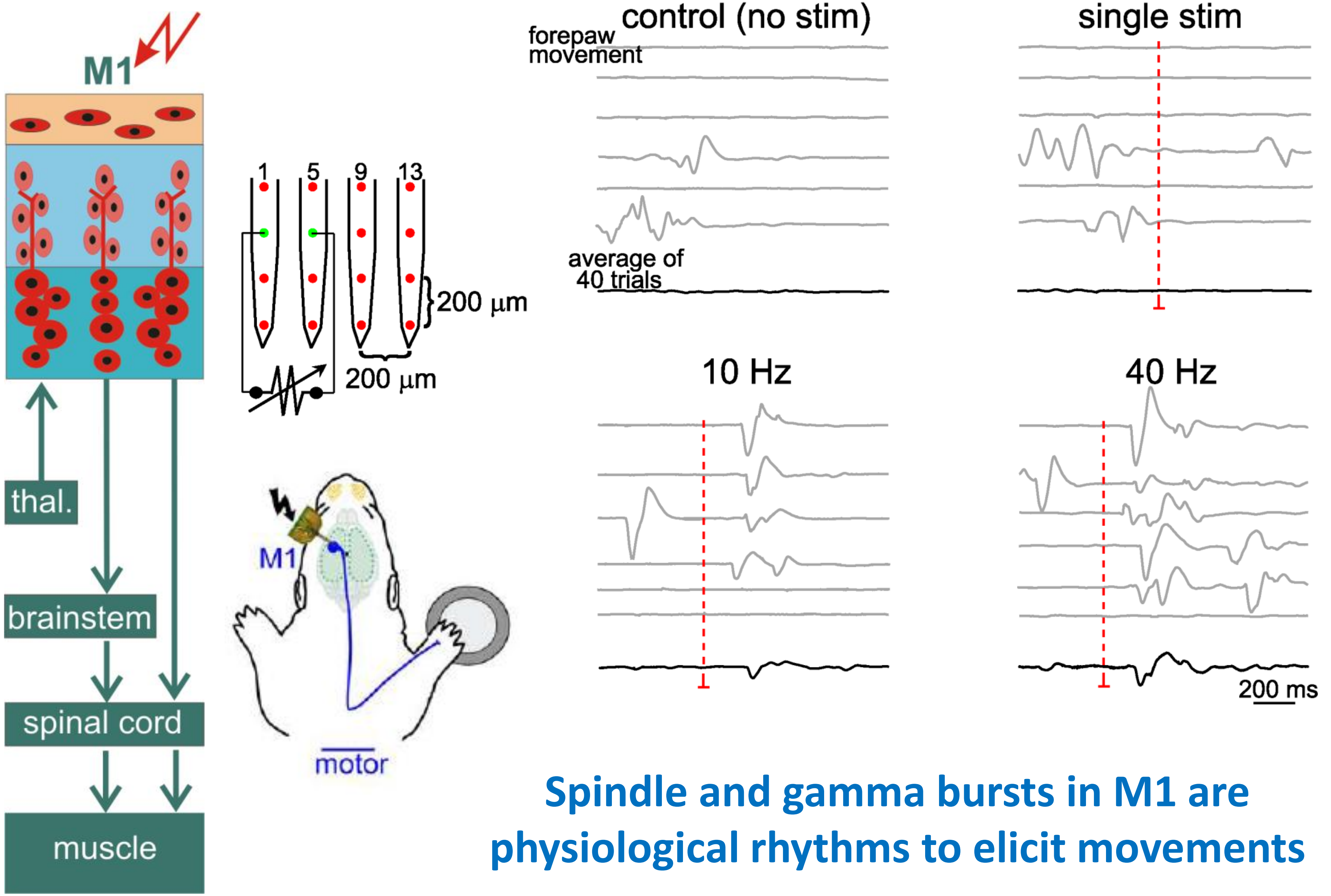
Role of the motor system?

Monitoring of spontaneous movements in sensory periphery!

Simultaneous recordings of spontaneous activity in the forepaw representation in motor cortex (M1) and somatosensory cortex (S1)

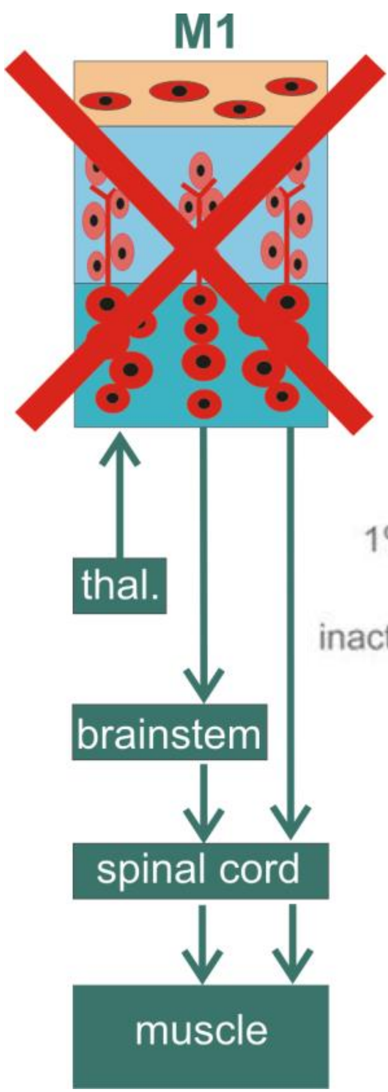


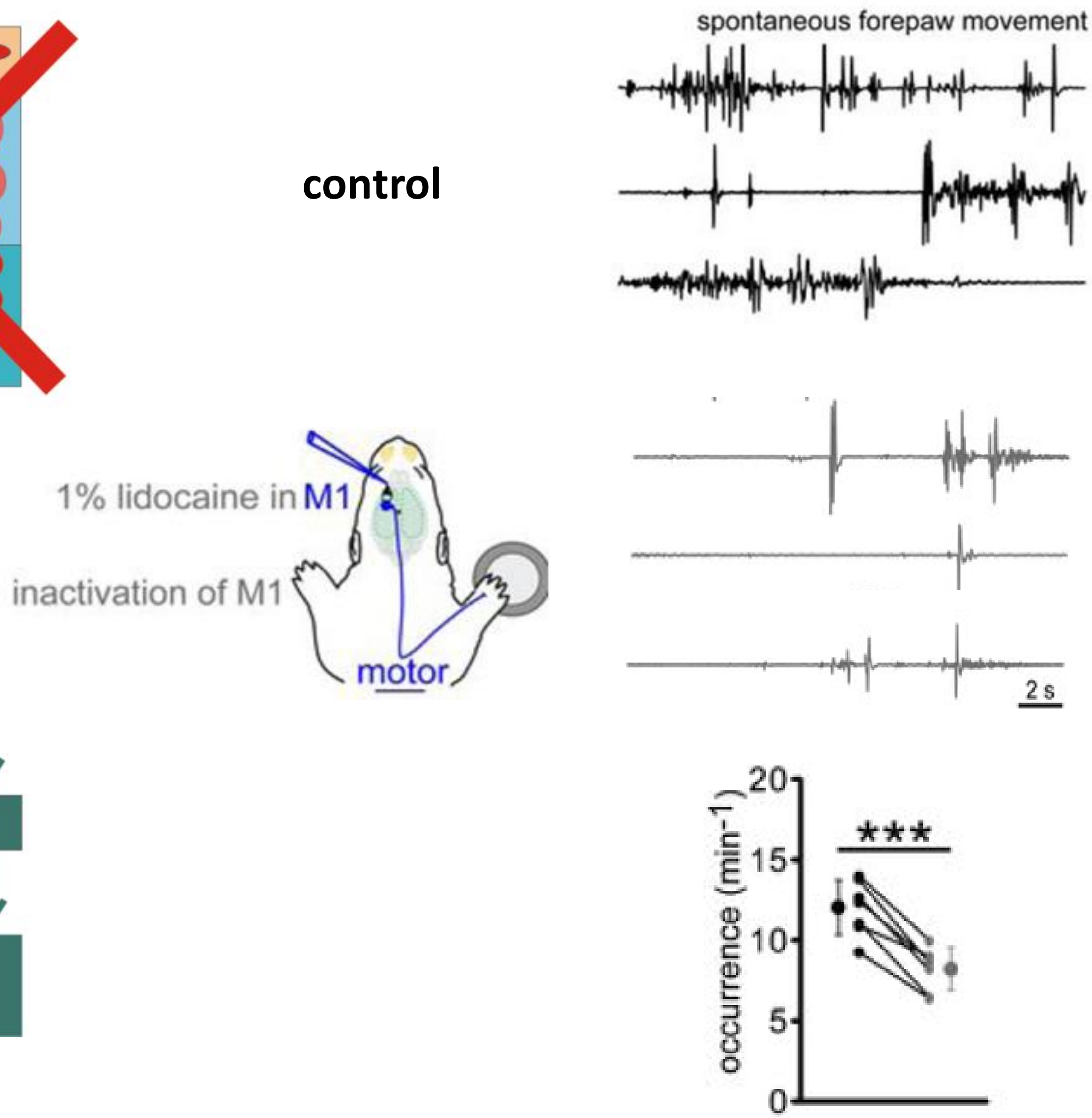
M1 activity in spindle and gamma range elicits movements

