Parahippocampal networks in epileptic ictogenesis

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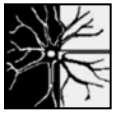
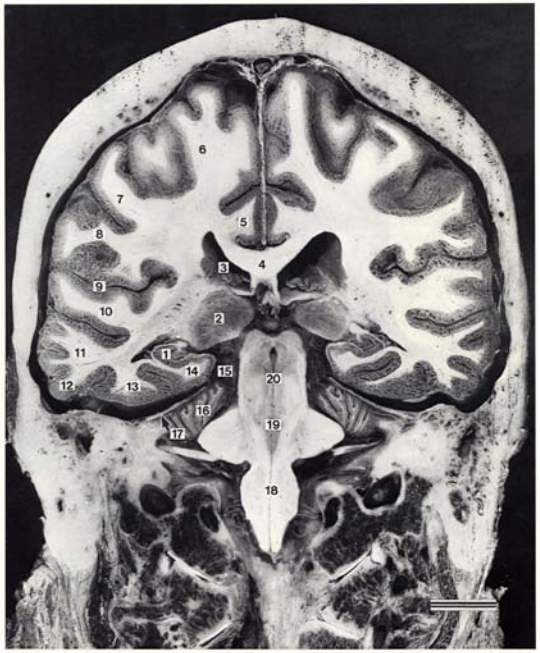
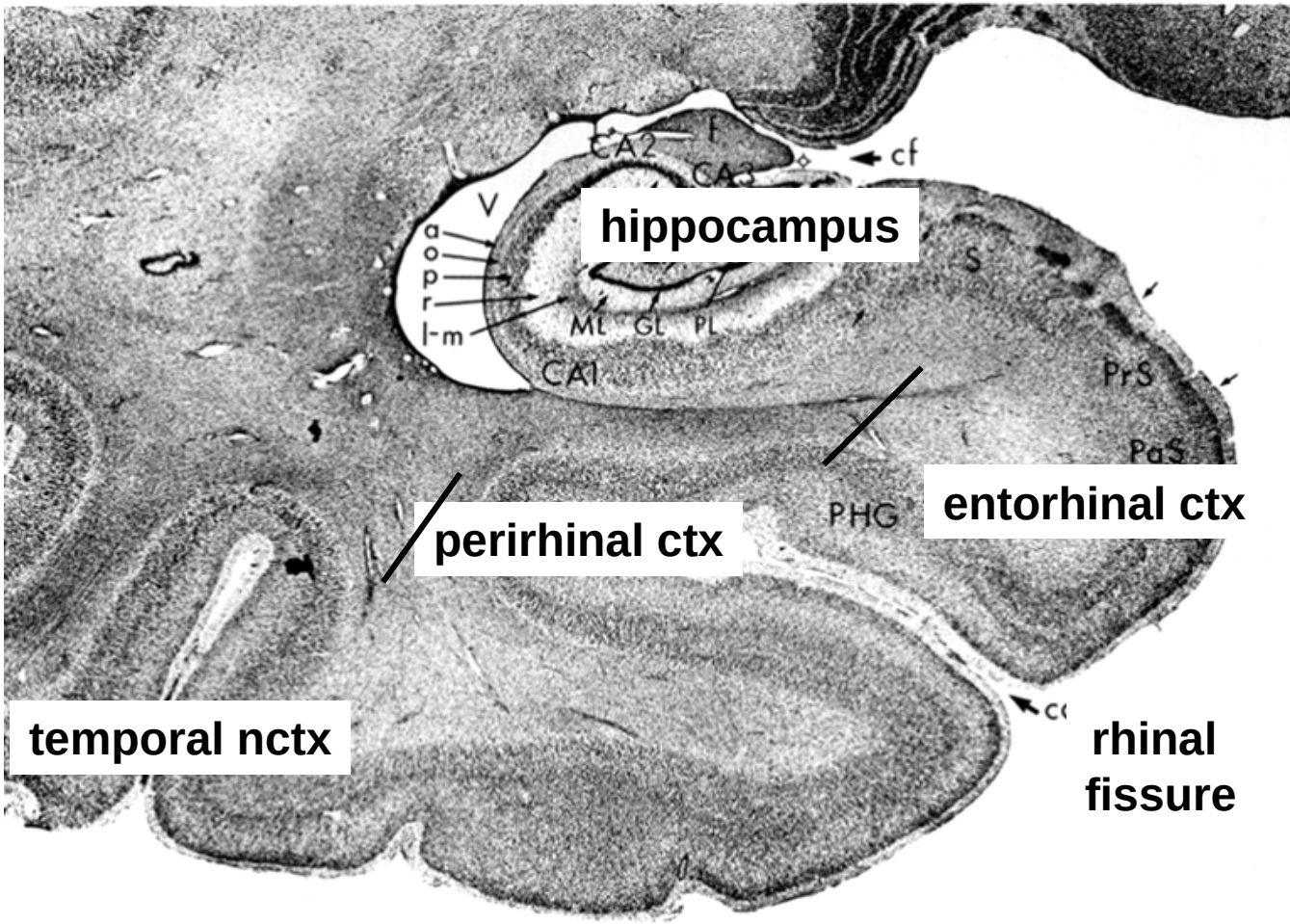
Milano - Italy

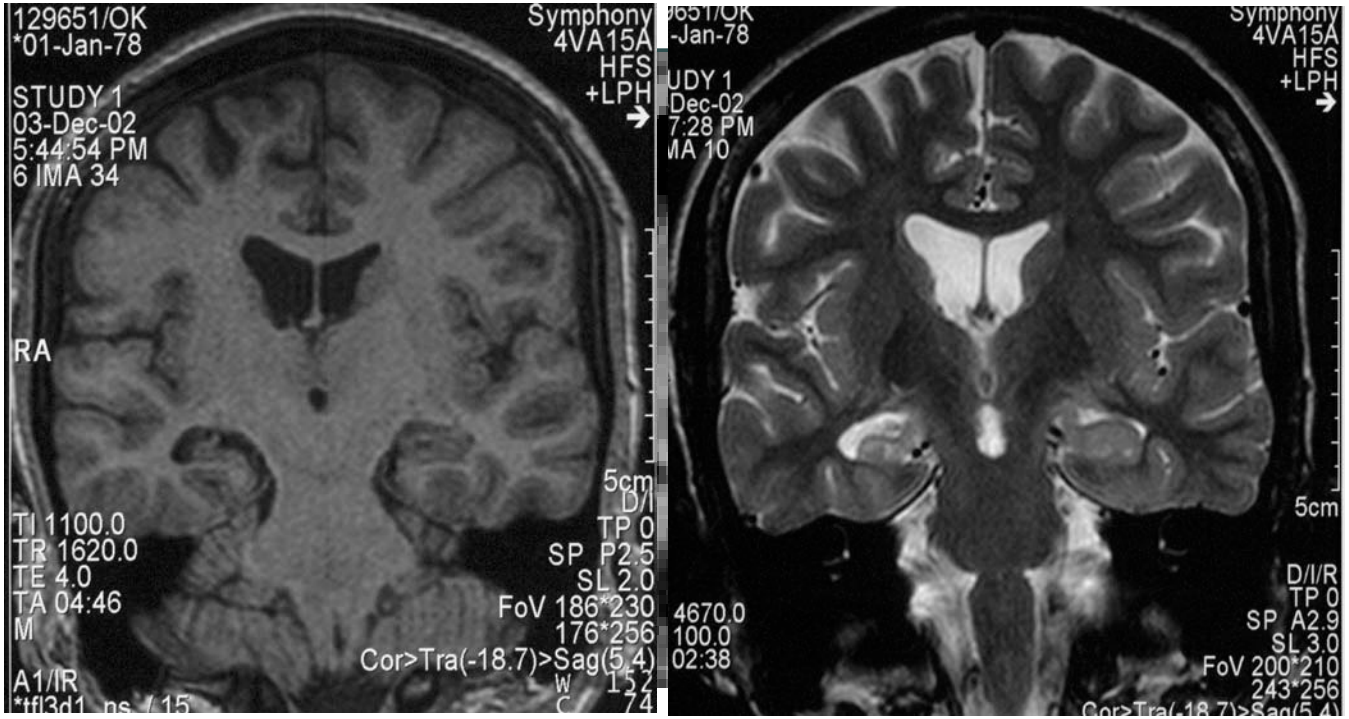


Amaral, 1999




hippocampus
entorhinal ctx
perirhinal ctx
temporal nctx
rhinal fissure
CA2
CA3
CA1
cf
V
a
o
p
r
l-m
Ml
Gl
Pl
S
PrS
PaS
PHG

Temporal lobe epilepsy



- Changes in parahippocampal cortex volume are associated with and may precede hippocampal sclerosis
- Seizure activity originates from both entorhinal cortex and hippocampus
- Ictal onset is characterized by the appearance of fast activity at 20-30 Hz

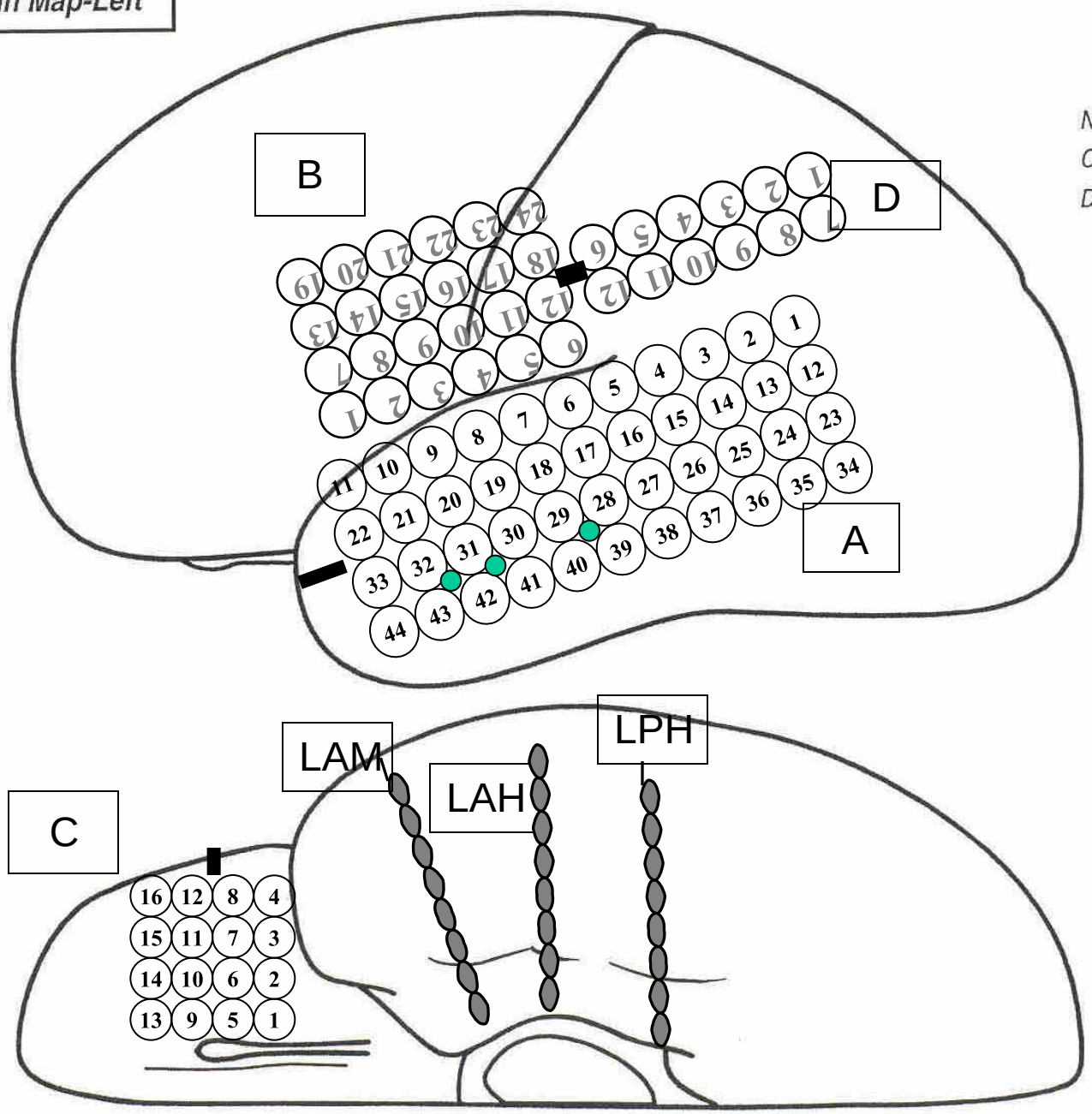
Brain Map-Left

THE CLEVELAND CLINIC FOUNDATION
9500 Euclid Avenue Cleveland Ohio 44195
Comprehensive Epilepsy Program

Name: _____

Clinic Number: _____

Date: Sept. 15, 2005



Grids

A: 4x11: Left Lat. Temp

B: 4x6 : Lat. Fronto-Par.