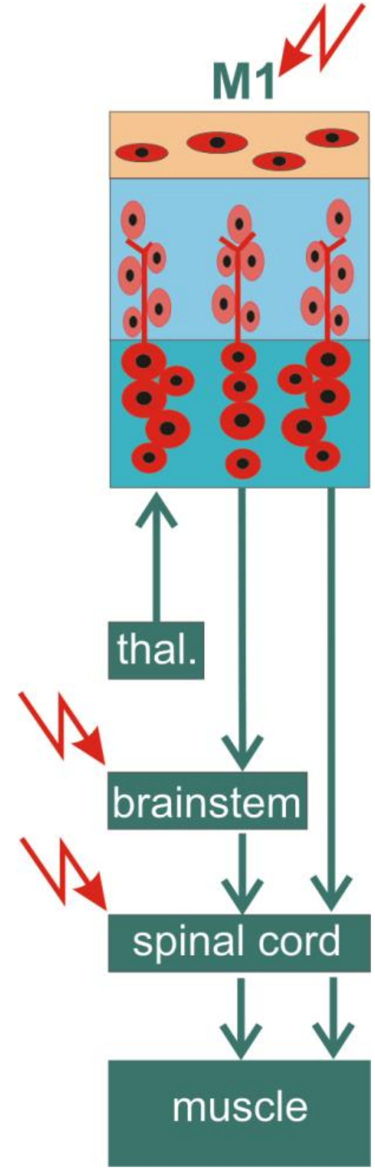


Spindle and gamma bursts in M1 are physiological rhythms to elicit movements

More than one central pattern generator

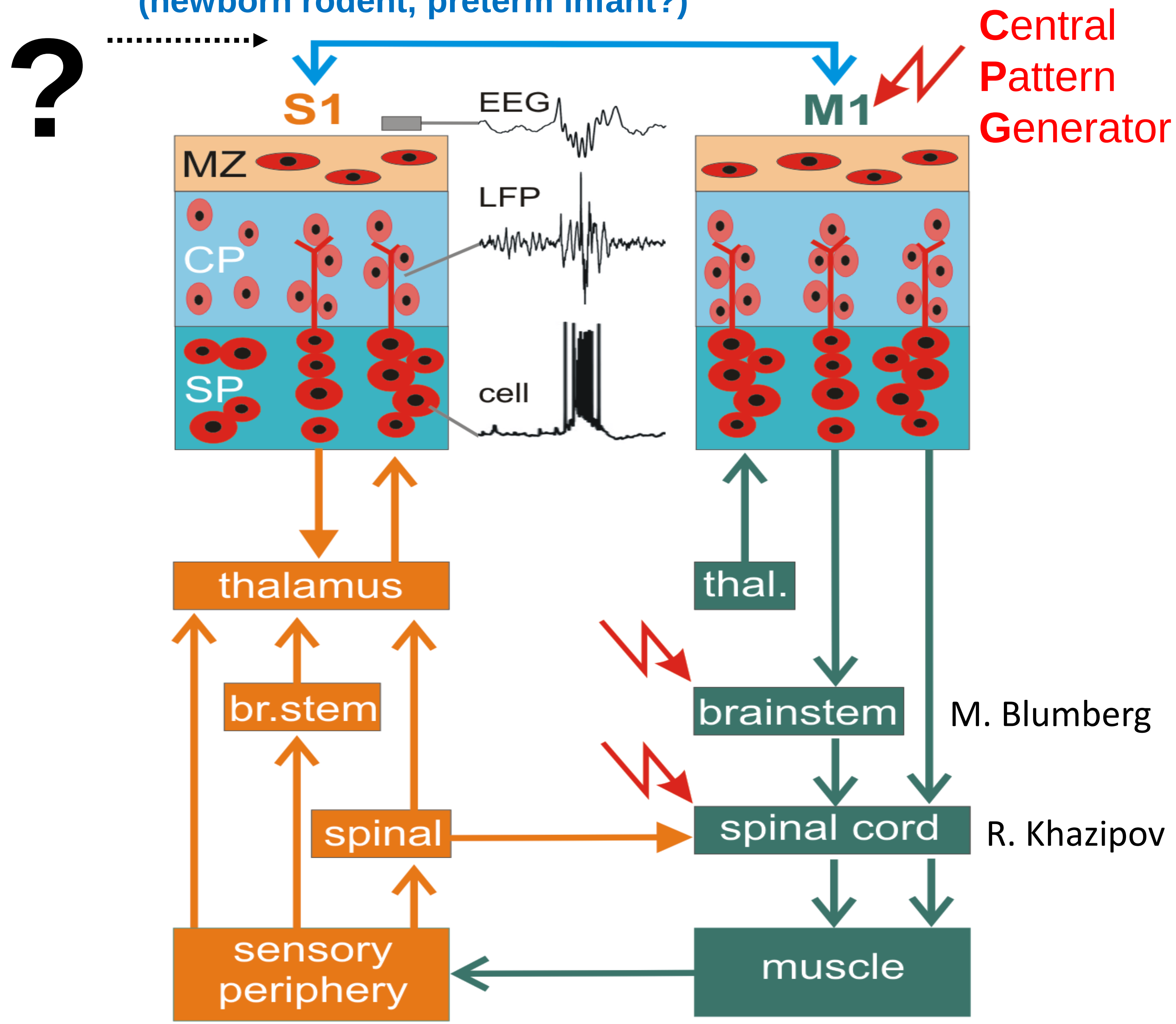




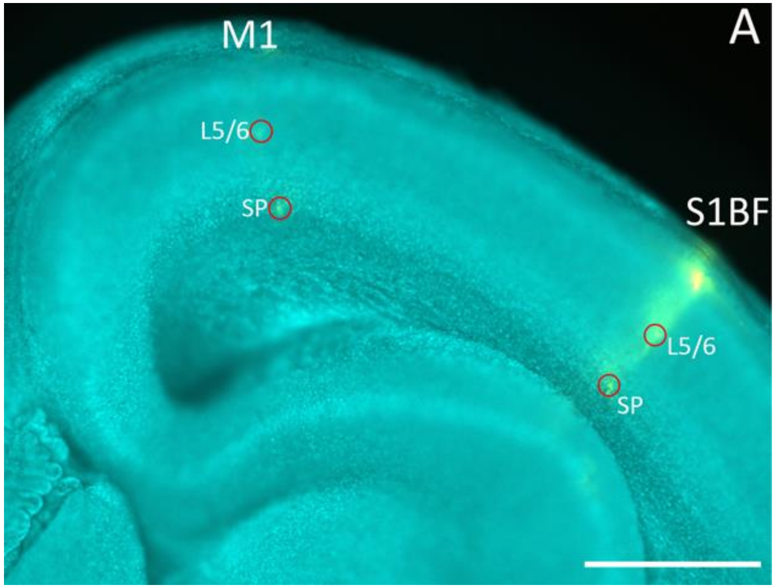


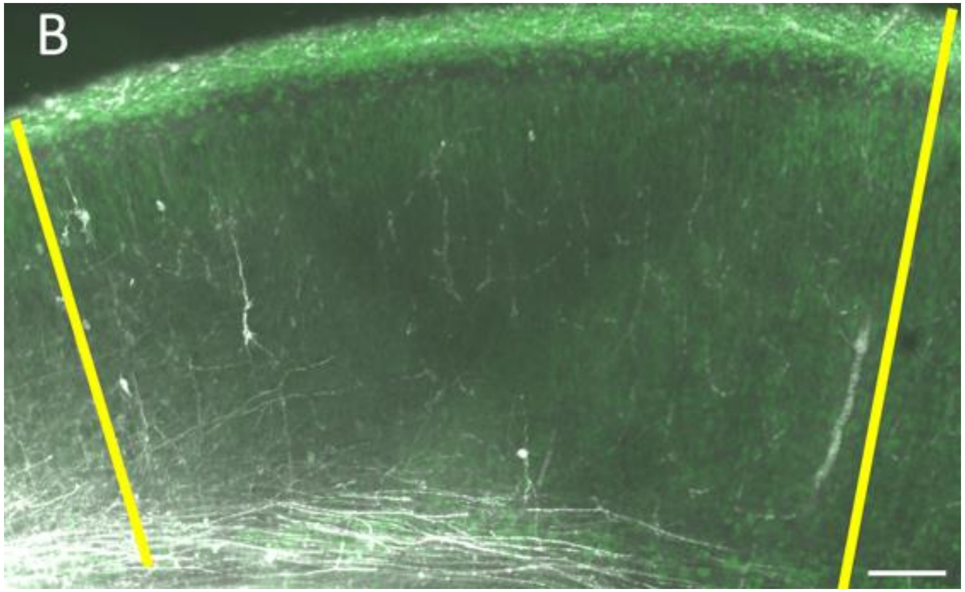
Functional connectivity in the immature sensory-motor system

(newborn rodent, preterm infant?)