C: 4x4: Orb-Frontal

D: 2x6: Lat. Parietal

E: 1x6: Basal Mid-Temp

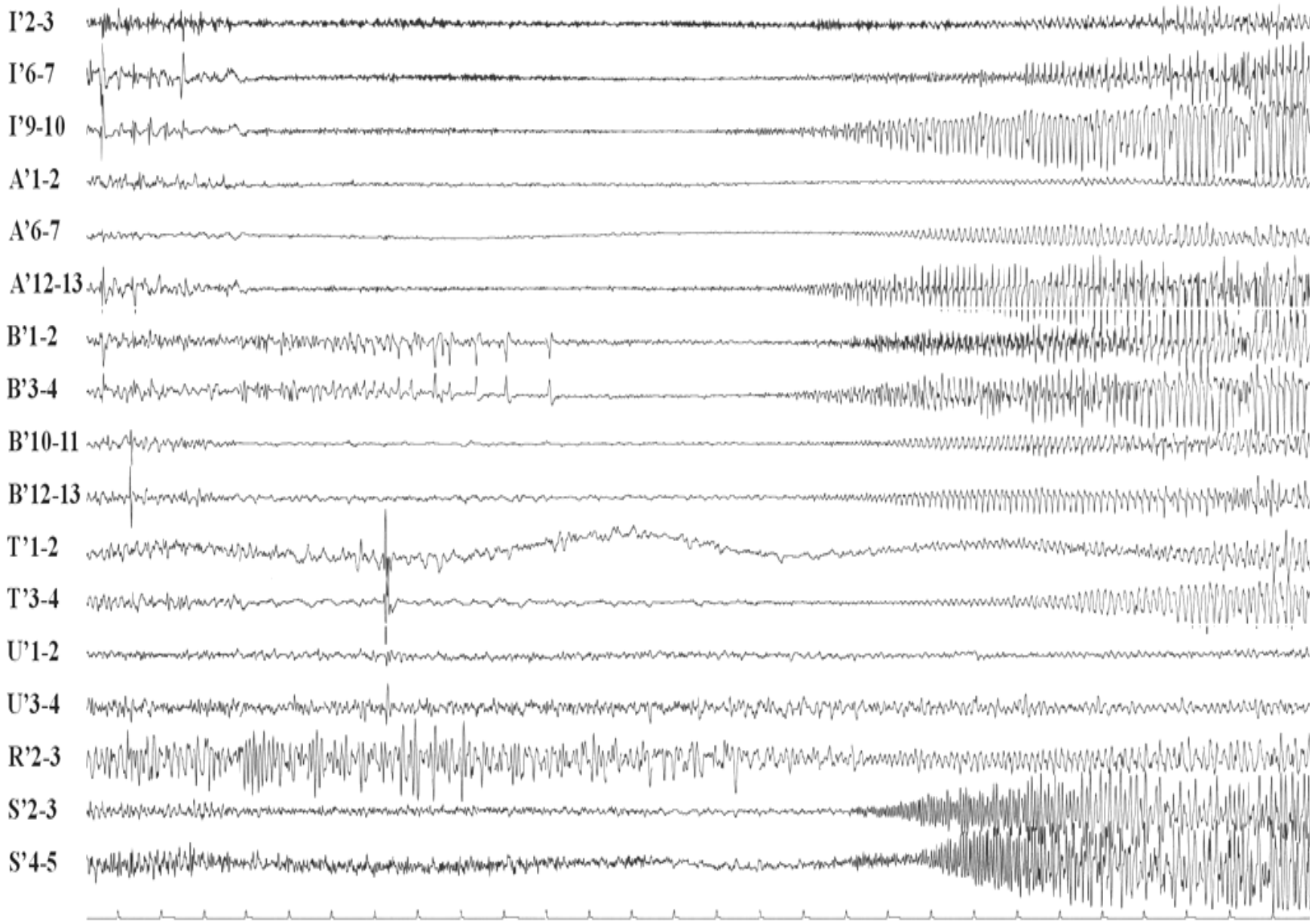
F: 1x6: Basal Post. Temp

Depths

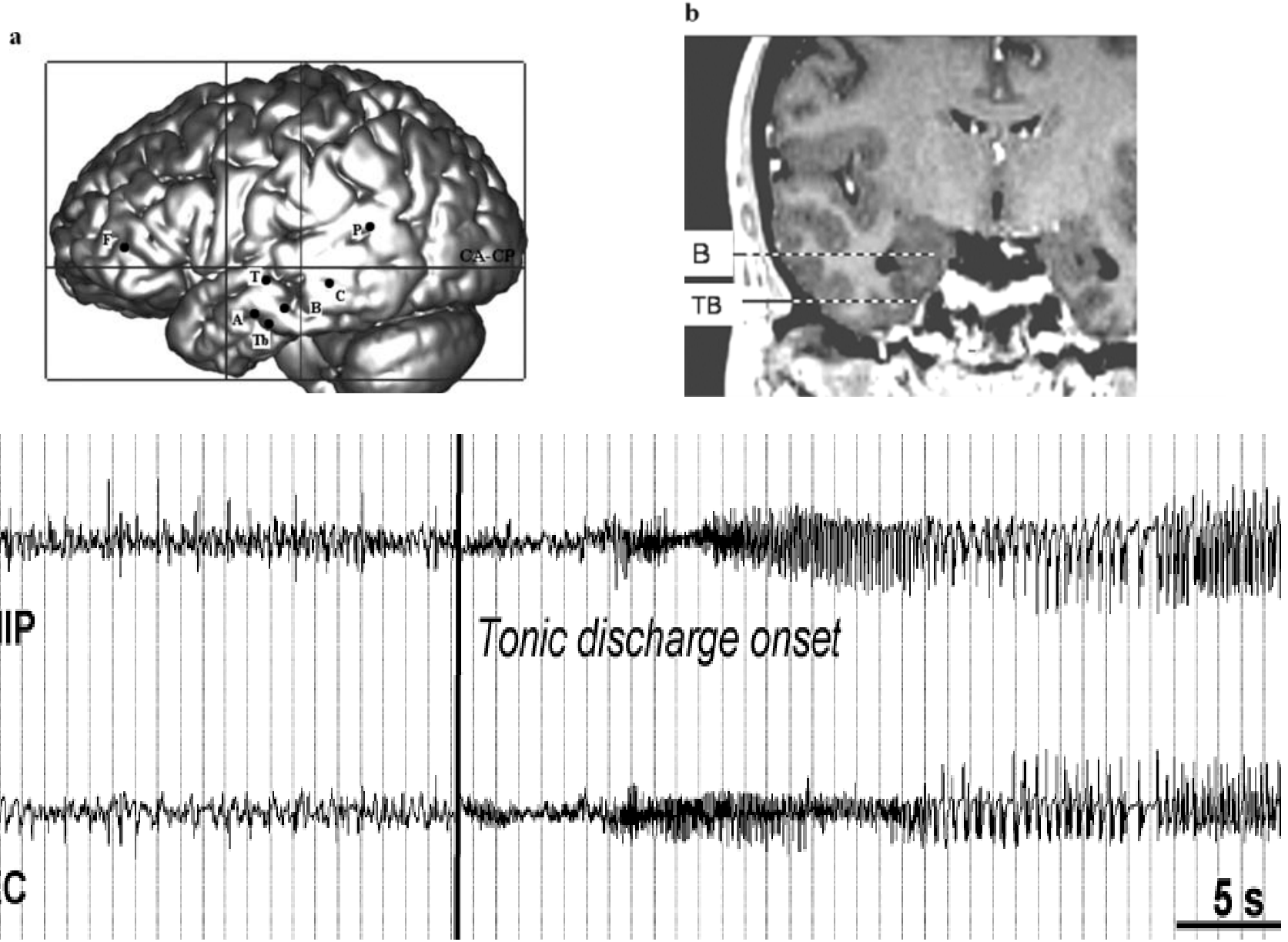
LA: Left amygdala

LAH: Left ant. hippo

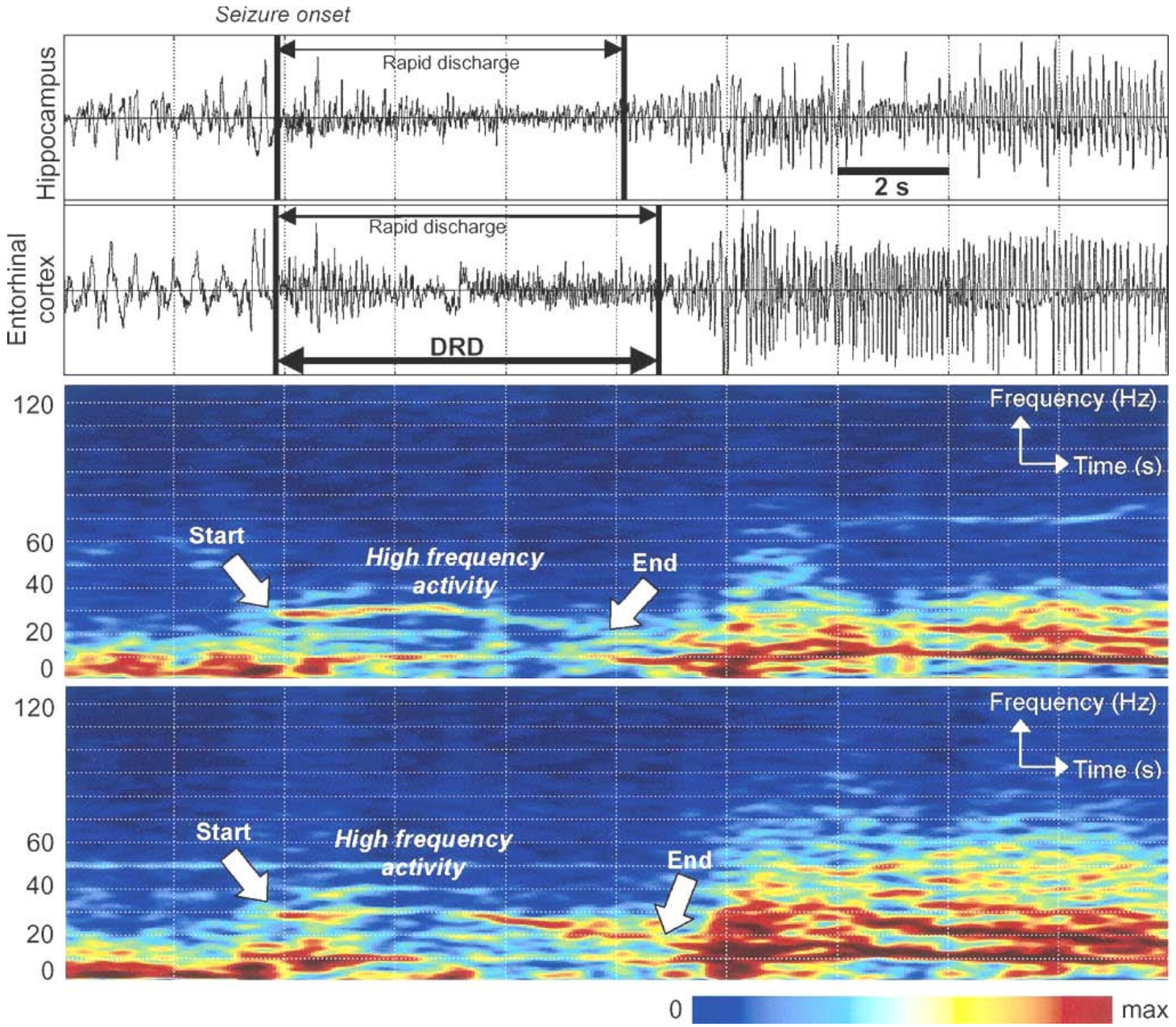
LPH: L post hippo



Francione et al, Center Epilepsy Surgery "Claudio Munari", Milano

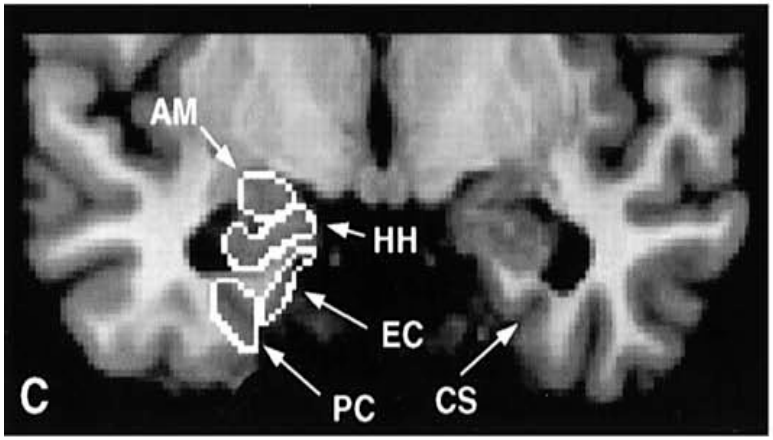


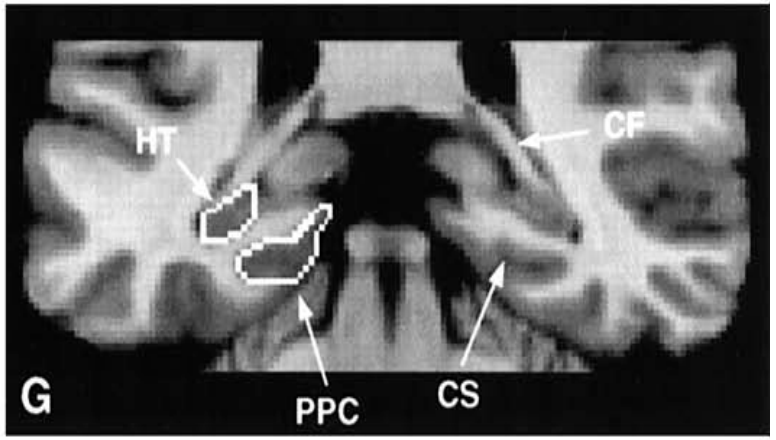
Bartolomei, Wendling et al. 2005

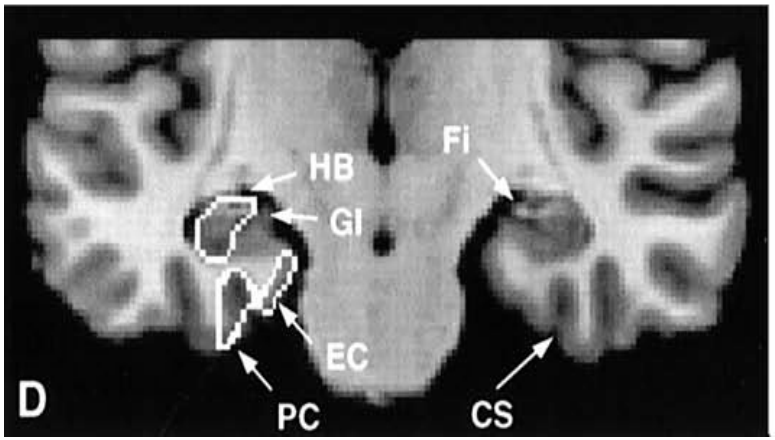


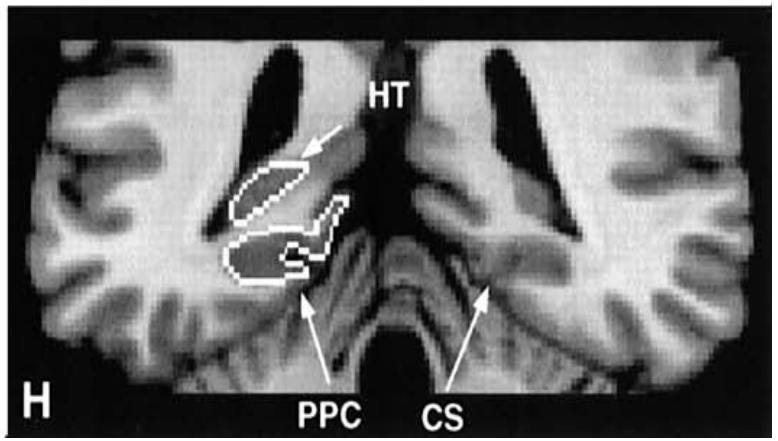
Bartolomei et al., 2004