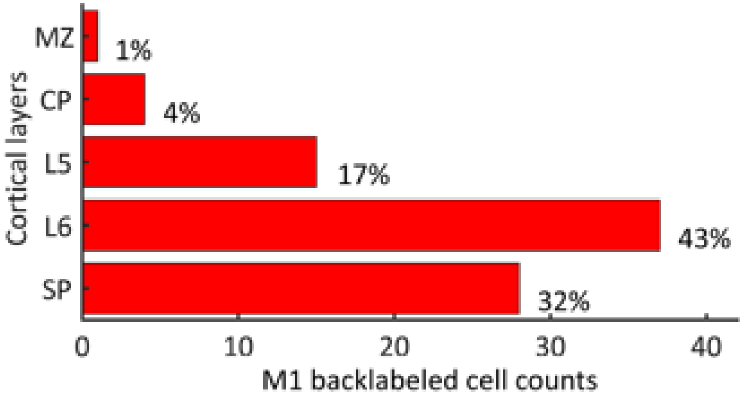


Anatomical M1-S1Bf connectivity in P0 mouse
using DiI injections

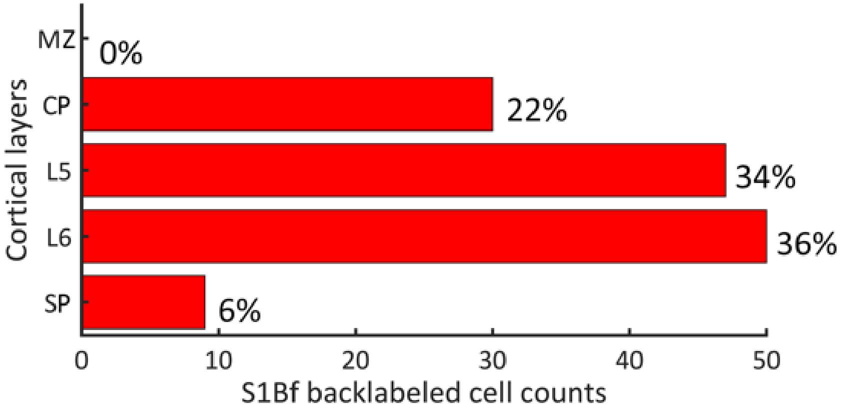




M1 -> S1Bf projections

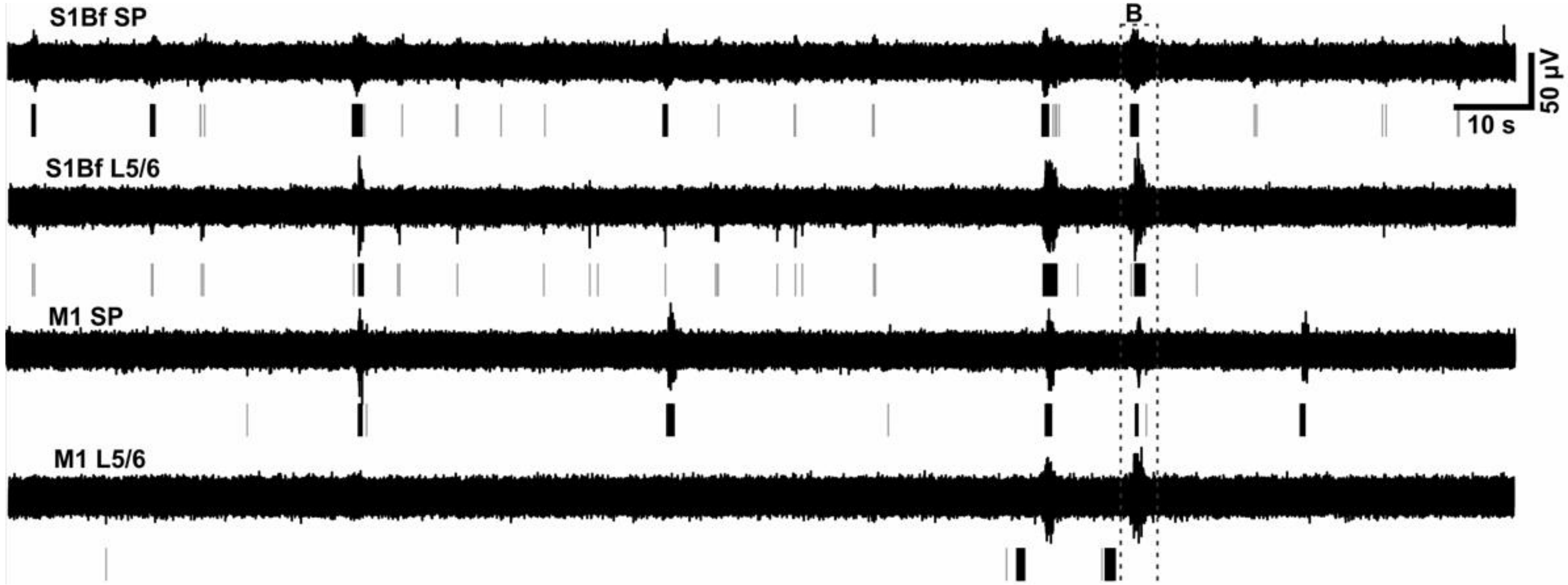


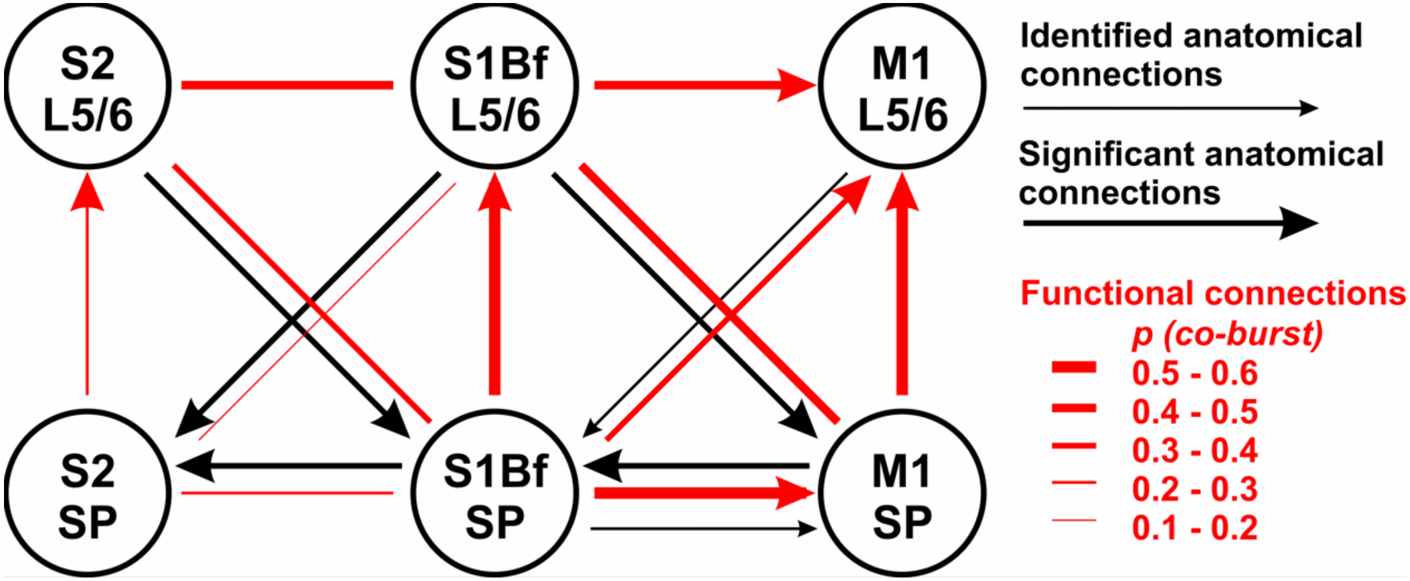
S1Bf -> M1 projections



Functional M1-S1Bf connectivity in P0 mouse

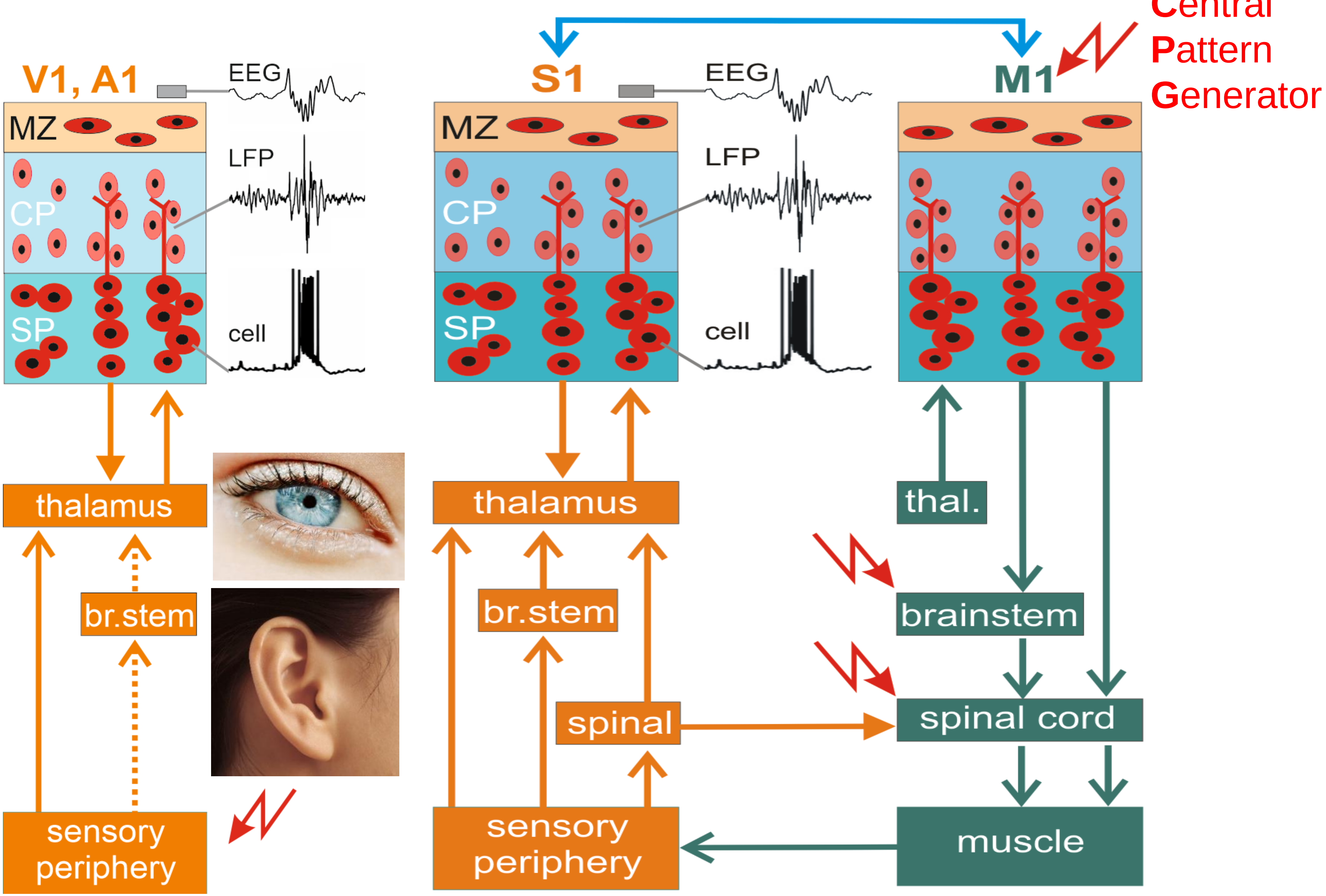
using in vitro MEA recordings and spike cross correlograms





Functional connectivity in immature sensory systems

(newborn rodent, preterm infant?)