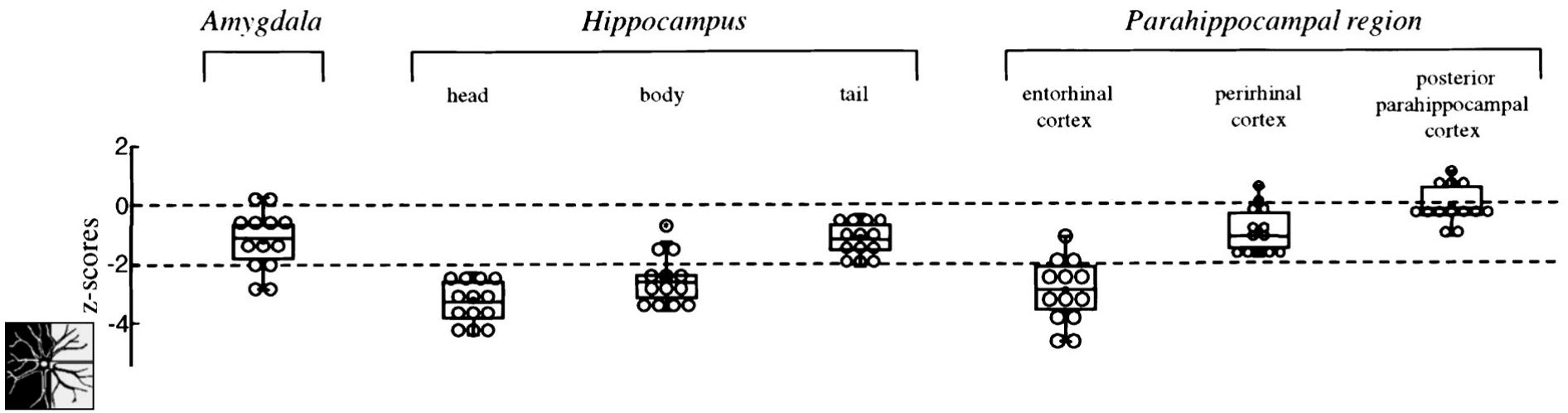
Bernasconi et al, 2003





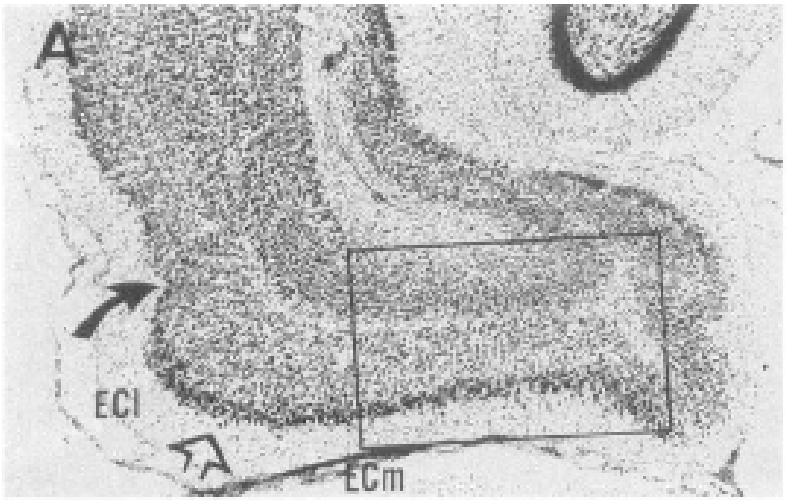


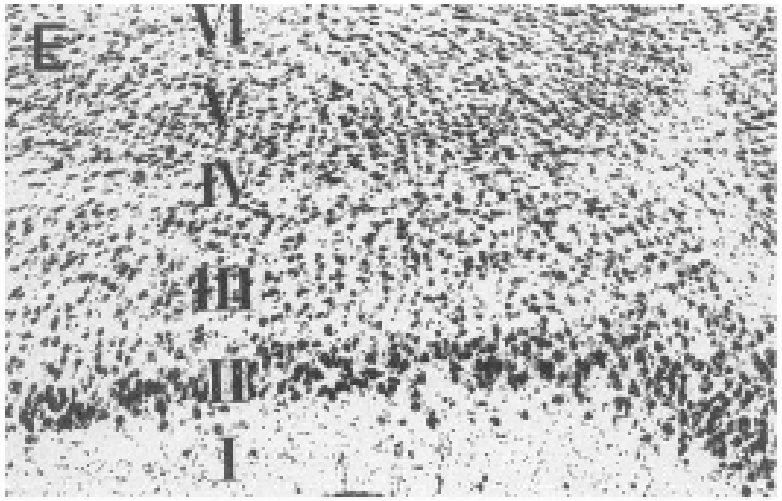


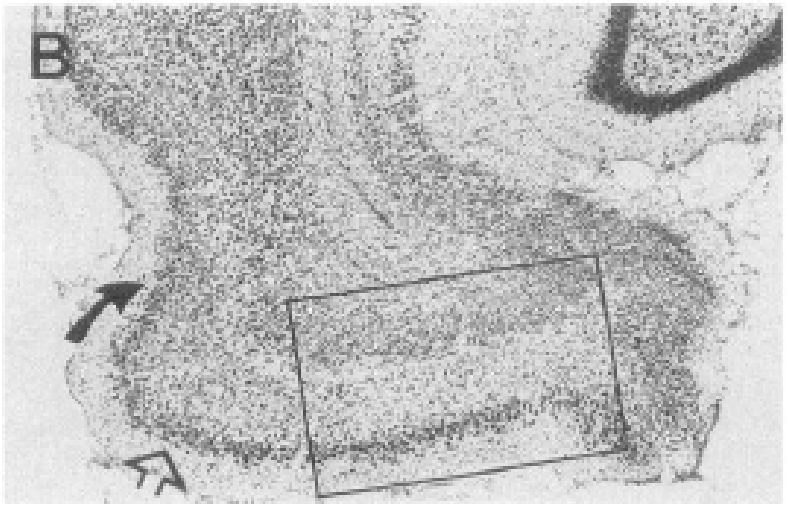


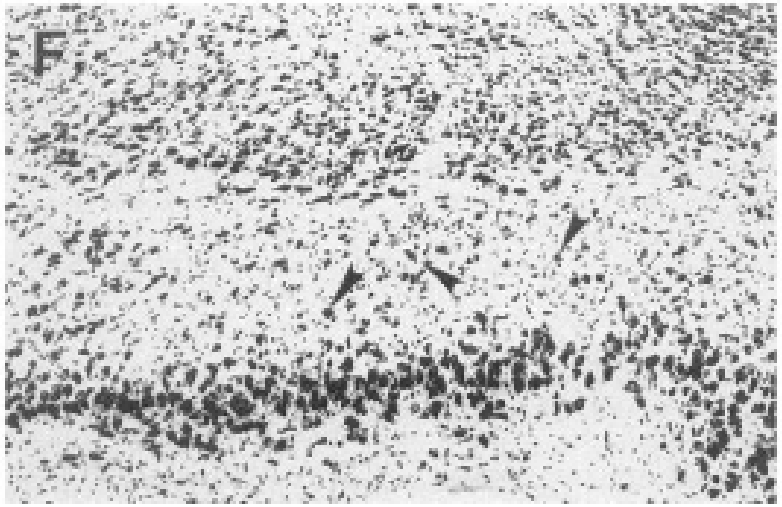
controllo

TLE

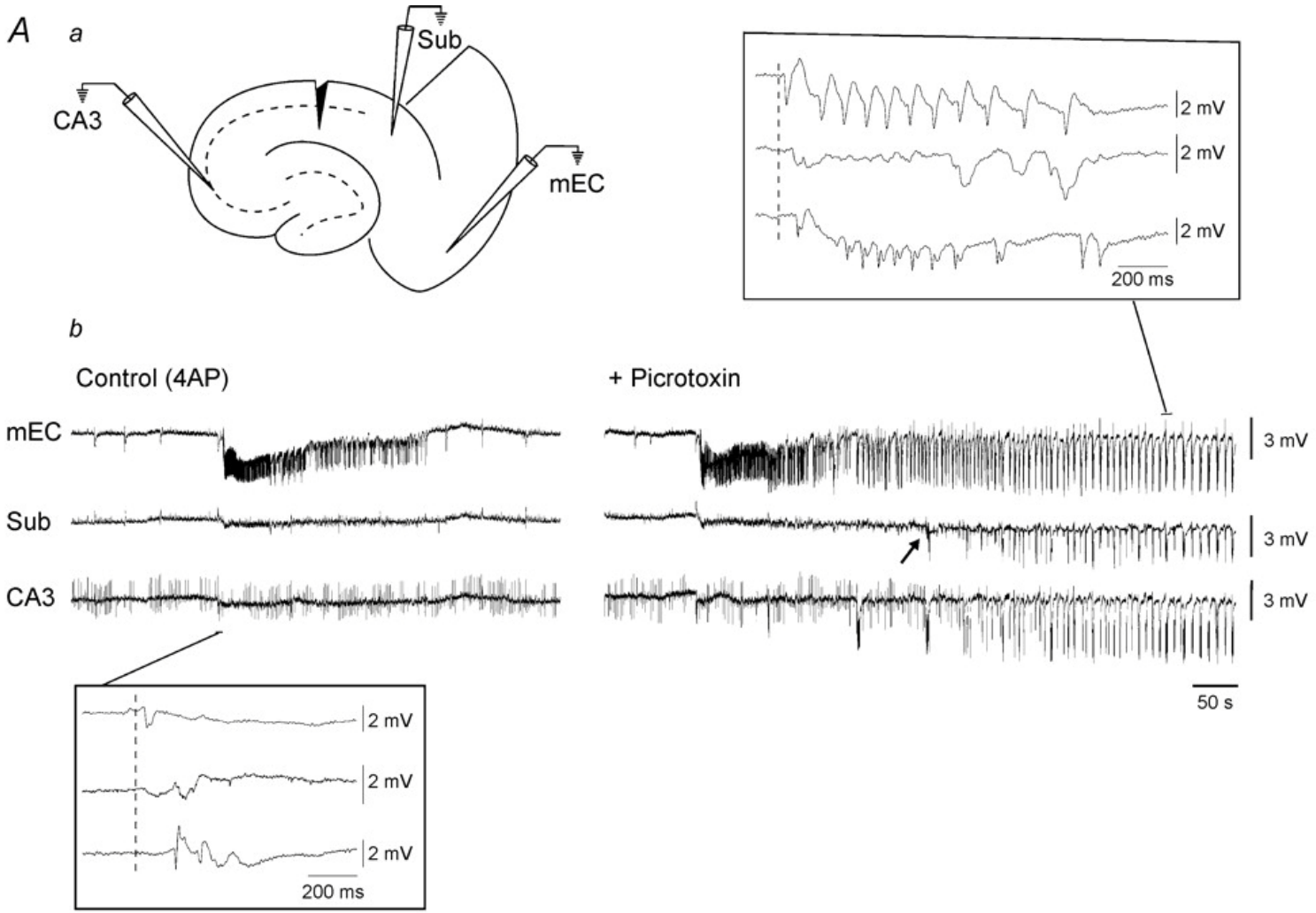






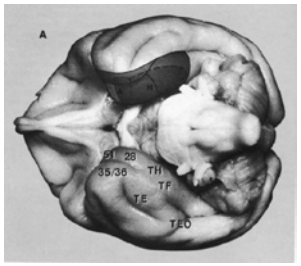


Du et al, 1997

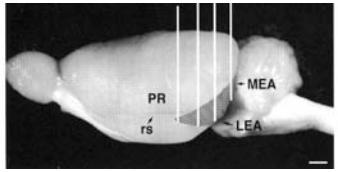


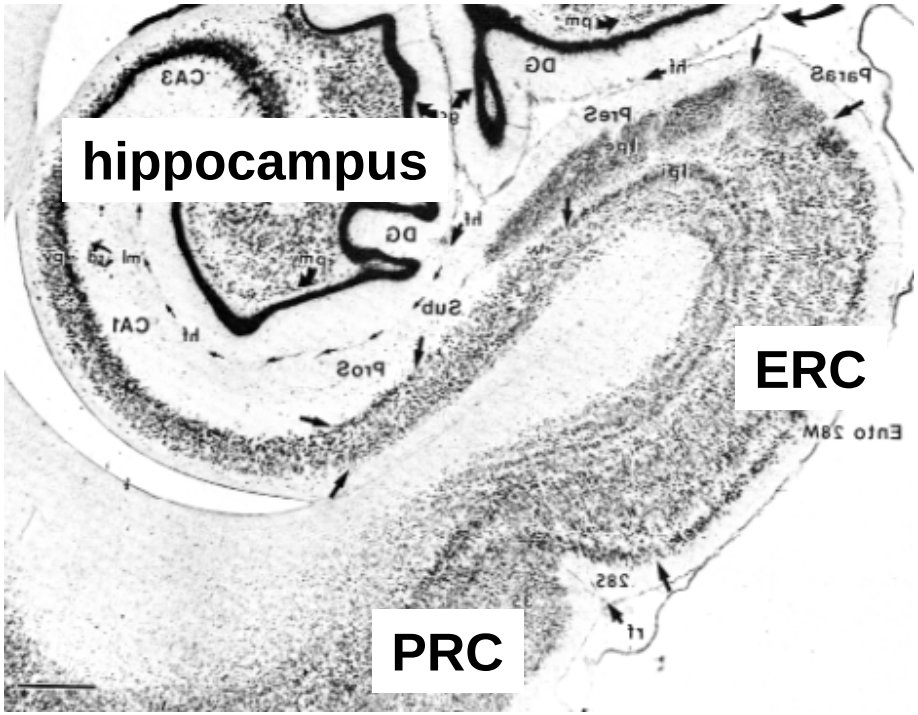
Avoli et al 2005

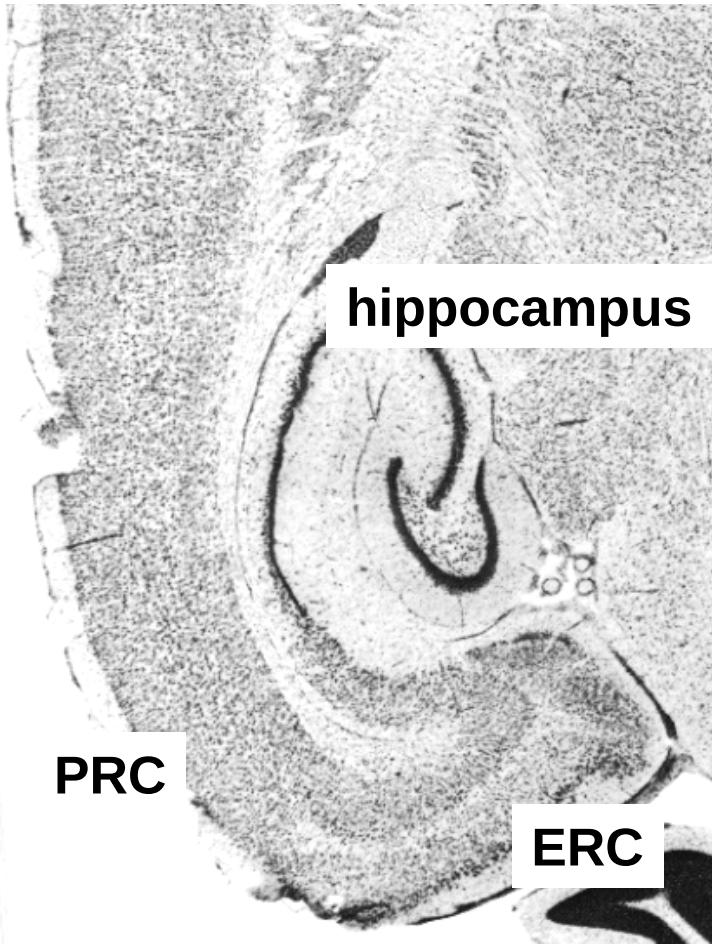
monkey

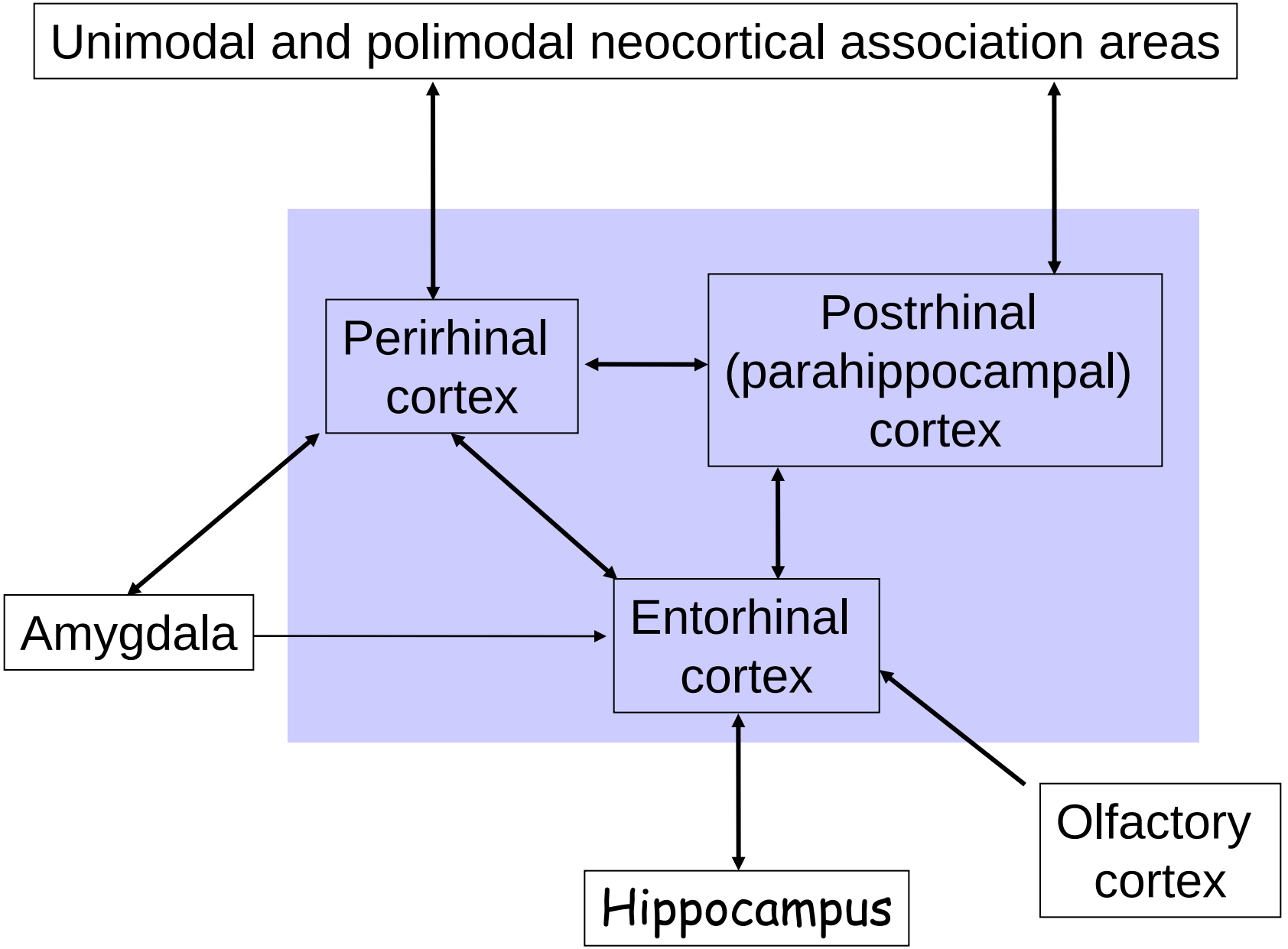

A
35/36
TH
TF
TE
TEO

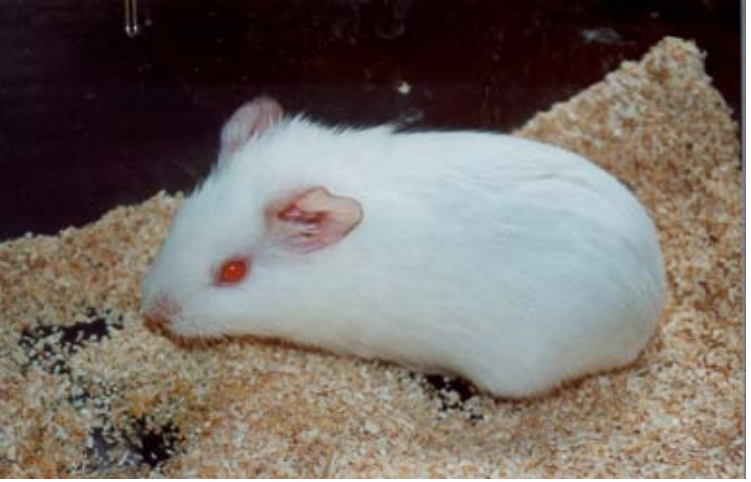
rat

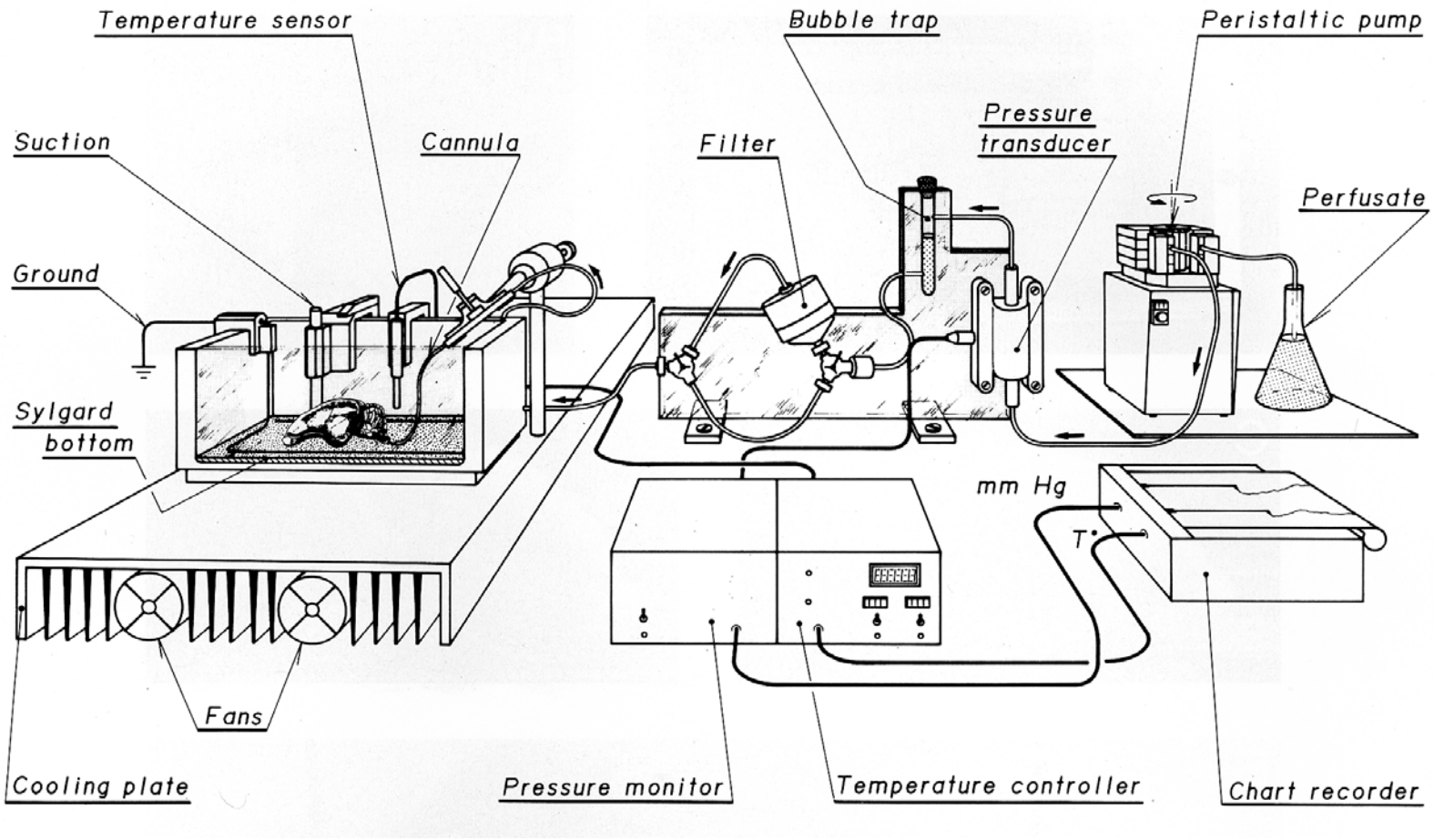

PR
rs
MEA
LEA

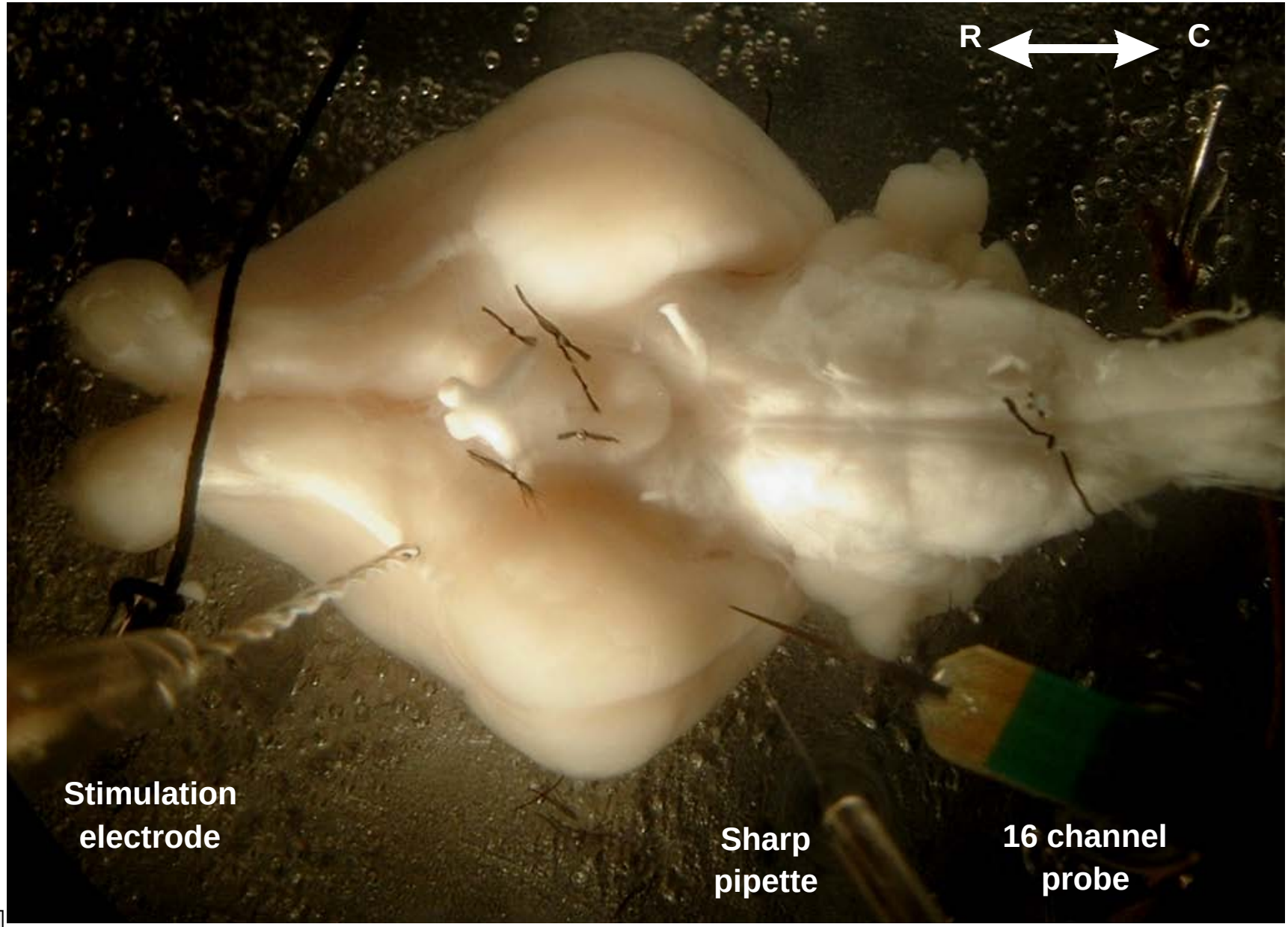

hippocampus
ERC
PRC

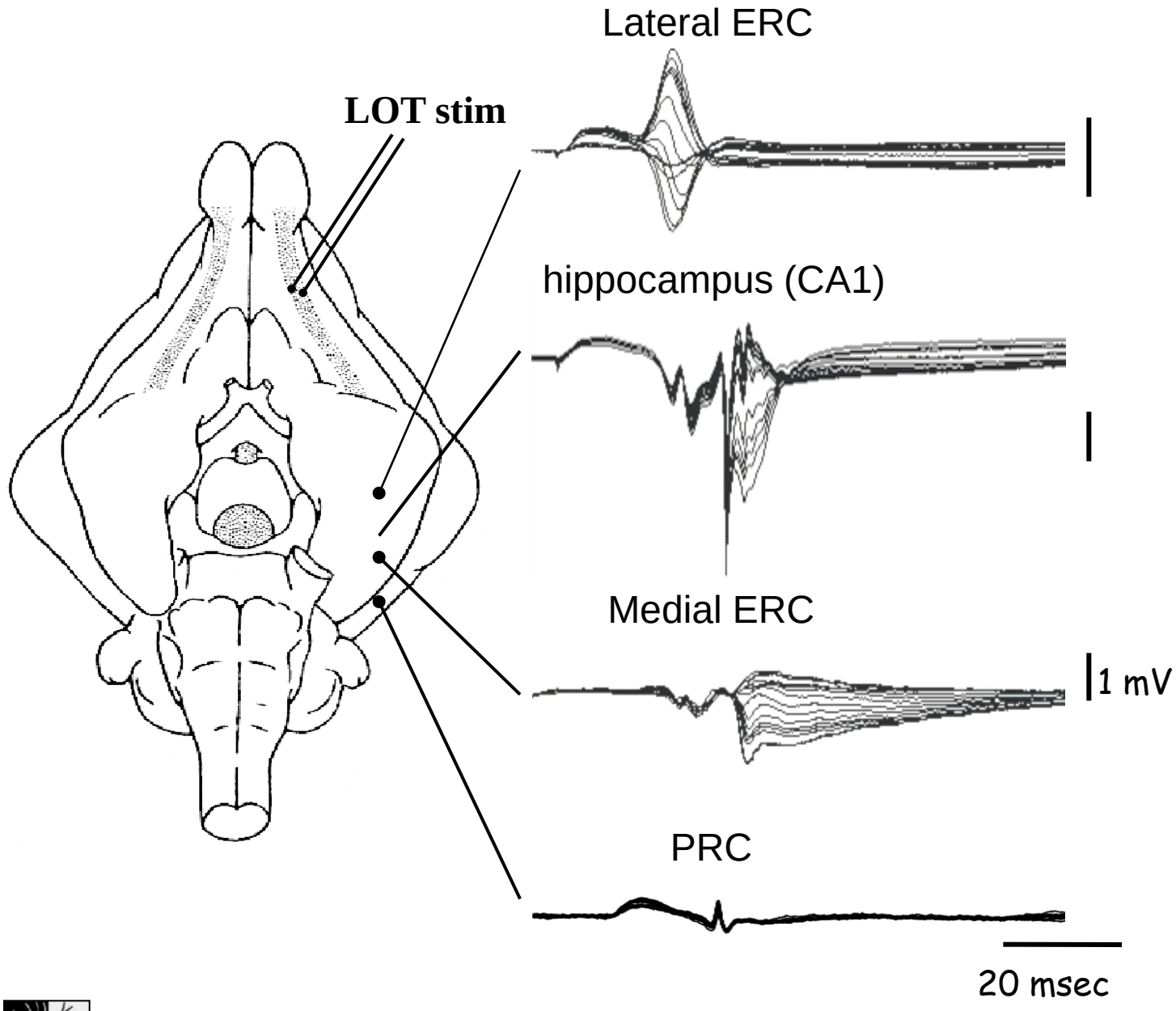

hippocampus
PRC
ERC


Unimodal and polimodal neocortical association areas
Perirhinal cortex
Postrhinal (parahippocampal) cortex
Amygdala
Entorhinal cortex
Olfactory cortex
Hippocampus

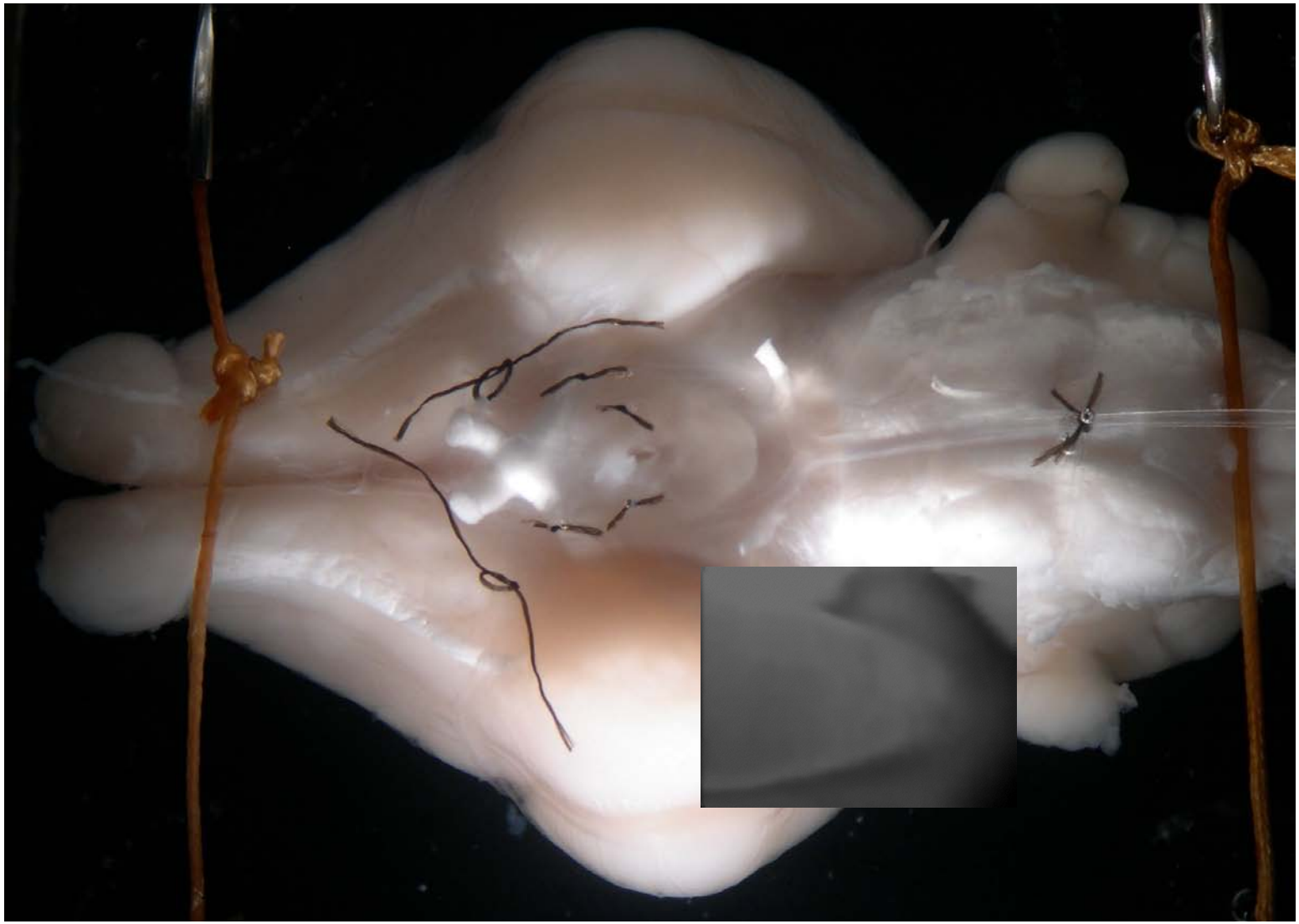



Temperature sensor
Bubble trap
Peristaltic pump
Suction
Cannula
Filter
Pressure transducer
Perfusate
Ground
Sylgard bottom
mm Hg
T
Fans
Cooling plate
Pressure monitor
Temperature controller
Chart recorder