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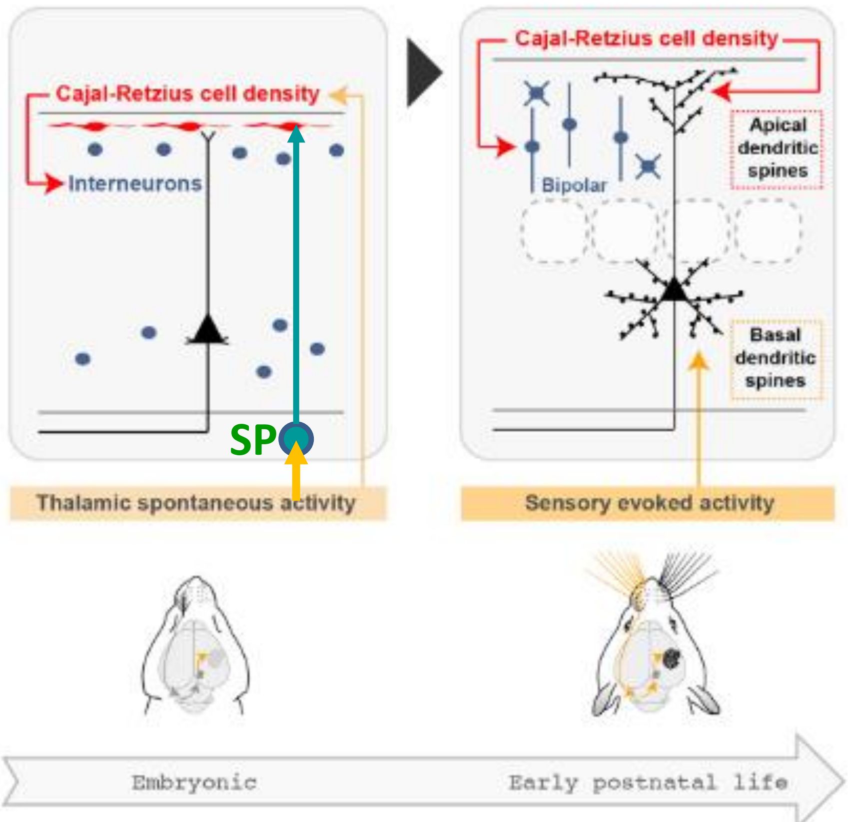
M3: Subplate receives early thalamic input and plays key role in generation of cortical network activity (which is driven by sensory periphery).

Q4: What is the physiological function of this early activity?

Dynamic interplay between thalamic activity and Cajal-Retzius cells regulates the wiring of cortical layer 1

2022, Cell Reports *39*

Ioana Genescu,[1] Mar Aníbal-Martínez,[2] Vladimir Kouskoff,[3] Nicolas Chenouard,[3] Caroline Mailhes-Hamon,[4] Hugues Cartonnet,[1] Ludmilla Lokmane,[1] Filippo M. Rijli,[5,6] Guillermina López-Bendito,[2] Frédéric Gambino,[3] and Sonia Garel[1,7,8,*]



Highlights

- Prenatal thalamic waves of activity regulate CRc density in L1
- Prenatal and postnatal CRc manipulations alter specific interneuron populations
- Postnatal CRc shape L5 apical dendrite structural and functional properties
- Early sensory activity selectively regulates L5 basal dendrite spine formation

GABAergic projections from the subplate to Cajal–Retzius cells in the neocortex

Olga Myakhar[b], Petr Unichenko[a] and Sergei Kirischuk[a]

Q4: What is the physiological function of this early activity?