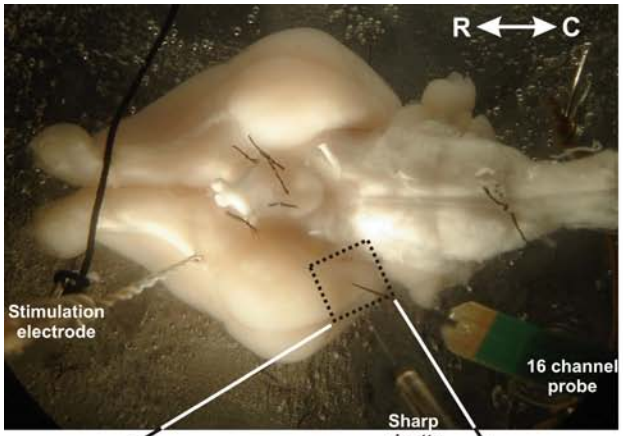

R
C
Stimulation electrode
Sharp pipette
16 channel probe

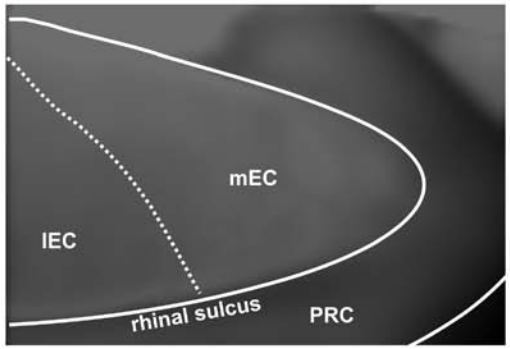


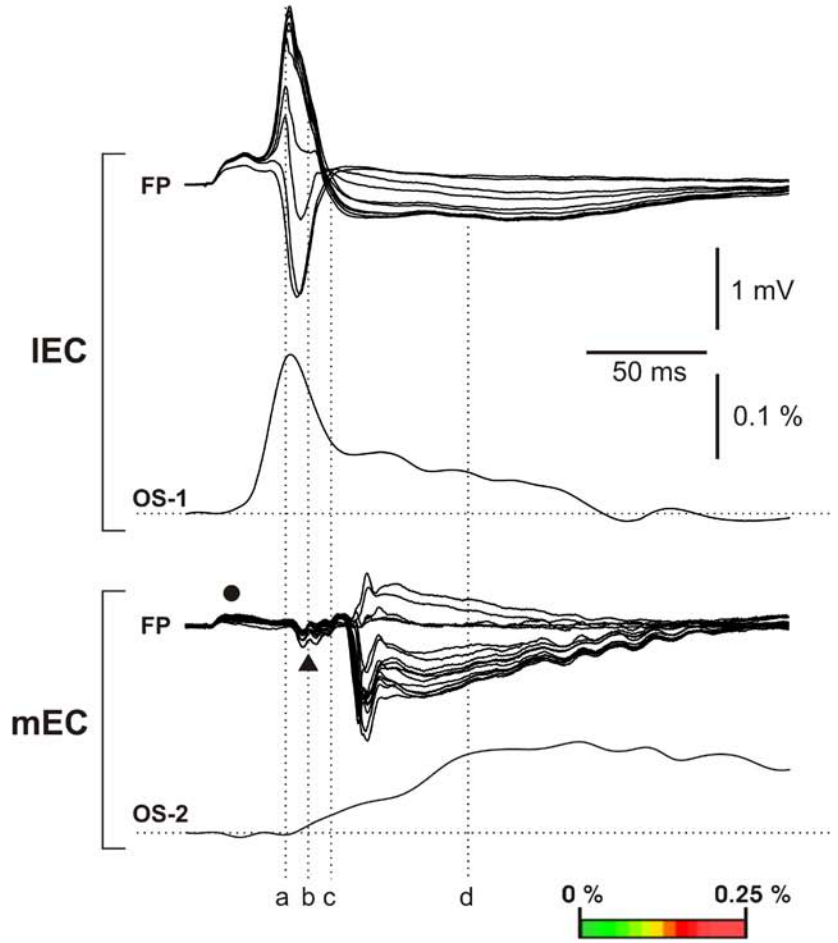
Uva et al, 2005

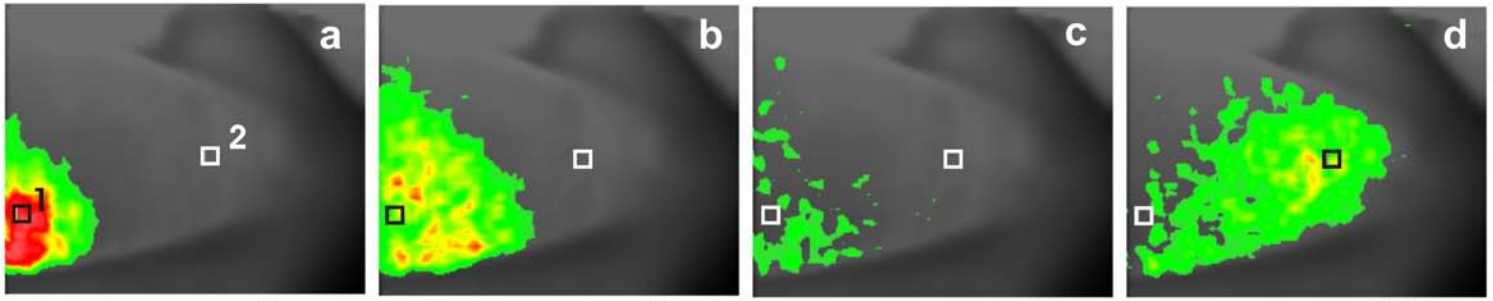


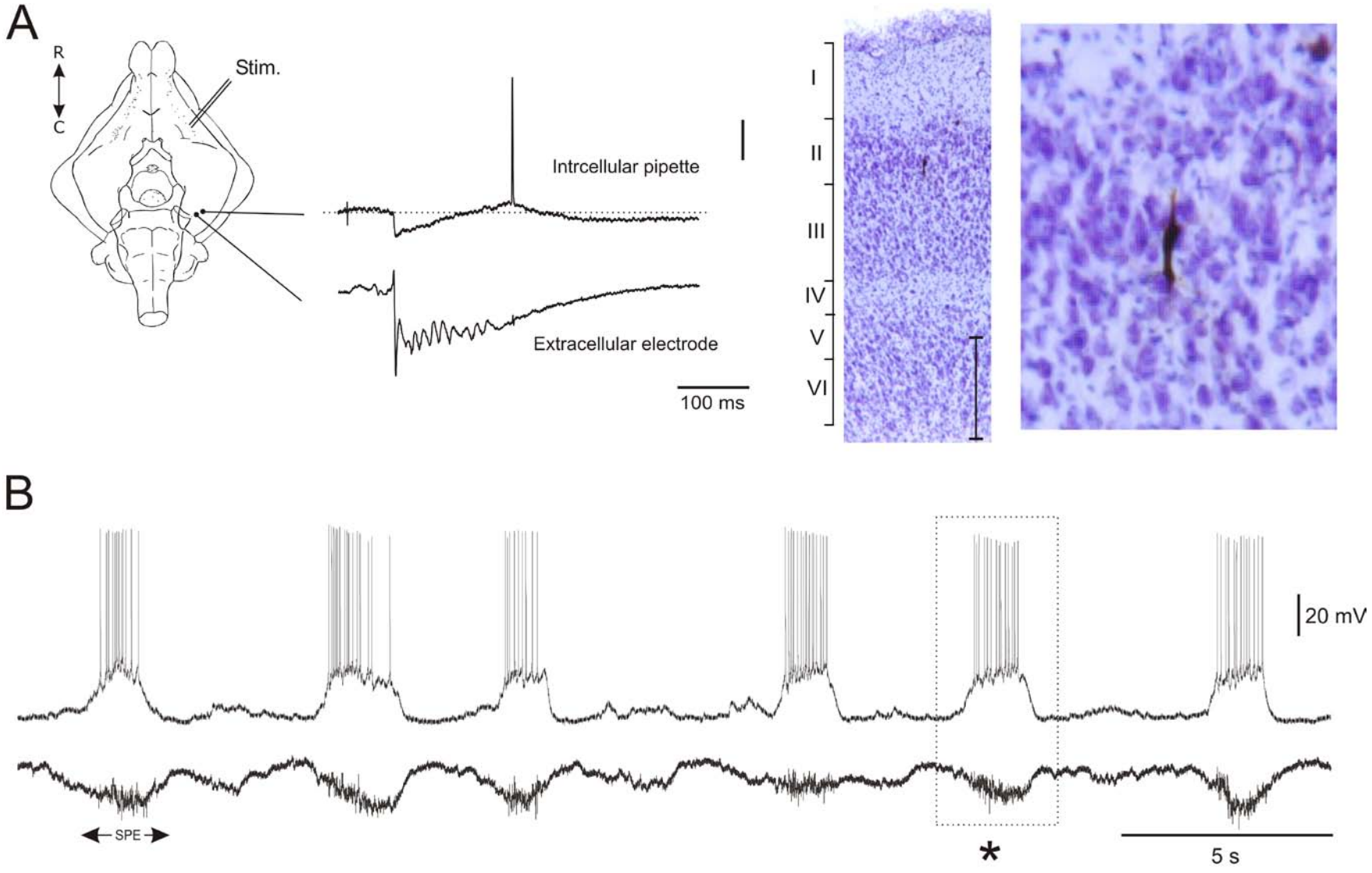
Xvid

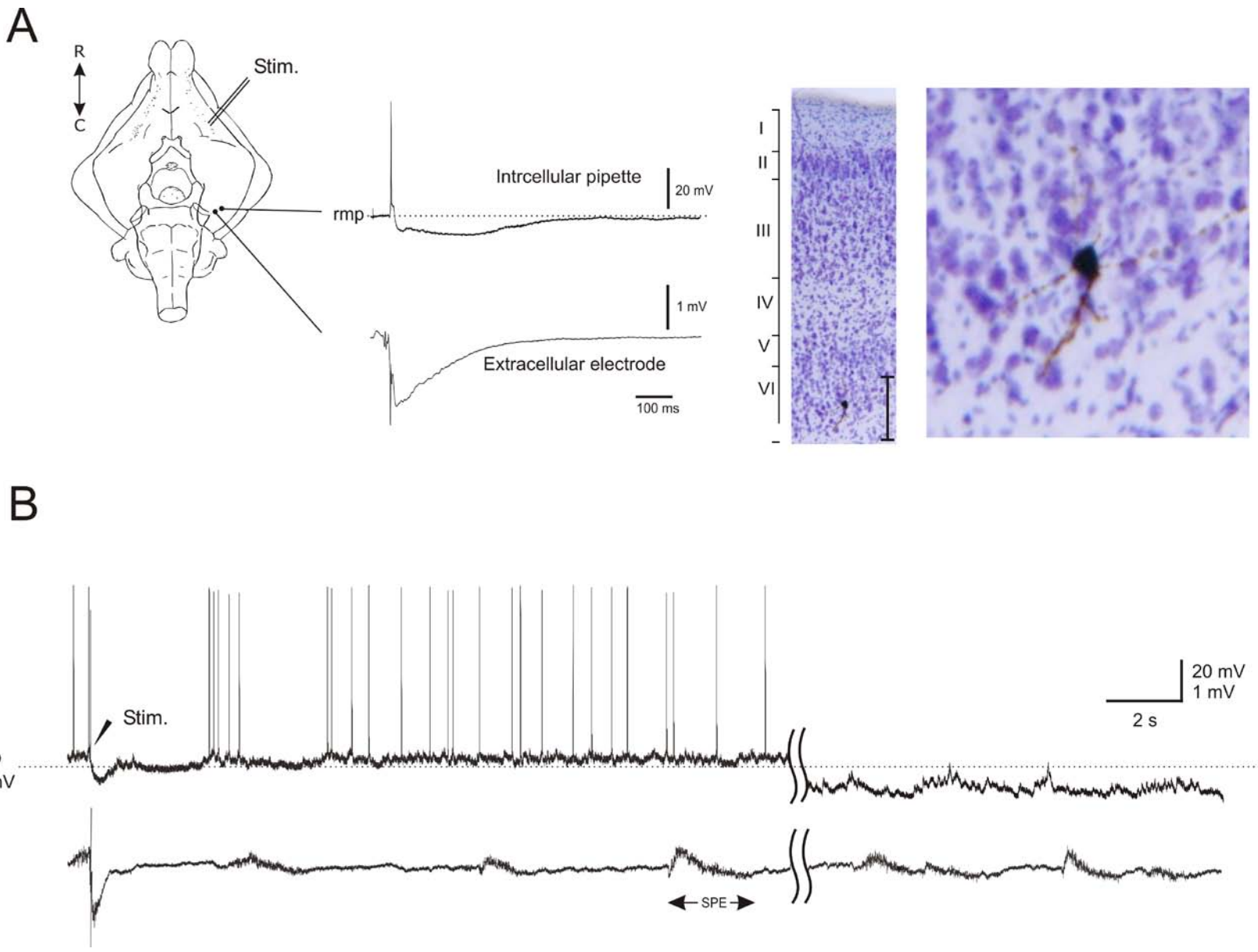

R
C
Stimulation electrode
16 channel probe
Sharp pipette

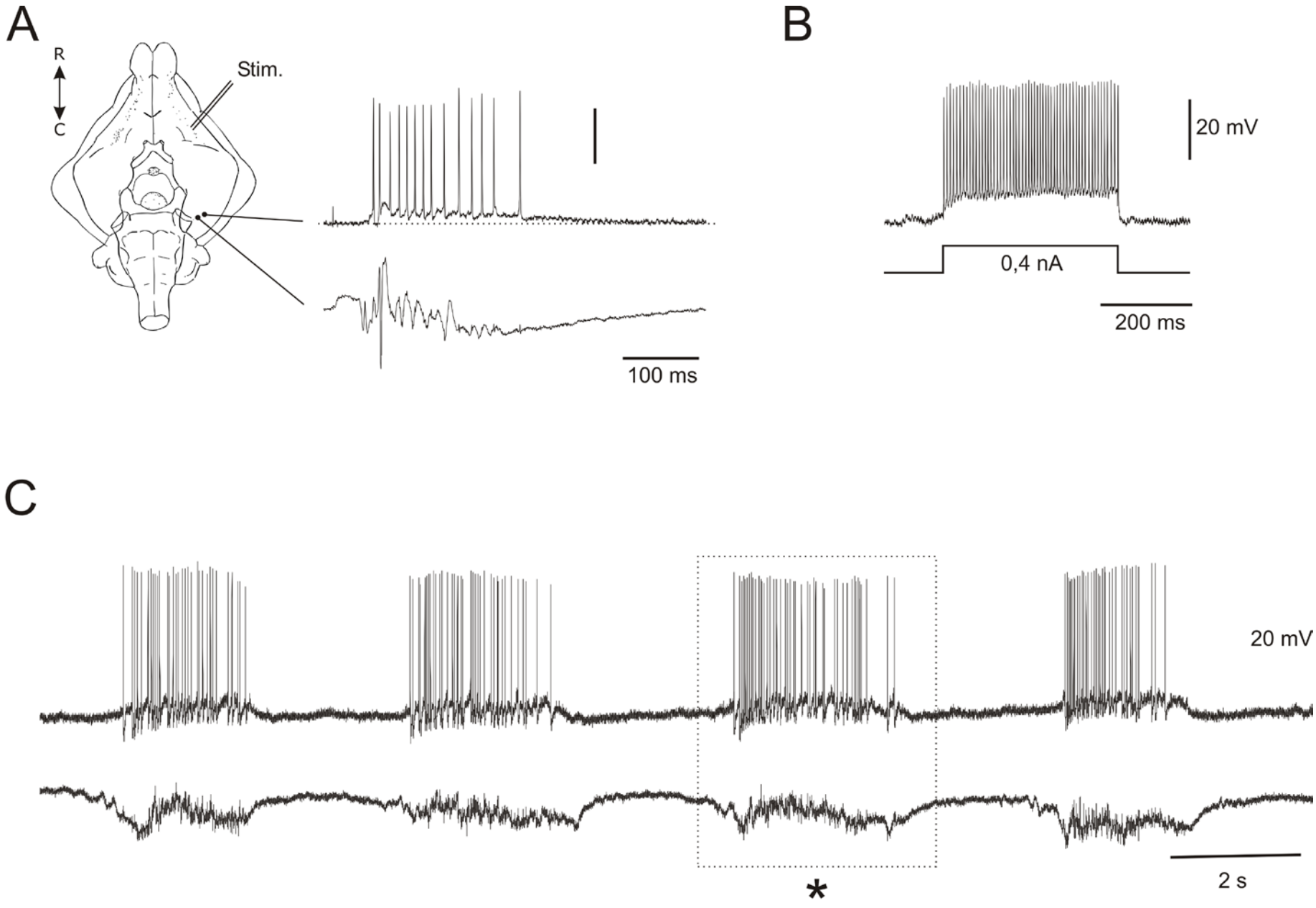

mEC
lEC
rhinal sulcus
PRC

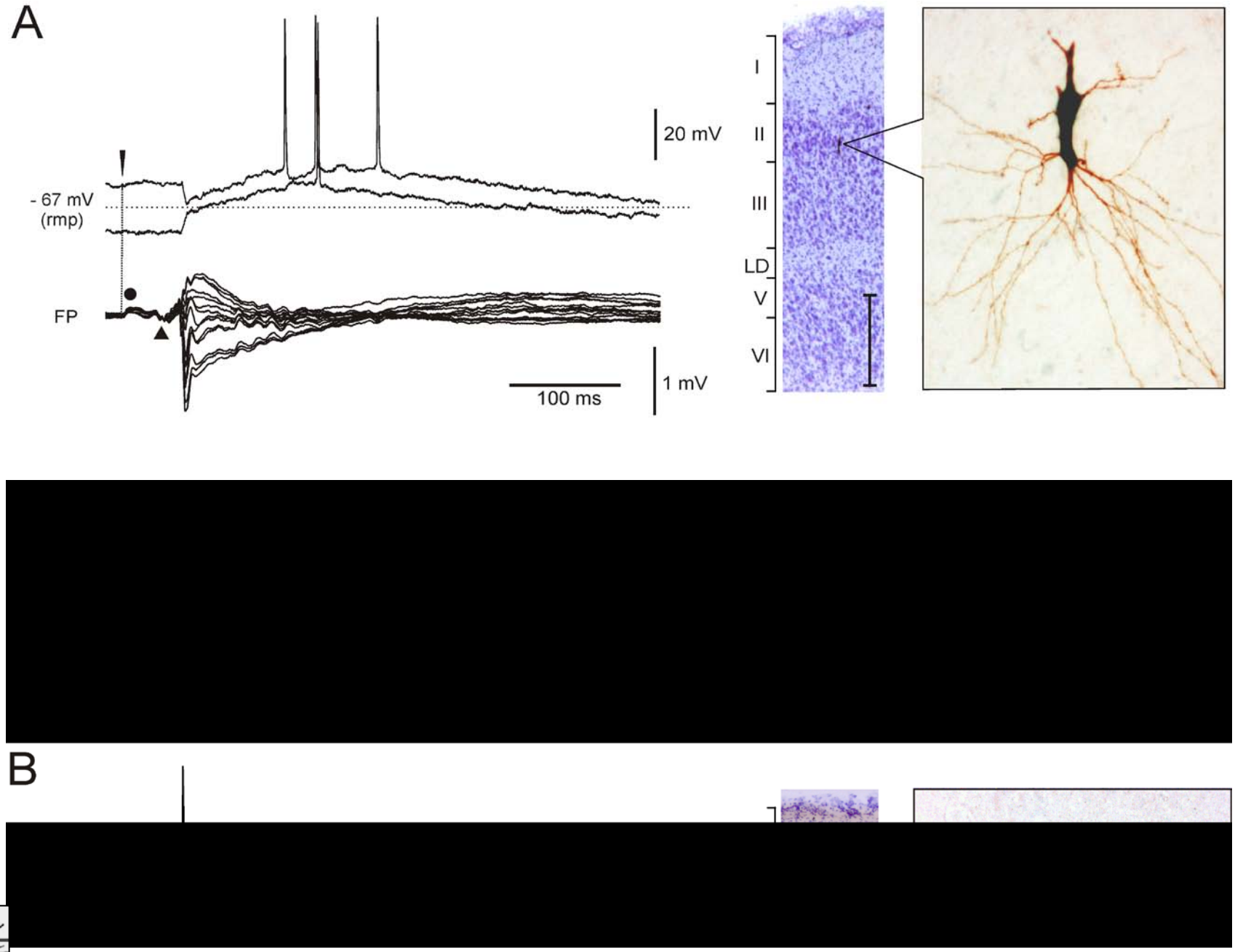

FP
1 mV
lEC
50 ms
0.1 %
OS-1
FP
mEC
OS-2
a b c
d
0 %
0.25 %


a
b
c
d
1
2
30 ms
40 ms
50 ms
110 ms

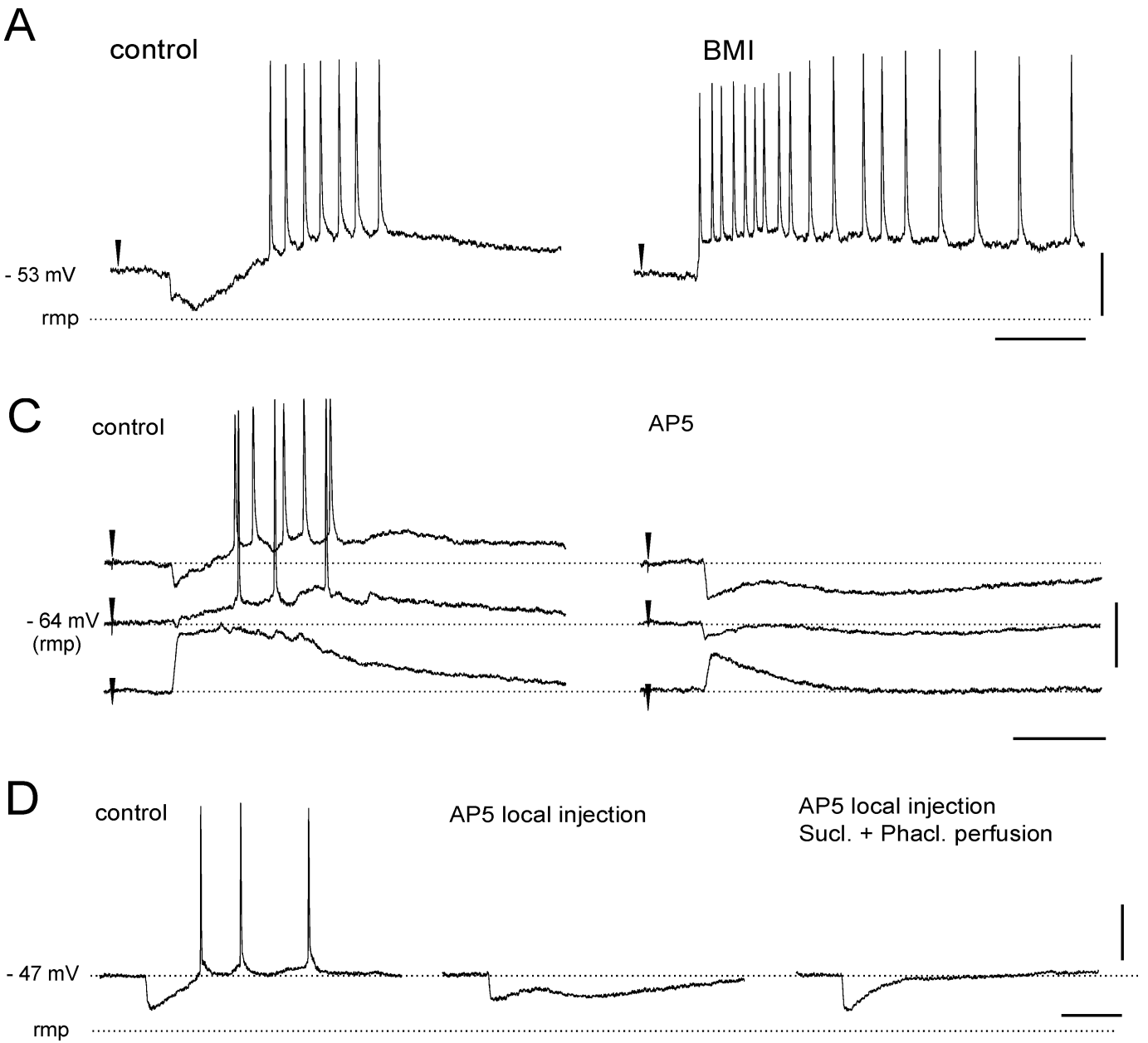

A
R
C
Stim.
Intrcellular pipette
Extracellular electrode
100 ms
I
II
III
IV
V
VI
B
20 mV
SPE
*
5 s

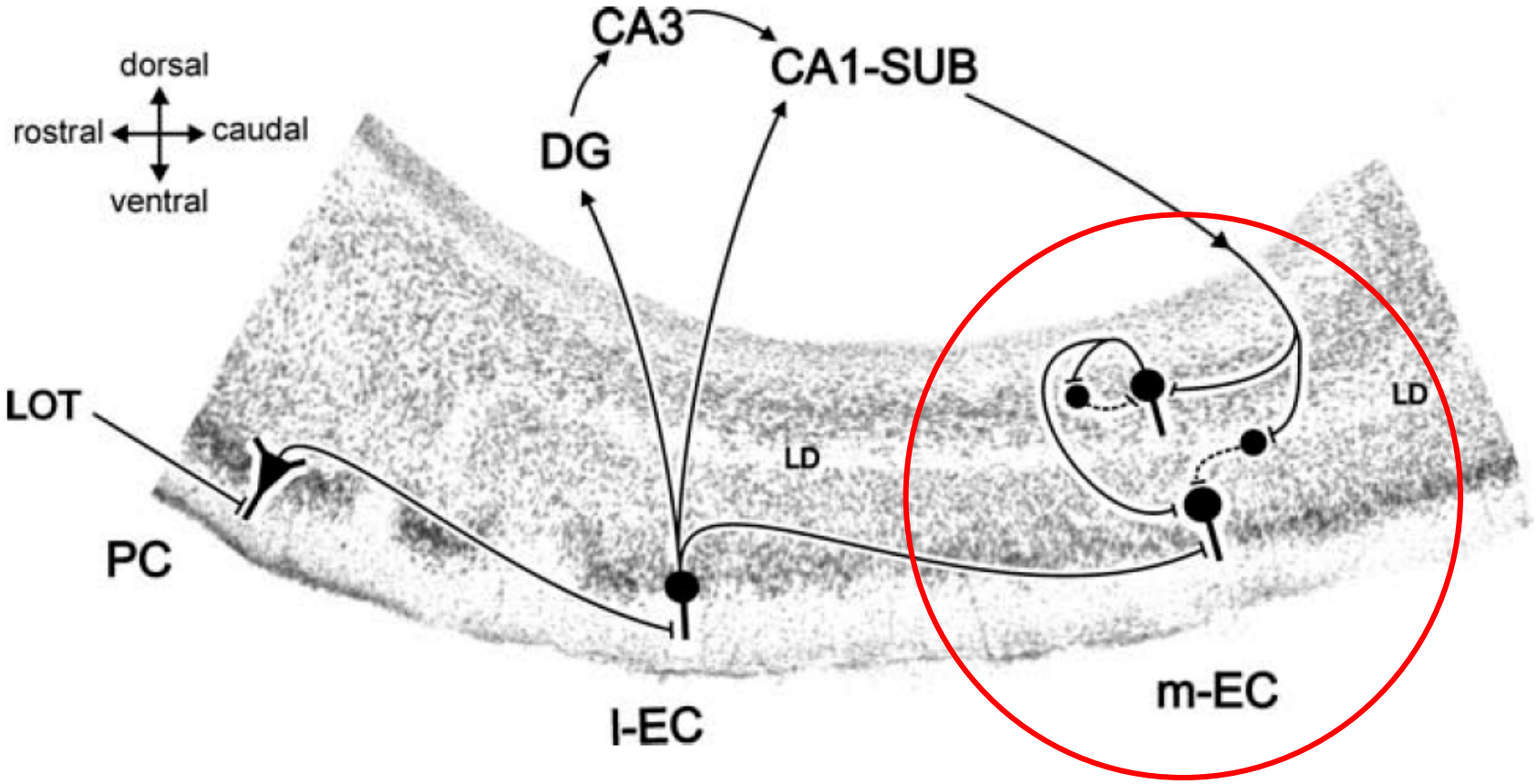

A
R
C
Stim.
rmp
Intrcellular pipette
20 mV
1 mV
Extracellular electrode
100 ms
I
II
III
IV
V
VI
B
Stim.
rmp
-62 mV
20 mV
1 mV
2 s
SPE