Activity-dependent control of neuronal apoptosis

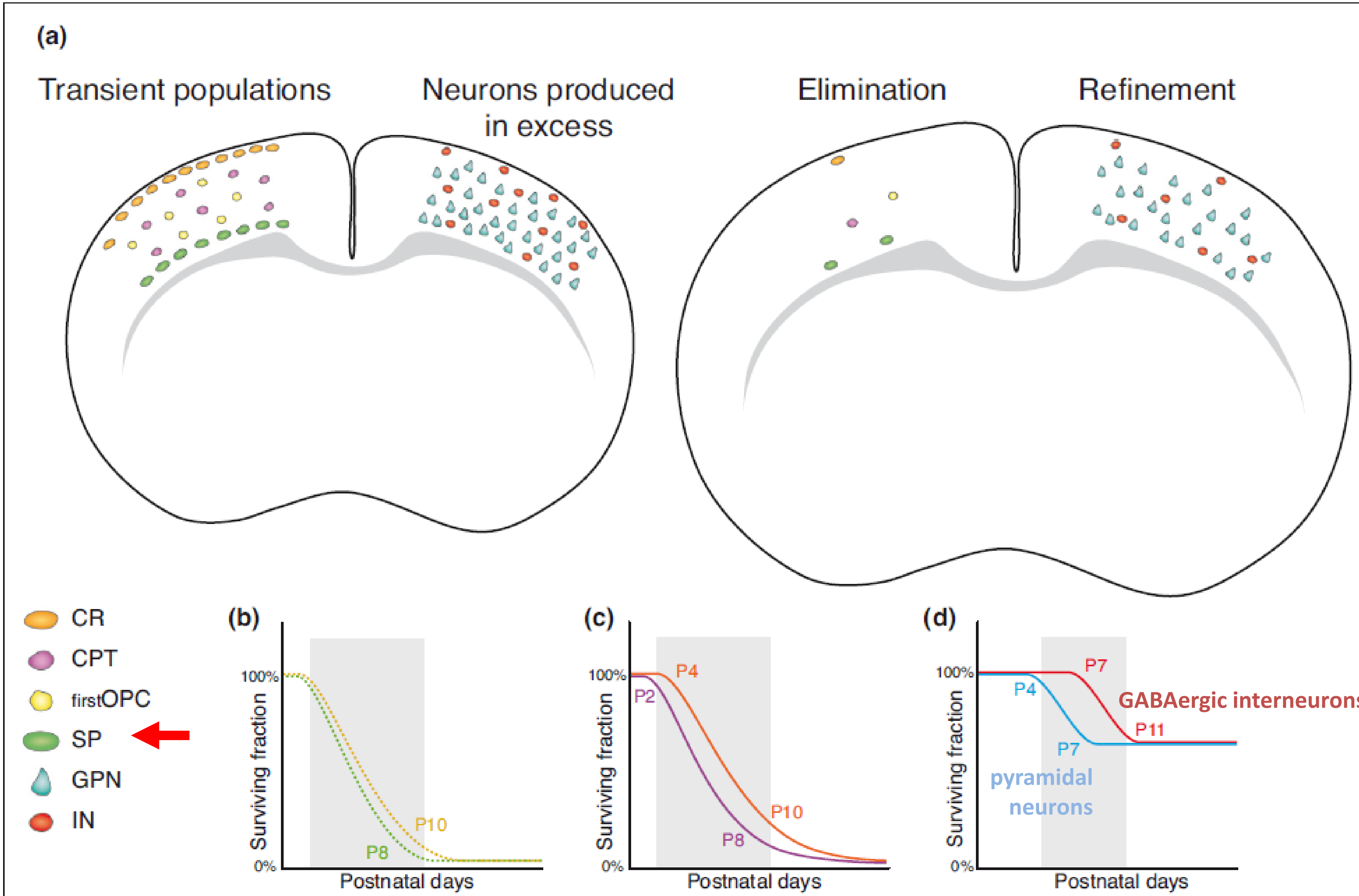
+/-   -/-

Caspase-9 ko mice

<u>From</u>: Kuida et al (1998) *Cell*

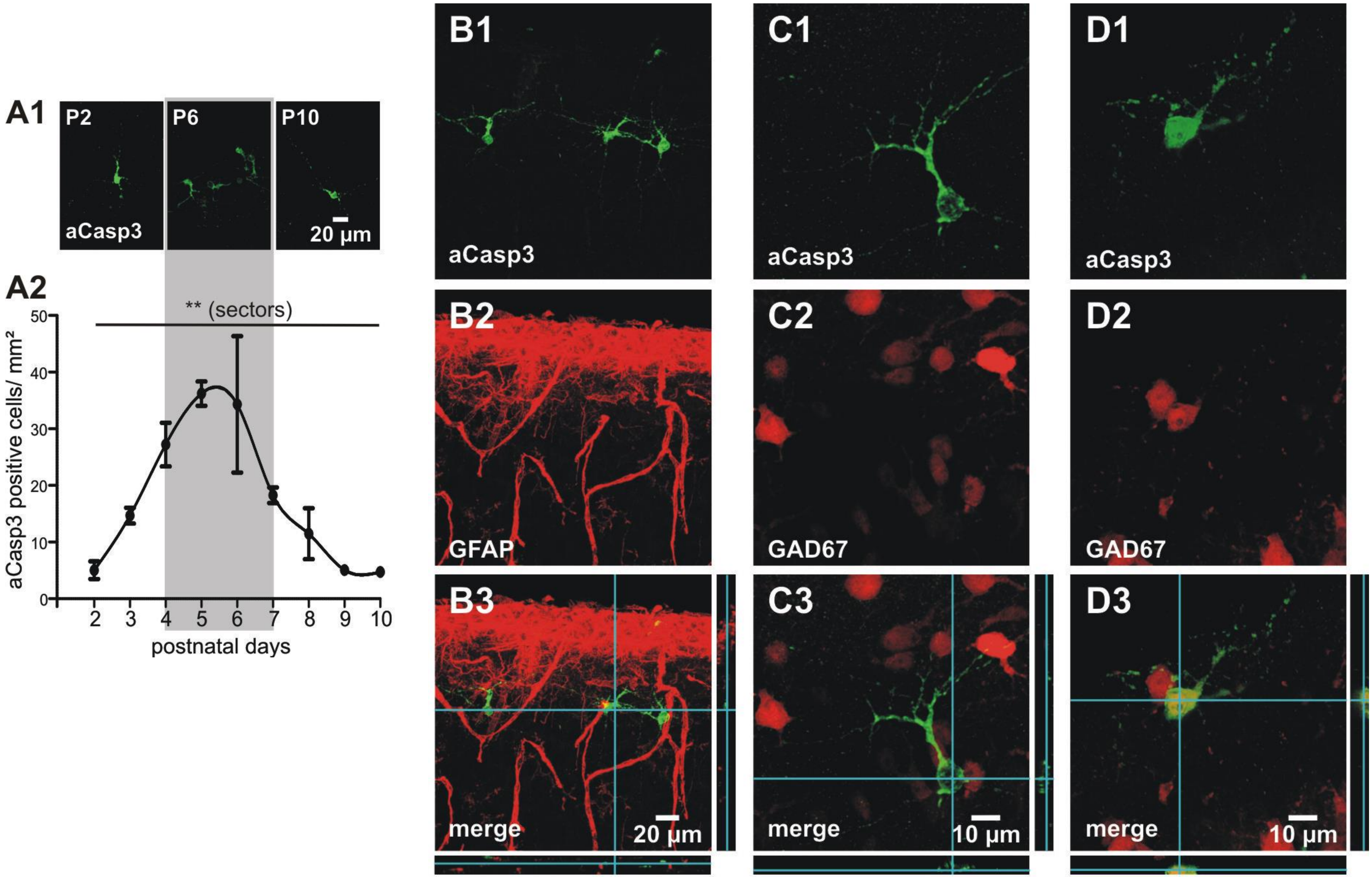
Cortical developmental death: selected to survive or fated to die

Frédéric Causeret[1,2,4], Eva Coppola[1,2,3,4] and Alessandra Pierani

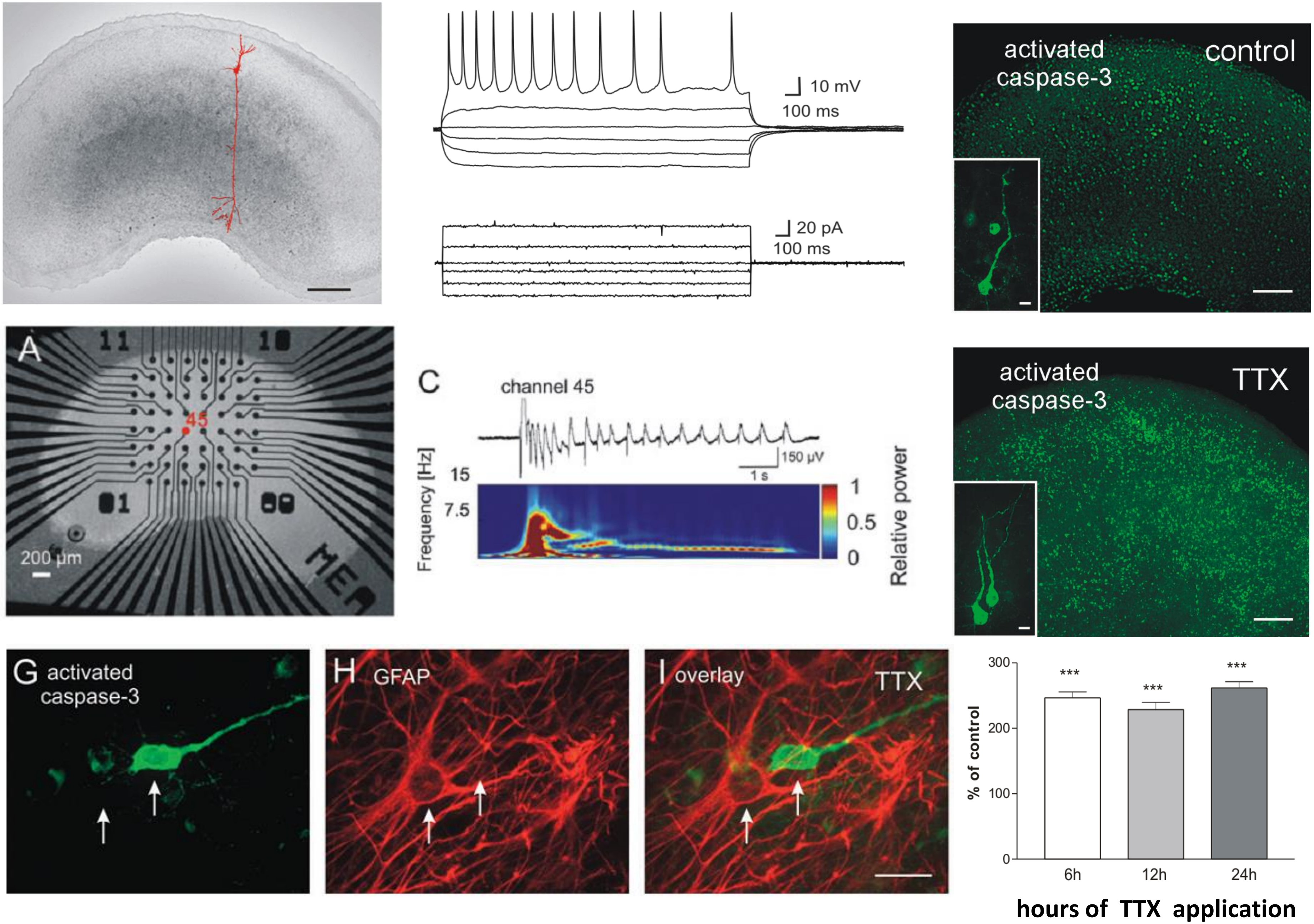


2018 Current Opinion in Neurobiology

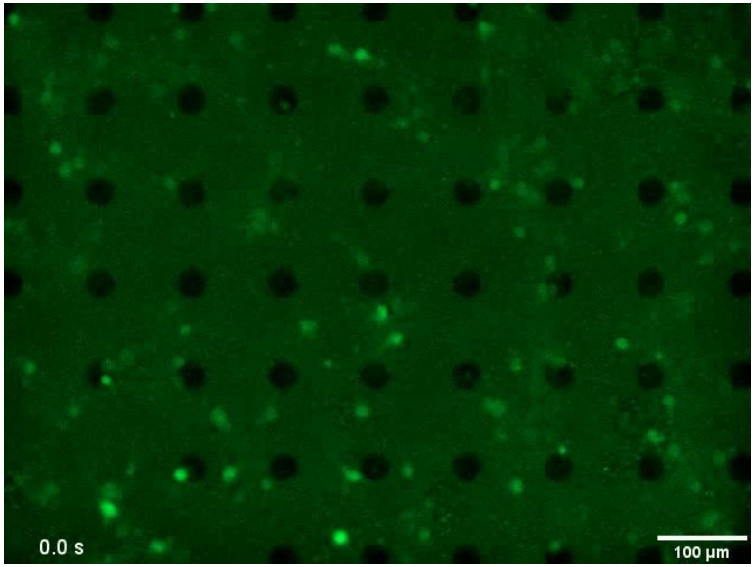
Programmed neuronal cell death (apoptosis) in newborn mouse cerebral cortex *in vivo* estimated with aCasp3

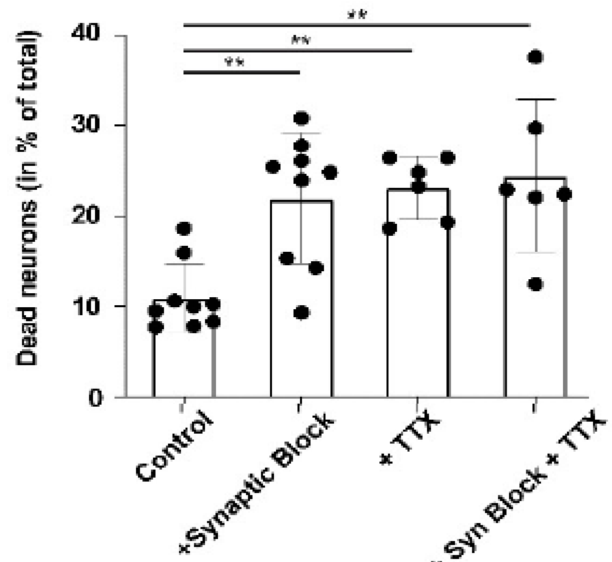


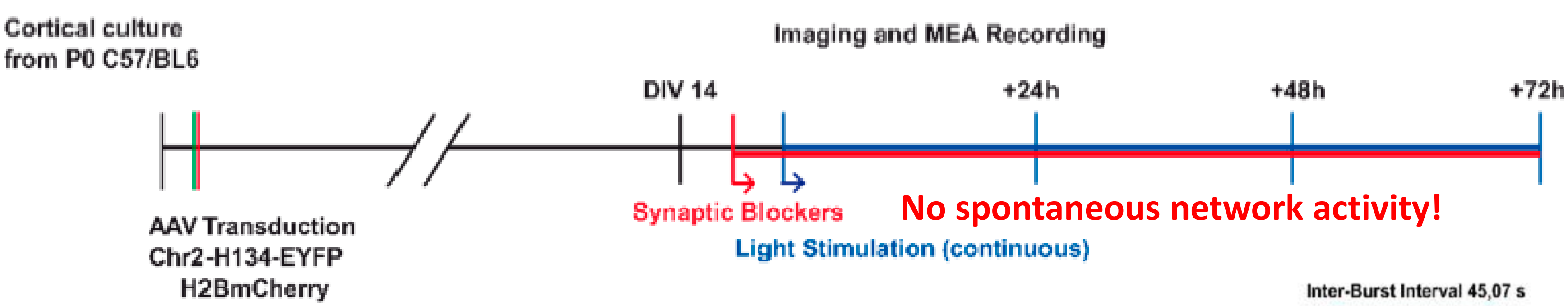
Analysis of Casp-3 dependent apoptosis in organotypic neocortical slice cultures