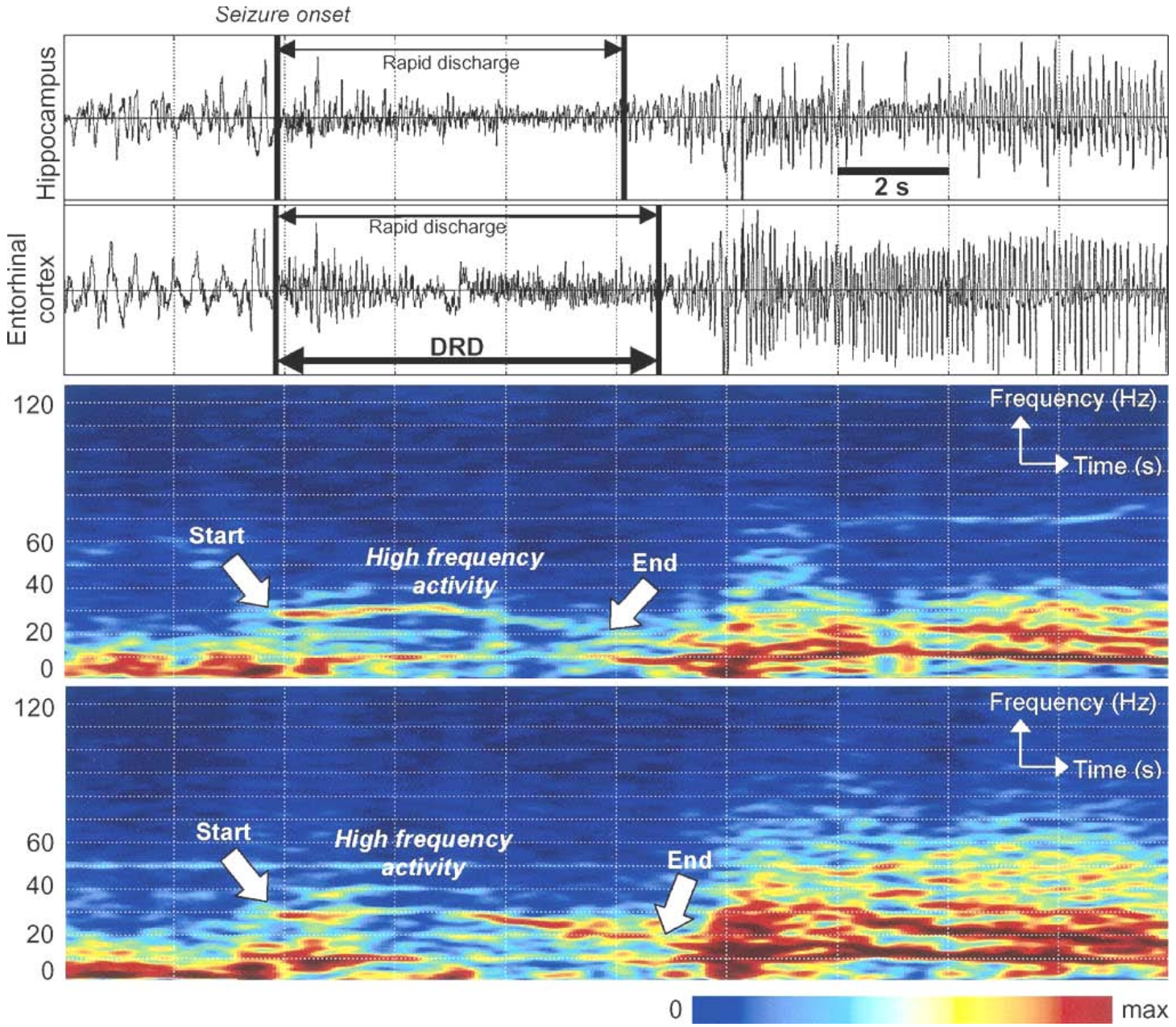

A
R
C
Stim.
100 ms
B
20 mV
0,4 nA
200 ms
C
20 mV
*
2 s


A
20 mV
- 67 mV
(rmp)
FP
100 ms
1 mV
I
II
III
LD
V
VI
B

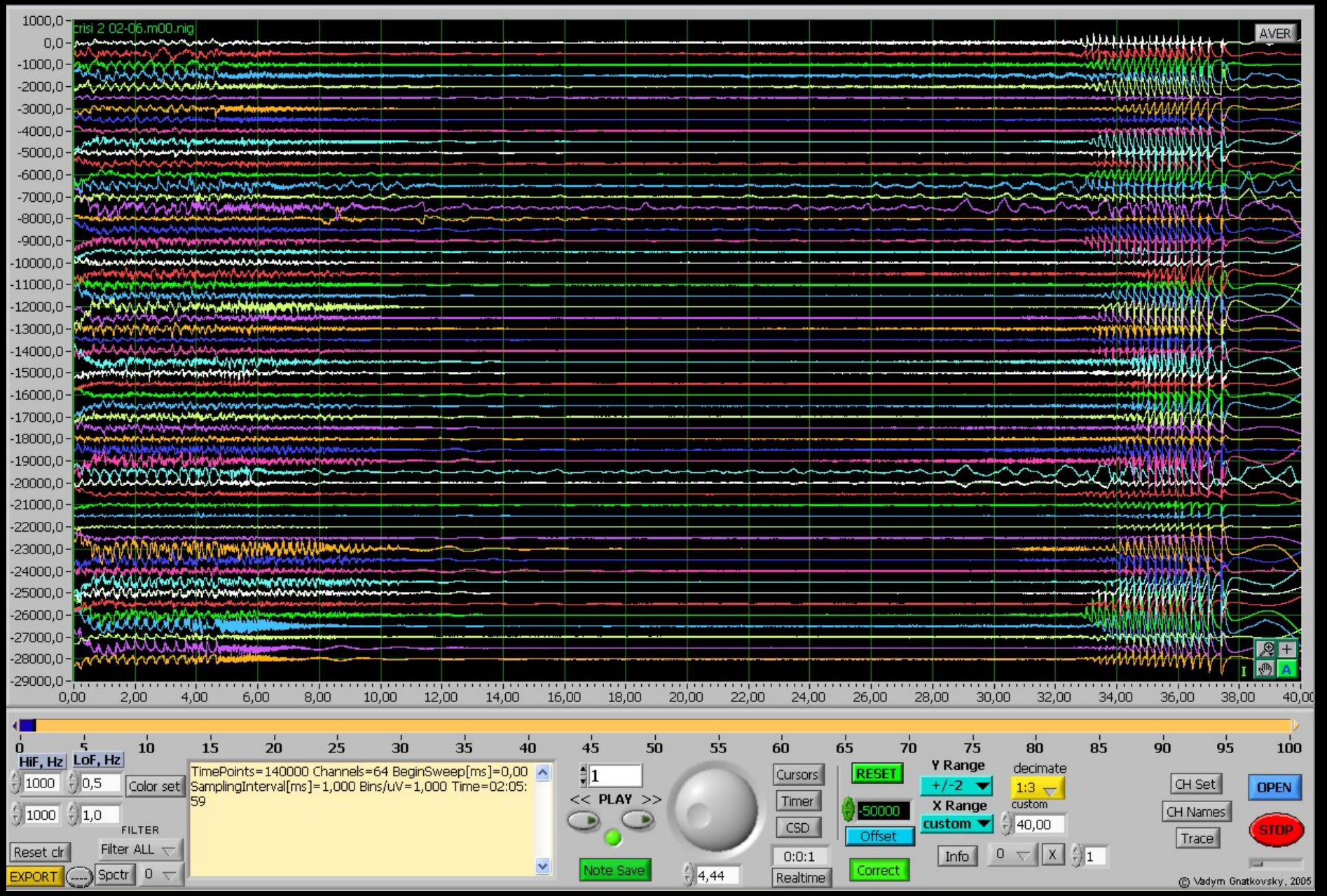
Superficial layers EC neurons




dorsal
rostral
caudal
ventral
CA3
CA1-SUB
DG
LOT
PC
LD
LD
l-EC
m-EC



Bartolomei et al., 2004


crisi 2 02-06.m00.nig
AVER
1000,0
0,0
-1000,0
-2000,0
-3000,0
-4000,0
-5000,0
-6000,0
-7000,0
-8000,0
-9000,0
-10000,0
-11000,0
-12000,0
-13000,0
-14000,0
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-19000,0
-20000,0
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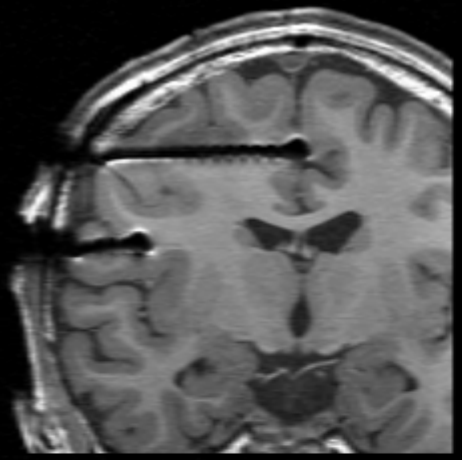
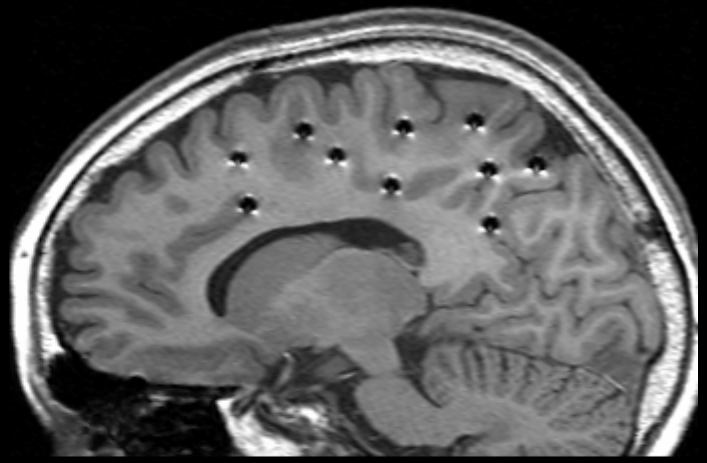
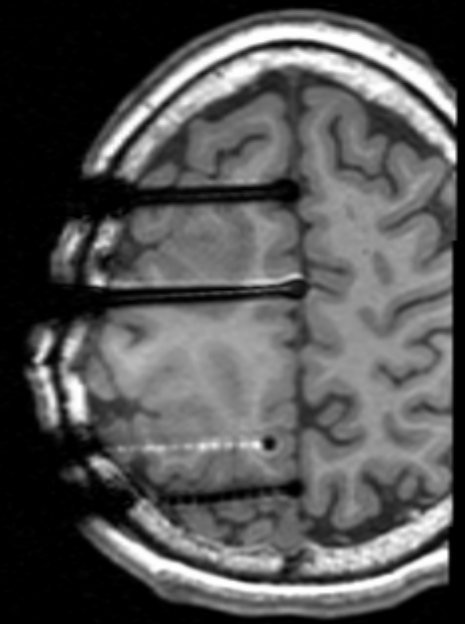
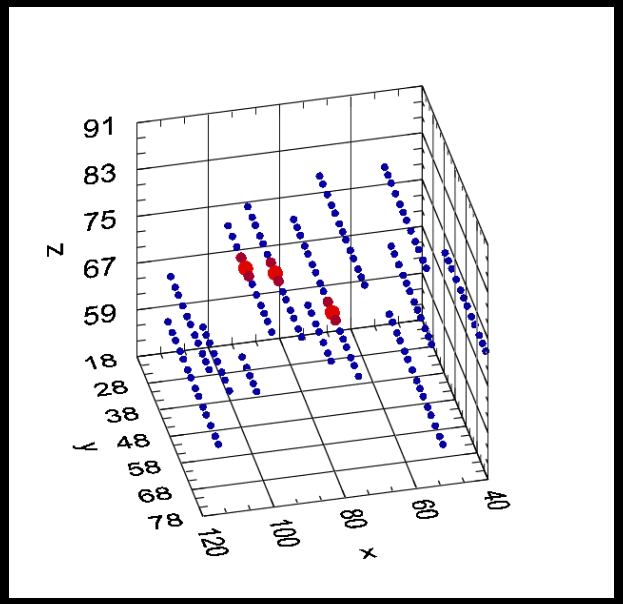
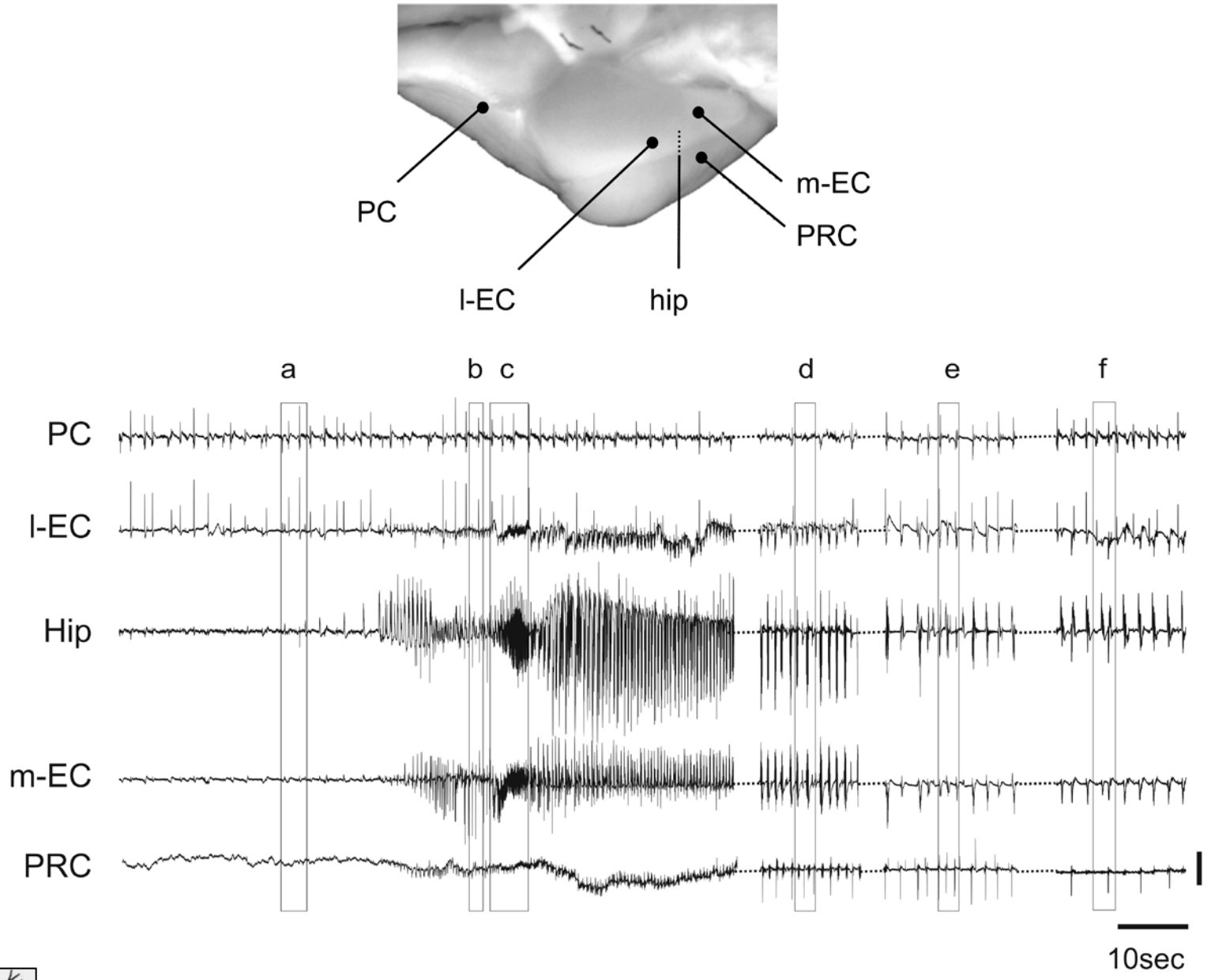
-24000,0
-25000,0
-26000,0
-27000,0
-28000,0
-29000,0
0,00
2,00
4,00
6,00
8,00
10,00
12,00
14,00
16,00
18,00
20,00
22,00
24,00
26,00
28,00
30,00
32,00
34,00
36,00
38,00
40,00
HiF, Hz
LoF, Hz
1000
0,5
Color set
1000
1,0
FILTER
Reset clr
Filter ALL
EXPORT
Spctr
0
TimePoints=140000 Channels=64 BeginSweep[ms]=0,00
SamplingInterval[ms]=1,000 Bins/uV=1,000 Time=02:05:
59
<< PLAY >>
Note Save
4,44
Cursors
Timer
CSD
0:0:1
Realtime
RESET
-50000
Offset
Correct
Y Range
+/-2
X Range
custom
decimate
1:3
custom
40,00
Info
X
CH Set
CH Names
Trace
OPEN
STOP
© Vadym Gnatkovsky, 2005