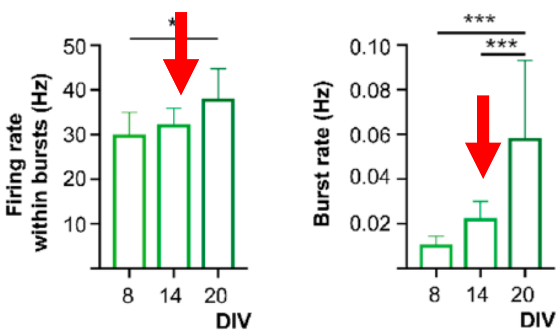
Apoptosis in dissociated neocortical cell cultures on 120-MEA transfected with Channelrhodopsin

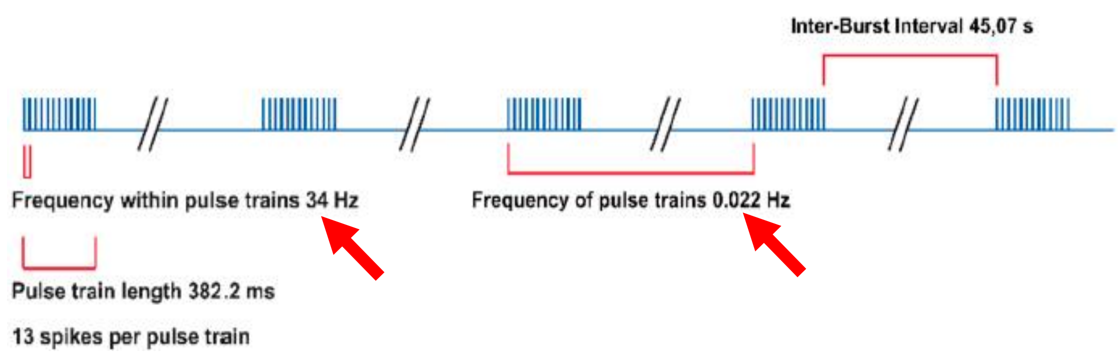




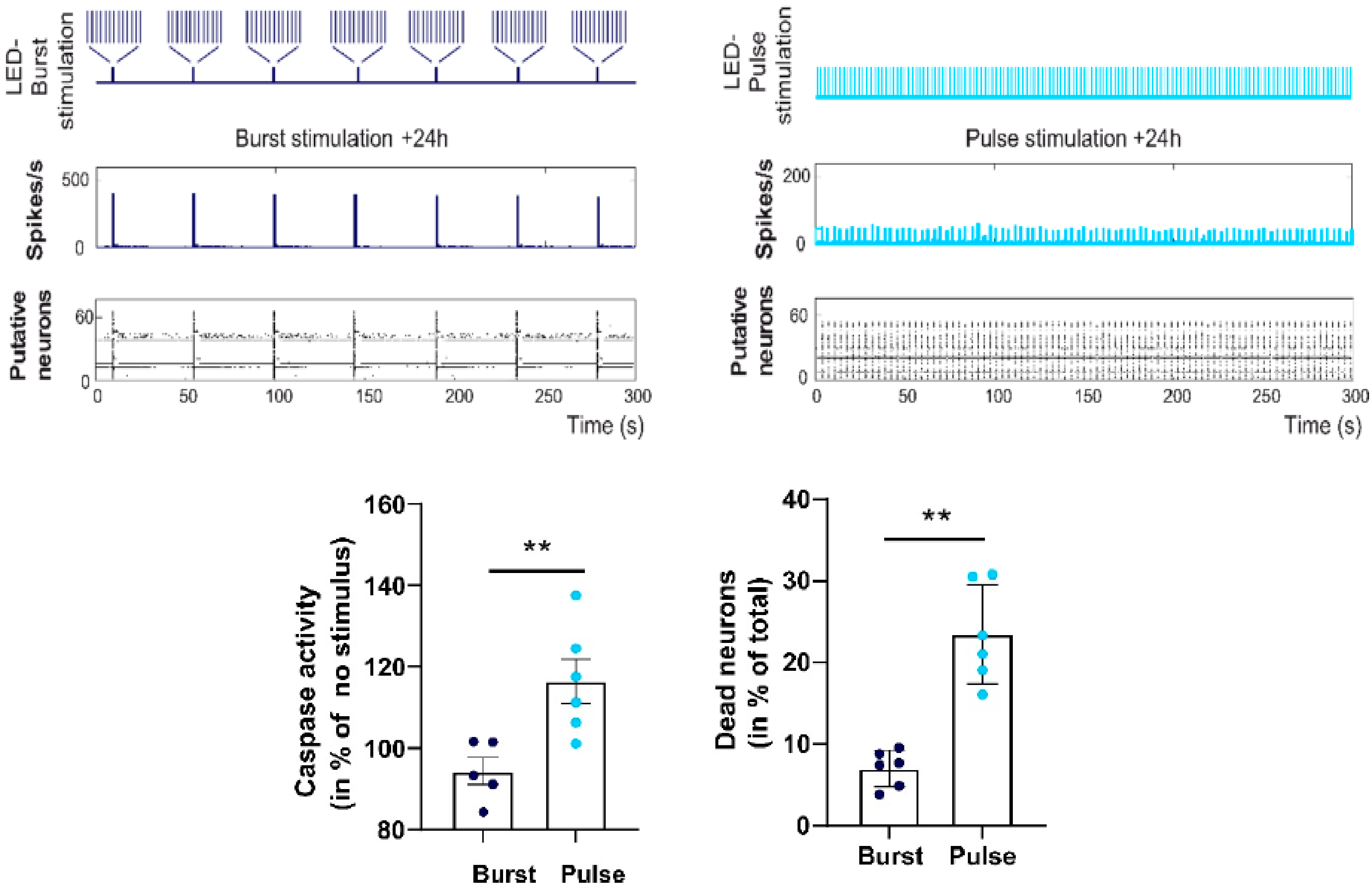


No spontaneous network activity!

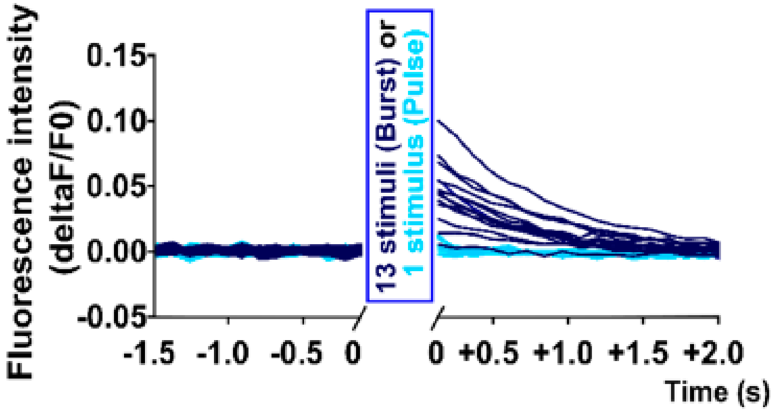


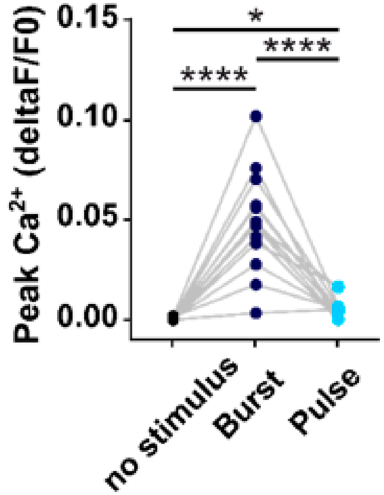


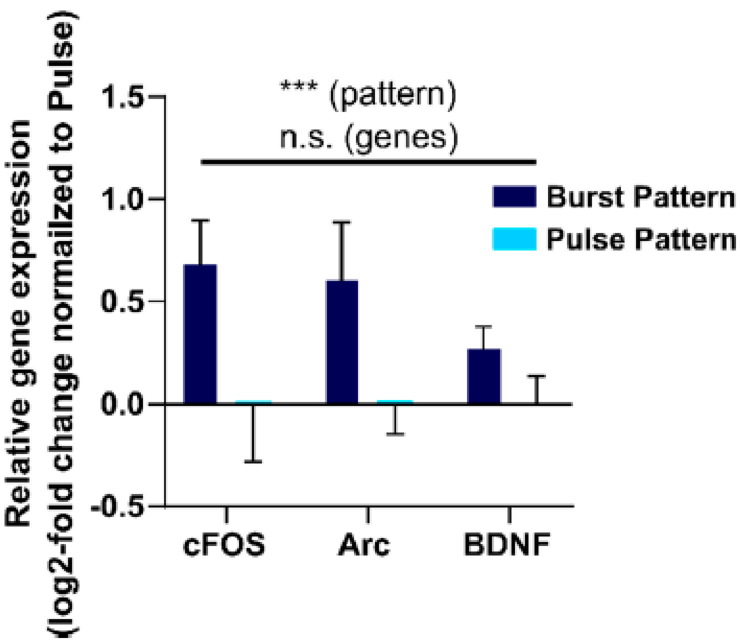
Optogenetically evoked burst firing, but not tonic firing, reduces apoptosis

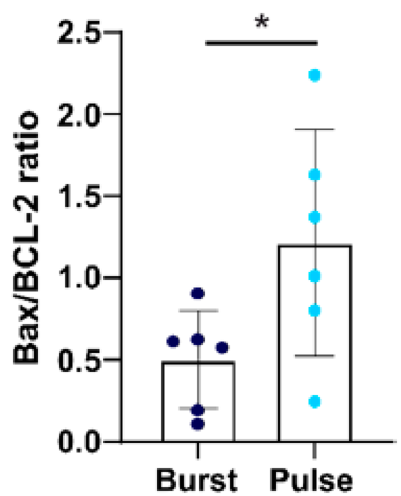


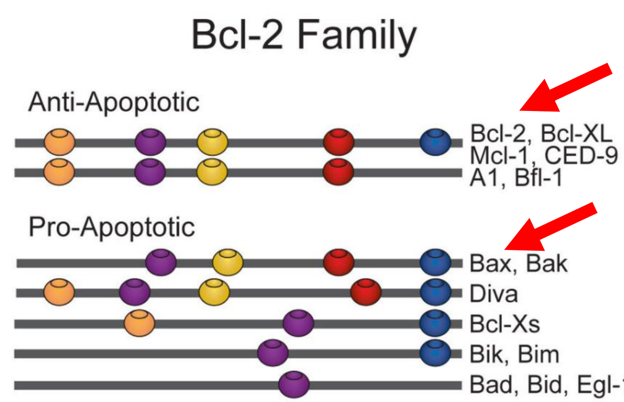
Burst firing, but not tonic firing, (i) causes intracellular calcium rise, (ii) activation of immediate early genes, (iii) increased BDNF expression, and (iv) decreased Bax/BCL-2 ratio.











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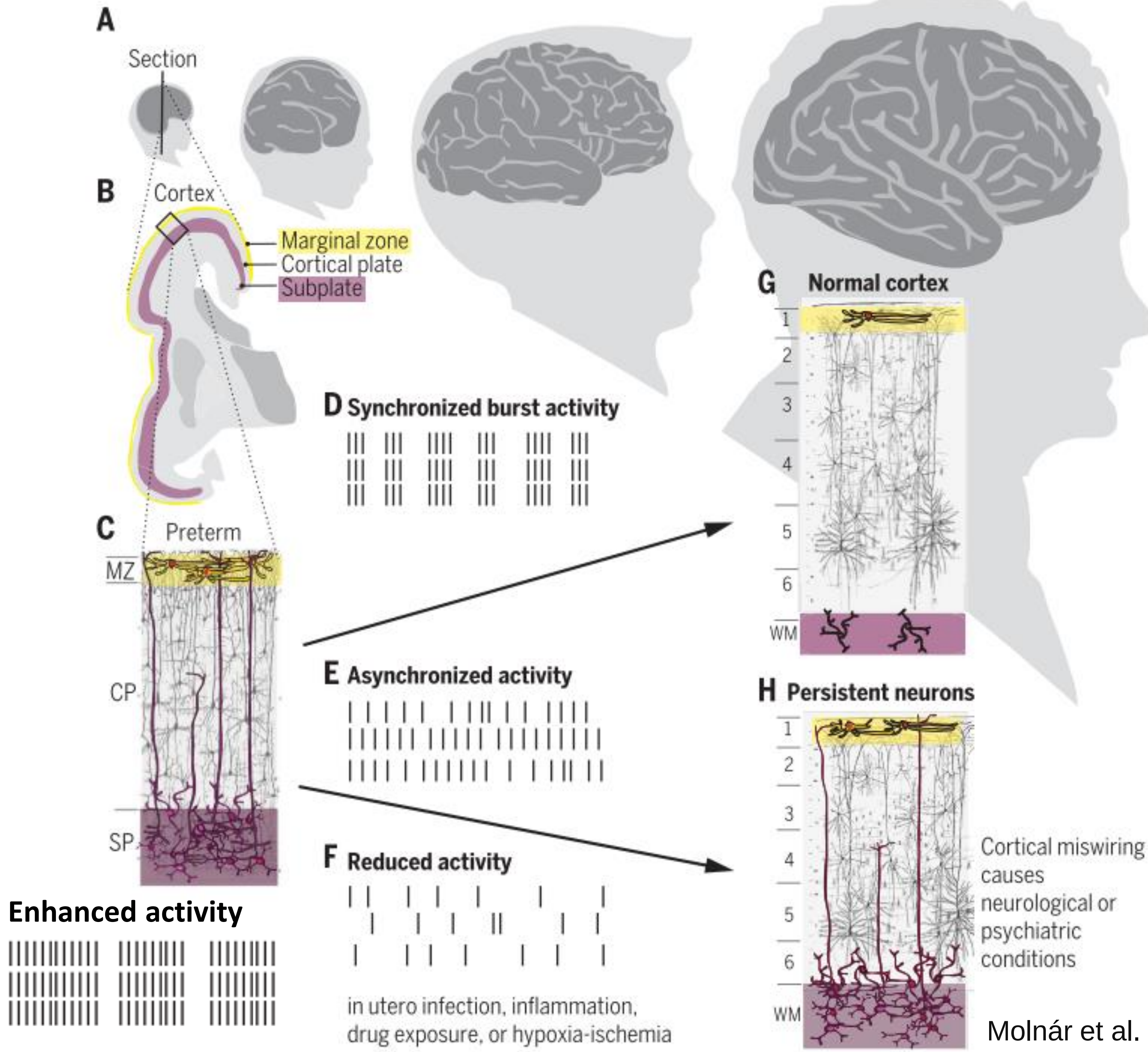
M3: Subplate receives early thalamic input and plays key role in generation of cortical network activity (which is driven by sensory periphery).

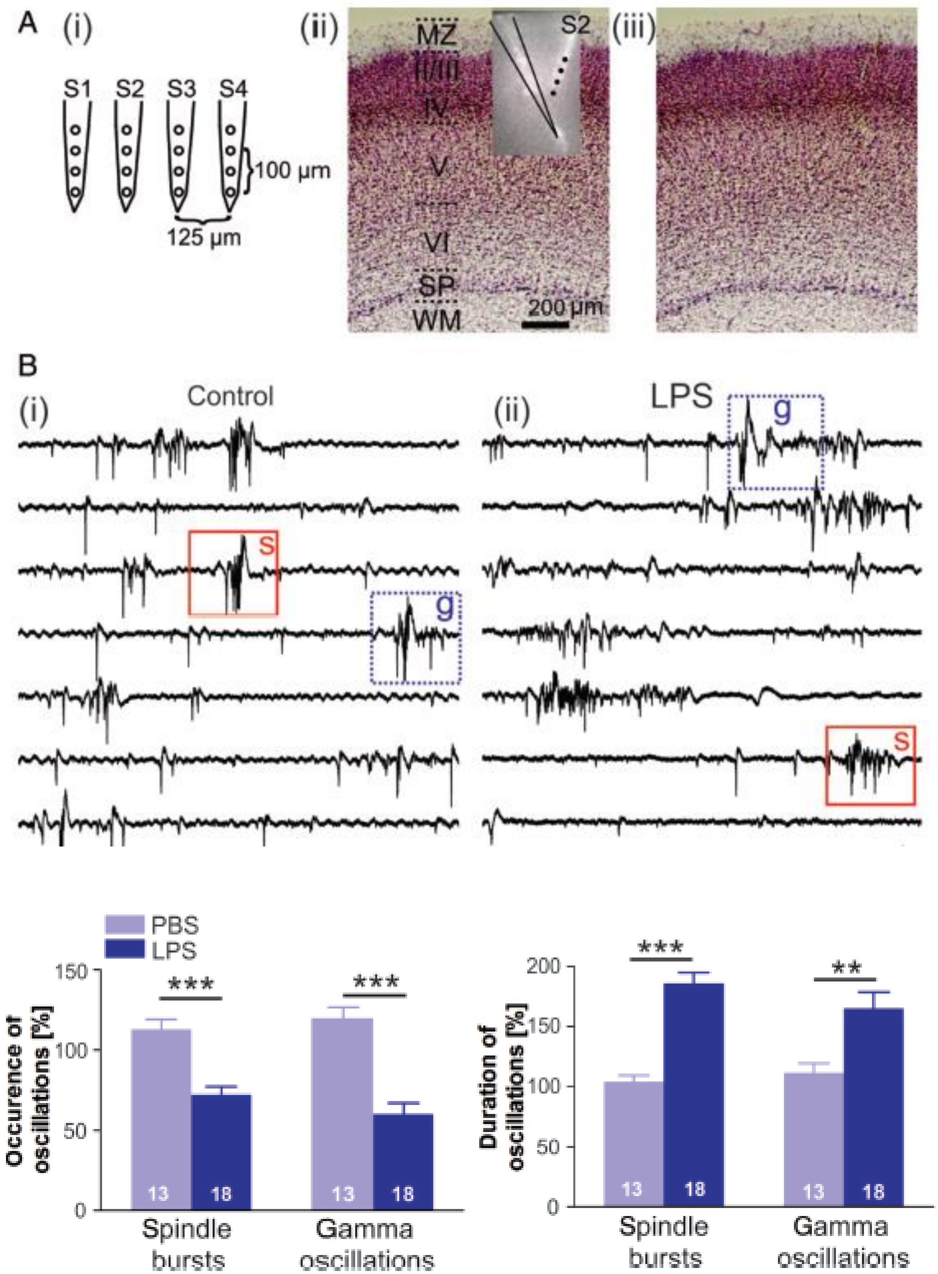
M4: Spontaneous synchronized burst activity controls progressive events (e.g. columnar organization, topographic maps) and regressive events (e.g. apoptosis).

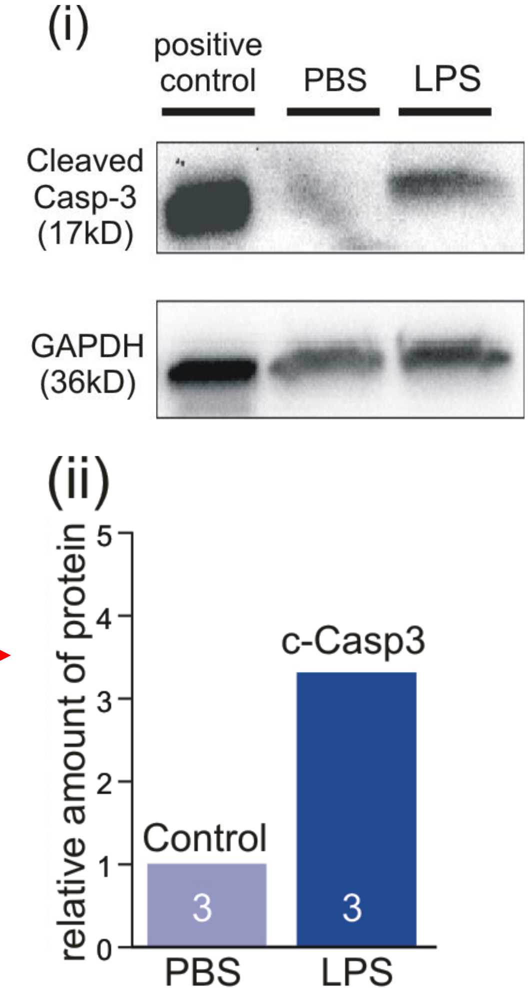


Molnár et al. (2020)

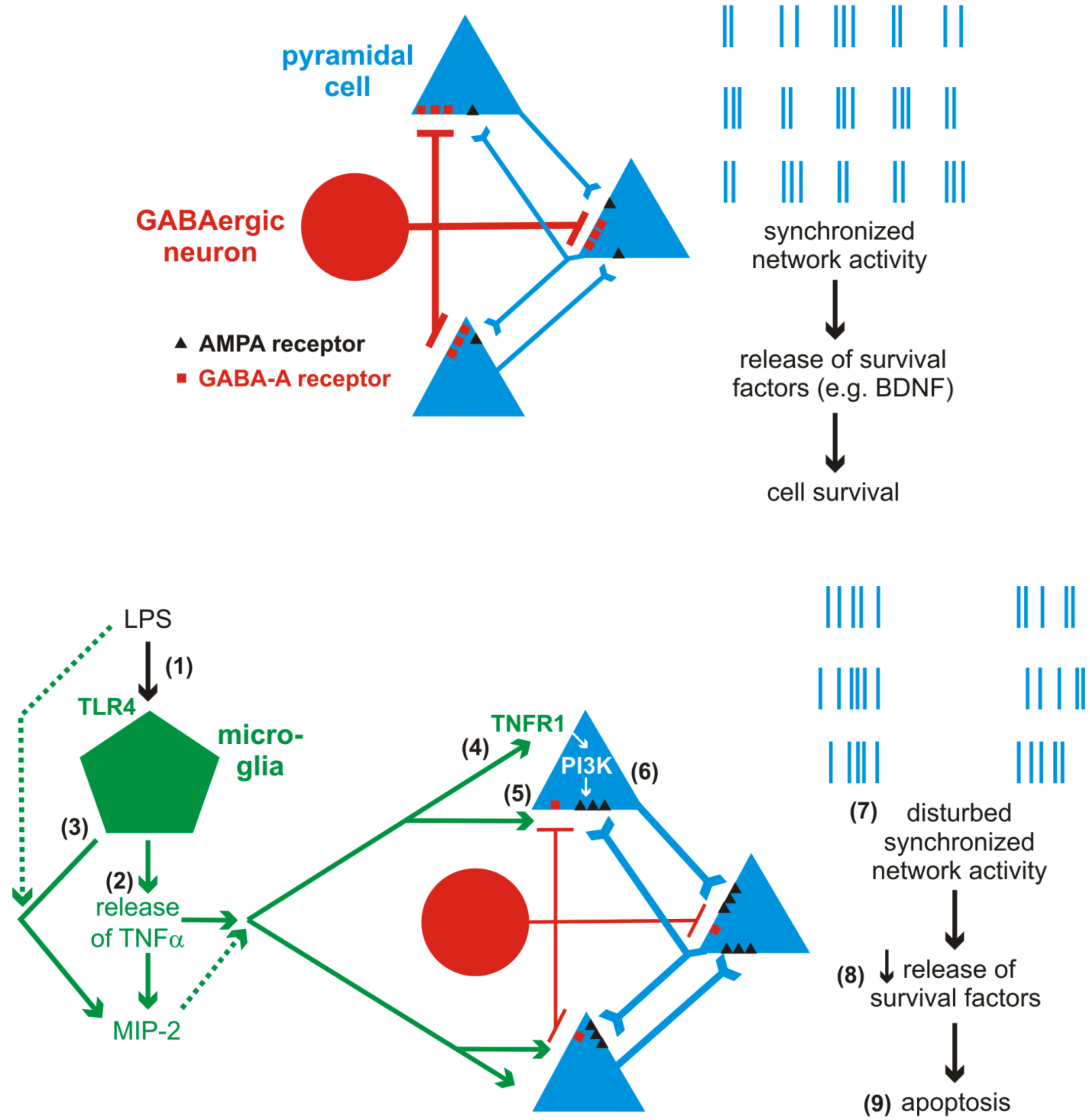
LPS-induced inflammation in the newborn rat somatosensory cortex in vivo leads to alterations in spontaneous neuronal network activity and increased caspase-3 expression

P3 rat, 3 h after PBS or LPS injection



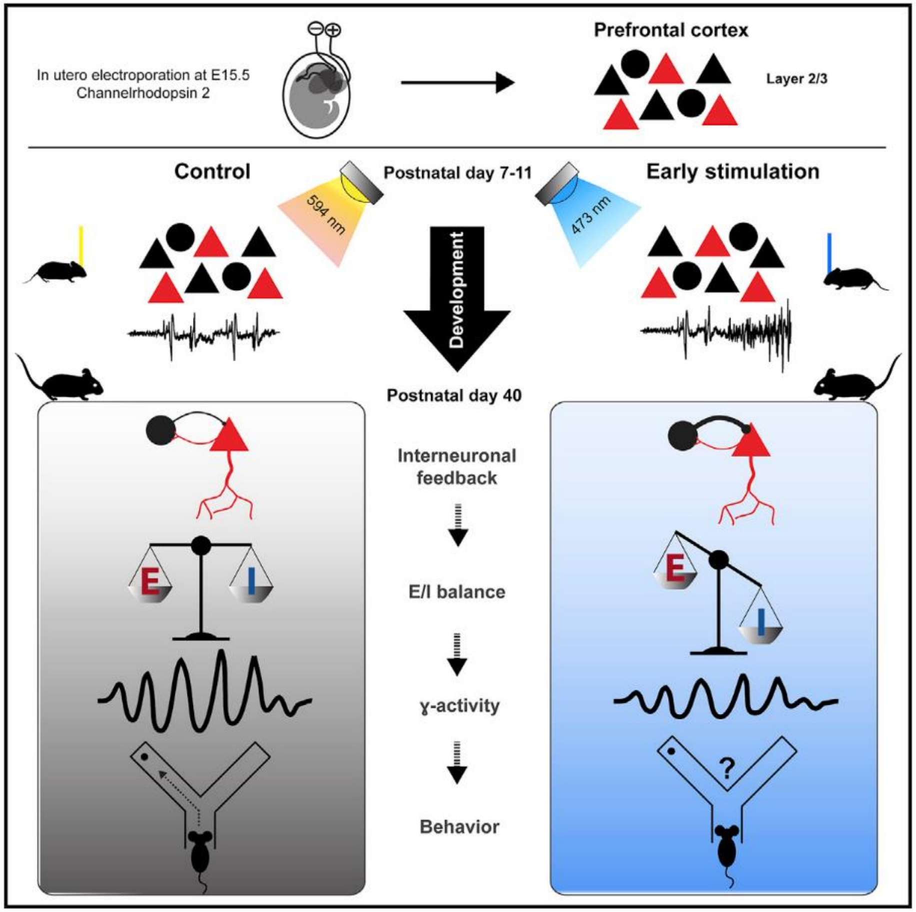


Nimmervoll et al. (2013)



pyramidal cell
GABAergic neuron
AMPA receptor
GABA-A receptor
synchronized network activity
release of survival factors (e.g. BDNF)
cell survival
LPS
(1)
TLR4
micro-glia
(3)
(2)
release of TNFα
MIP-2
(4)
TNFR1
PI3K
(5)
(6)
(7) disturbed synchronized network activity
(8) ↓ release of survival factors
(9) apoptosis

Q5: What are the long-term consequences of disturbances of this activity during early development?



- Increasing neonatal coordinated activity causes transient dendritic surge in mPFC
- Increasing neonatal activity disrupts gamma synchrony in adult prefrontal circuits
- Increasing neonatal activity causes excitation/inhibition imbalance in adult mPFC
- Increasing neonatal prefrontal activity disrupts adult cognitive abilities

A transient developmental increase in prefrontal activity alters network maturation and causes cognitive dysfunction in adult mice

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Take home messages

M1: During late prenatal and early postnatal development the cerebral cortex shows spontaneous synchronized burst activity, both in humans (e.g. *delta brush*) and rodents (*spindle bursts*).

M2: With development spont activity shows increase in entropy and parcellation and changes from correlated to decorrelated state. A functional somato-motor subnetwork exists from birth and retrosplenical cortex may serve as hub region.

M3: Subplate receives early thalamic input and plays key role in generation of cortical network activity (which is driven by sensory periphery).

M4: Spontaneous synchronized burst activity controls progressive events (e.g. columnar organization, topographic maps) and regressive events (e.g. apoptosis).

M5: Any disturbances in early cortical activity, induced by hypoxia, inflammation or infection *in utero*, drugs (e.g. antiepileptics, alcohol) may have an immediate impact on electrical activity patterns thereby causing long-term neuronal dysfunction.