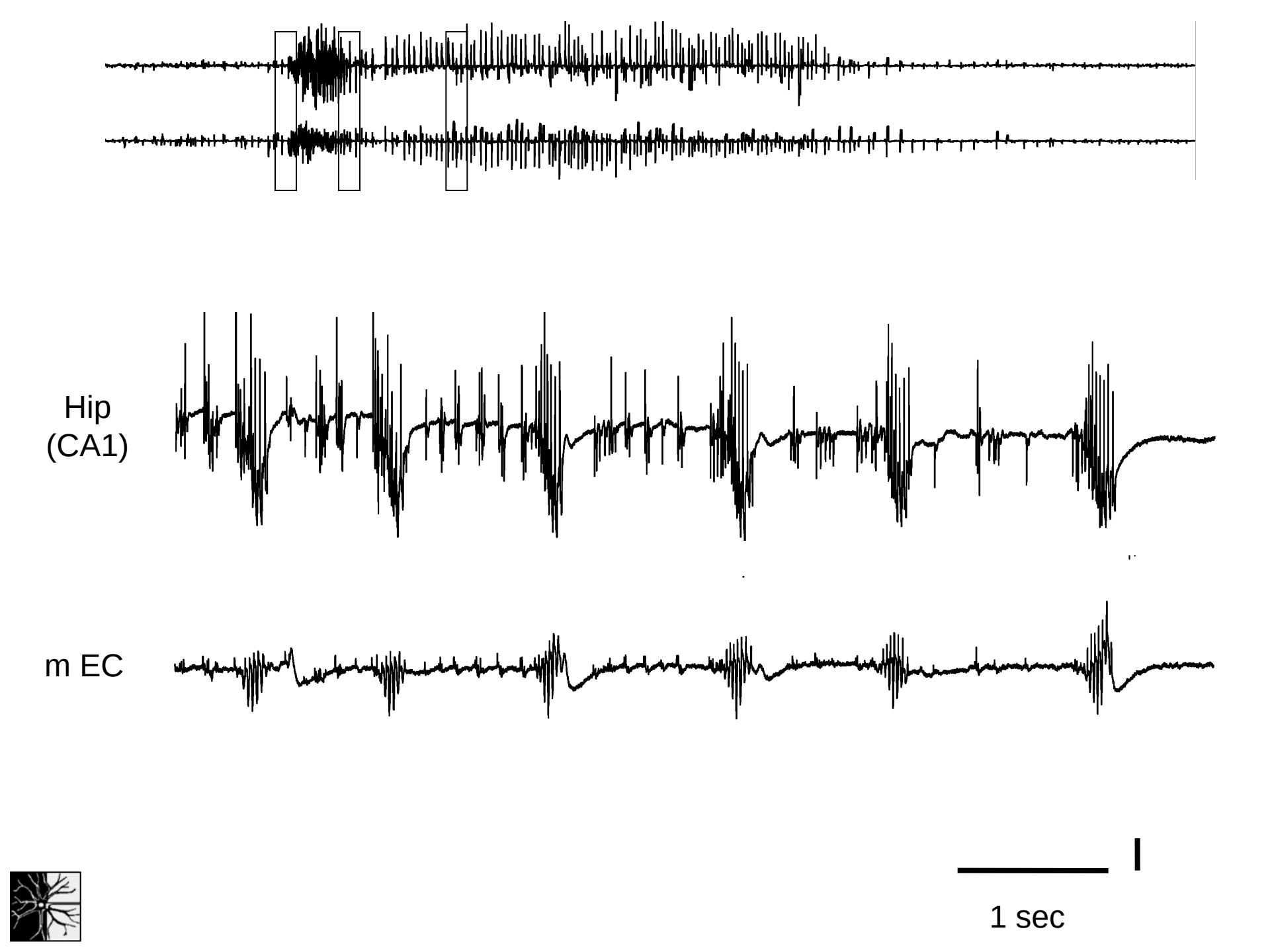


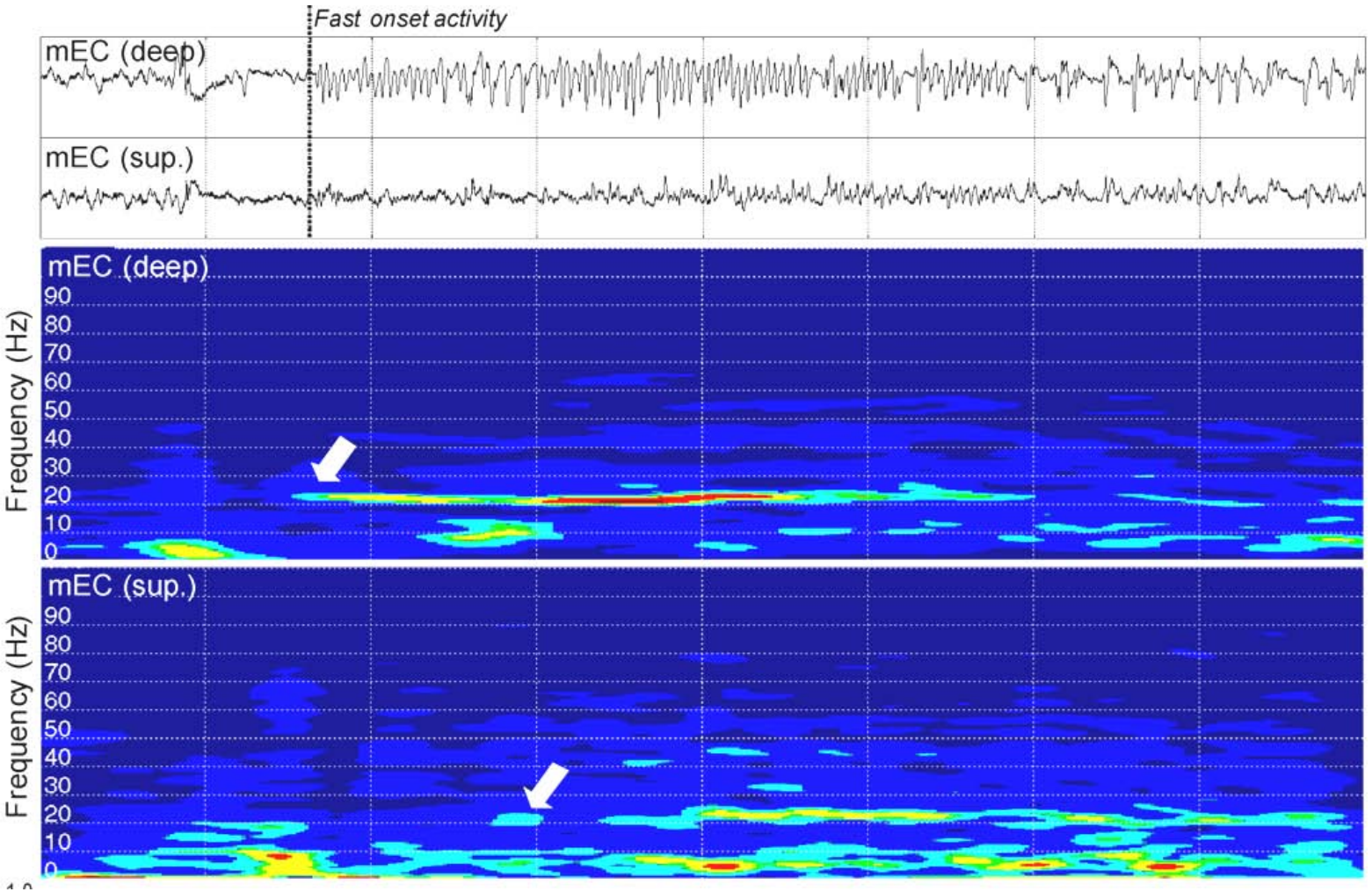



91
83
75
67
59
z
18
28
38
48
58
68
78
y
120
100
80
60
40
x

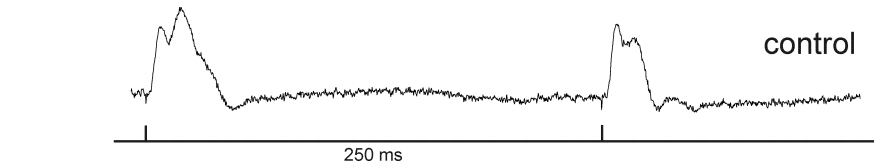


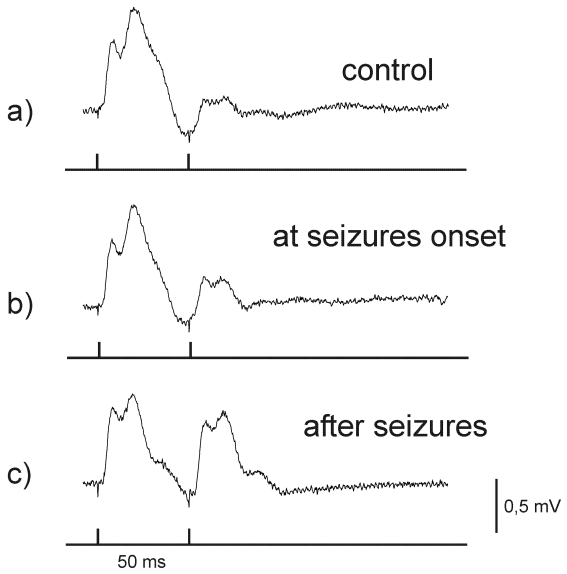
Uva et al, in press Epilepsia

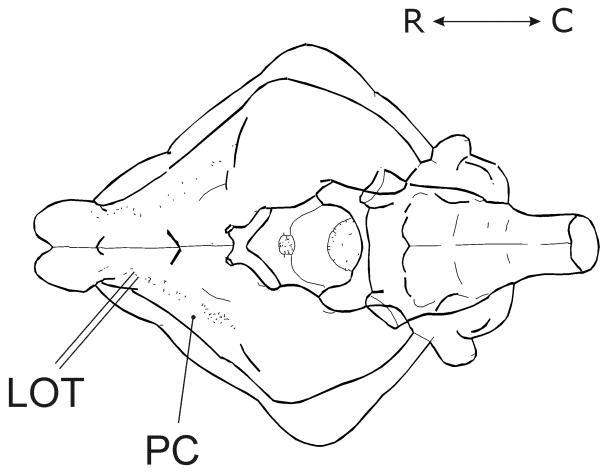

Hip
(CA1)
m EC
1 sec

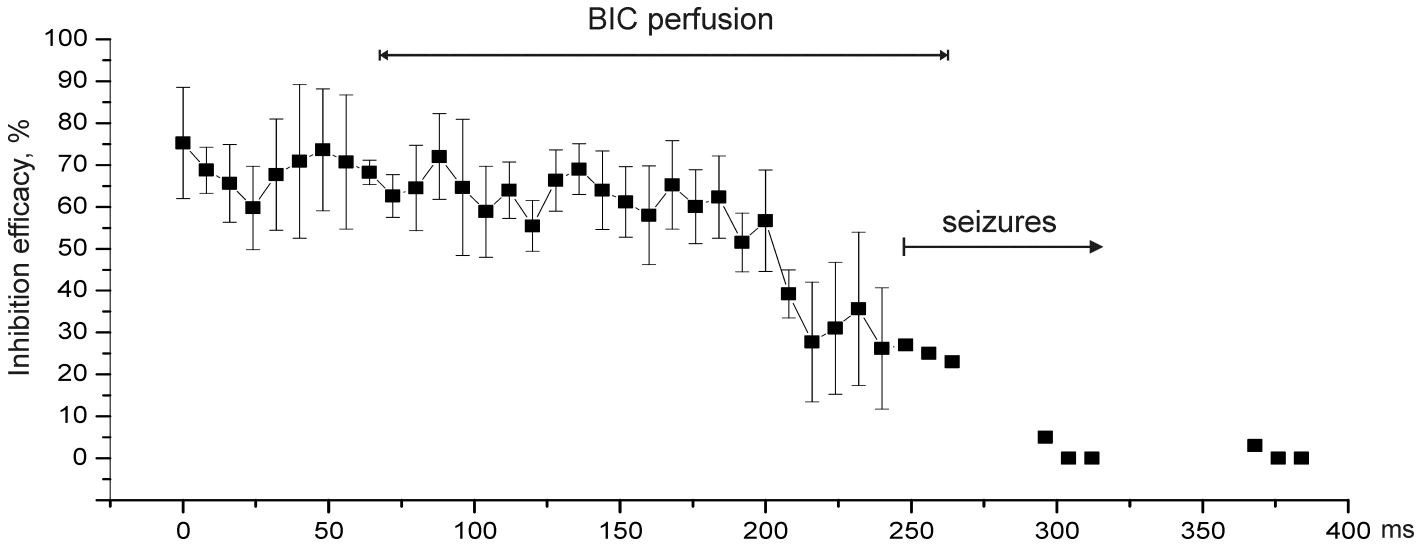


Labyt, Uva, de Curtis, Wendling, 2006

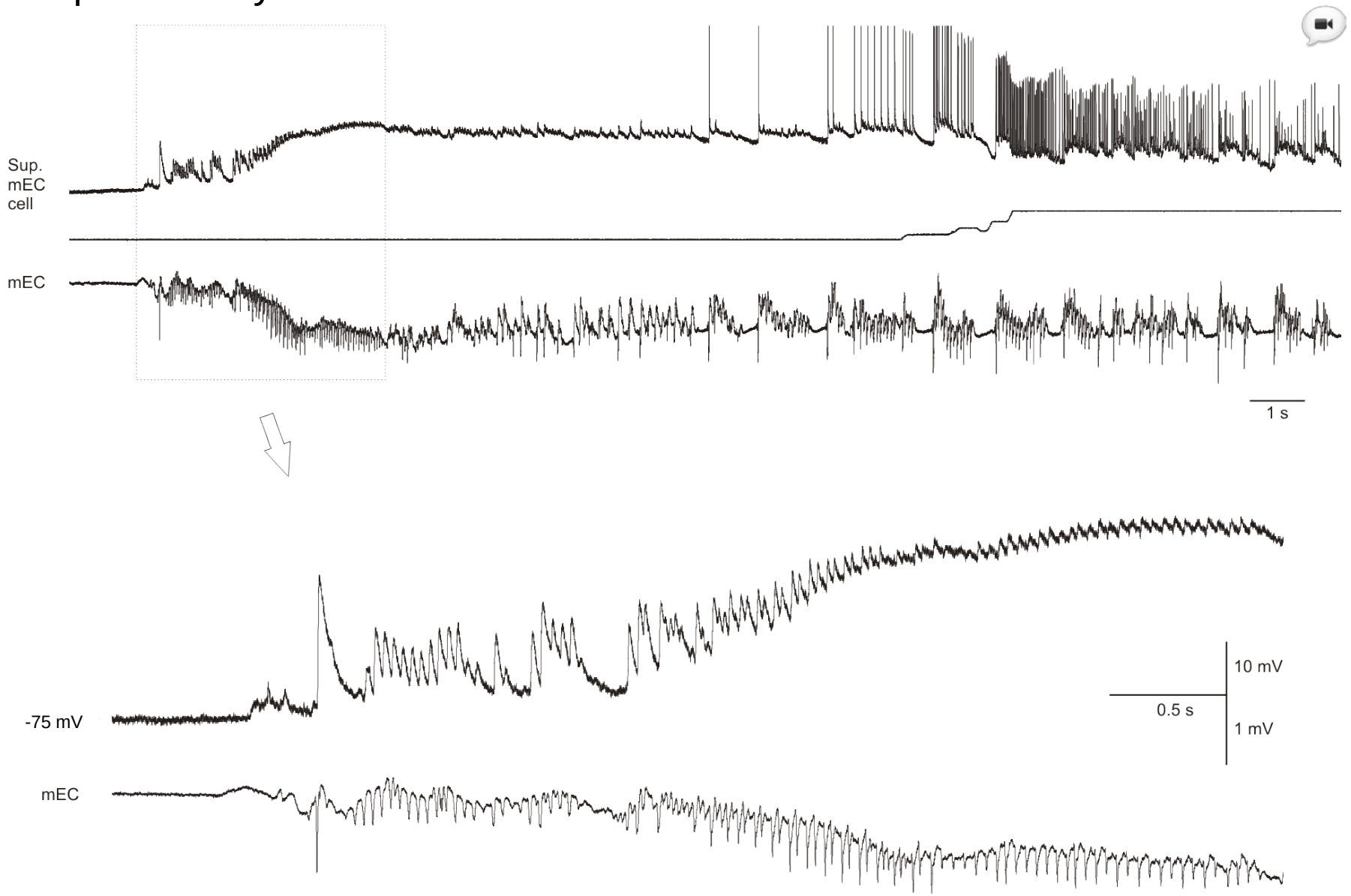

control
250 ms


a)
control
b)
at seizures onset
c)
after seizures
0,5 mV
50 ms

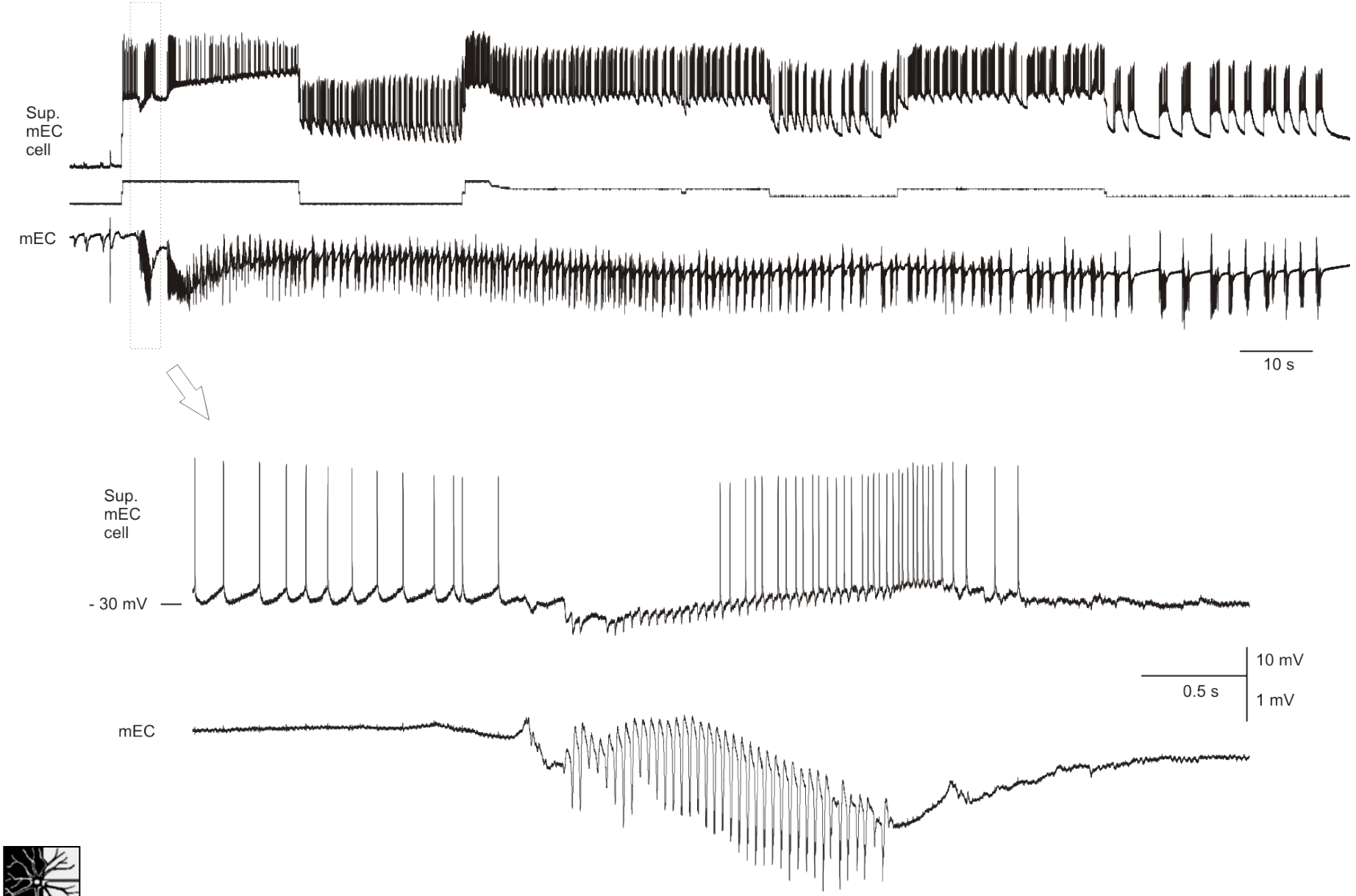

R
C
LOT
PC


BIC perfusion
seizures
Inhibition efficacy, %
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400 ms

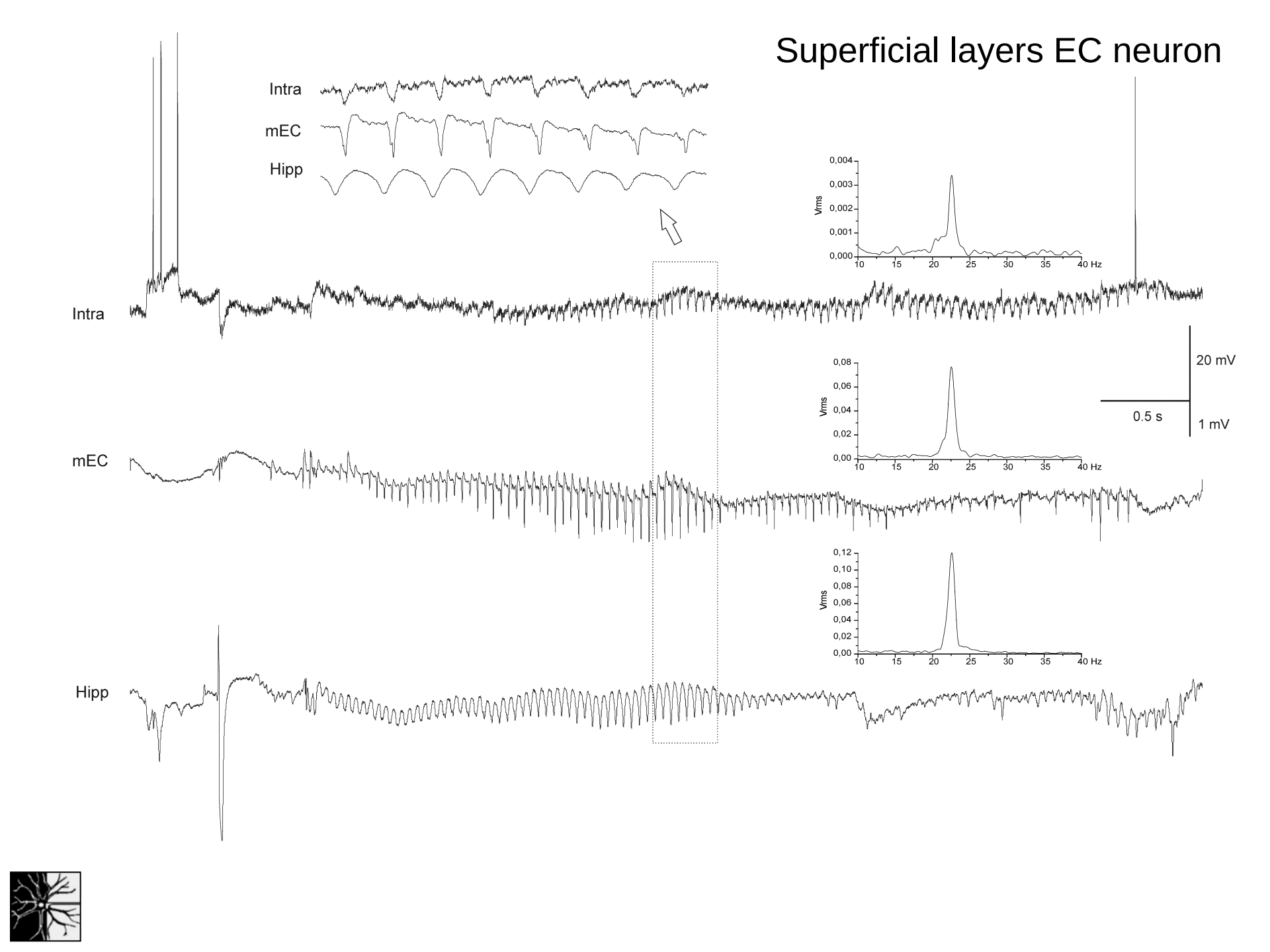
Superficial layers EC neuron



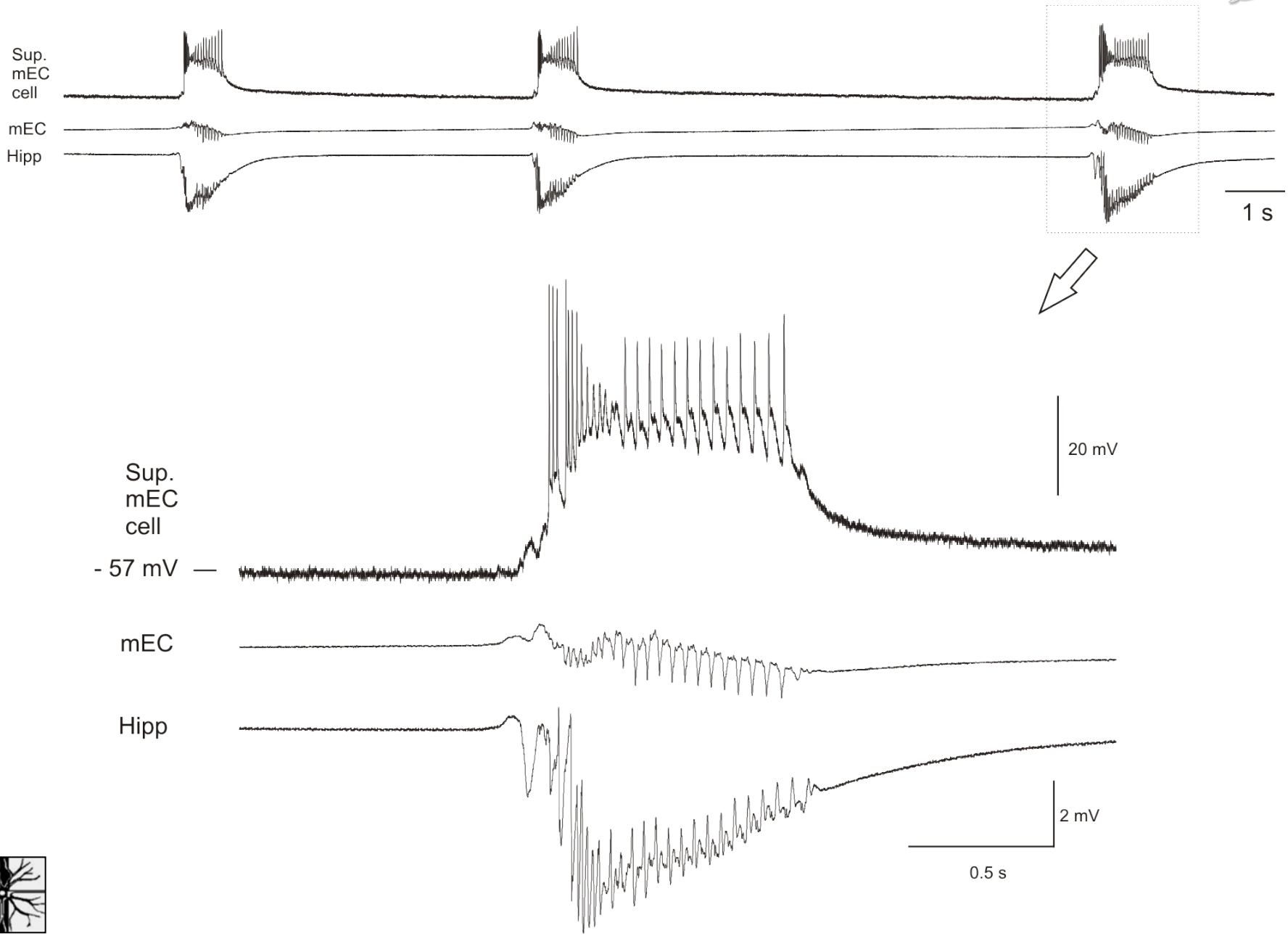
Superficial layers EC neuron



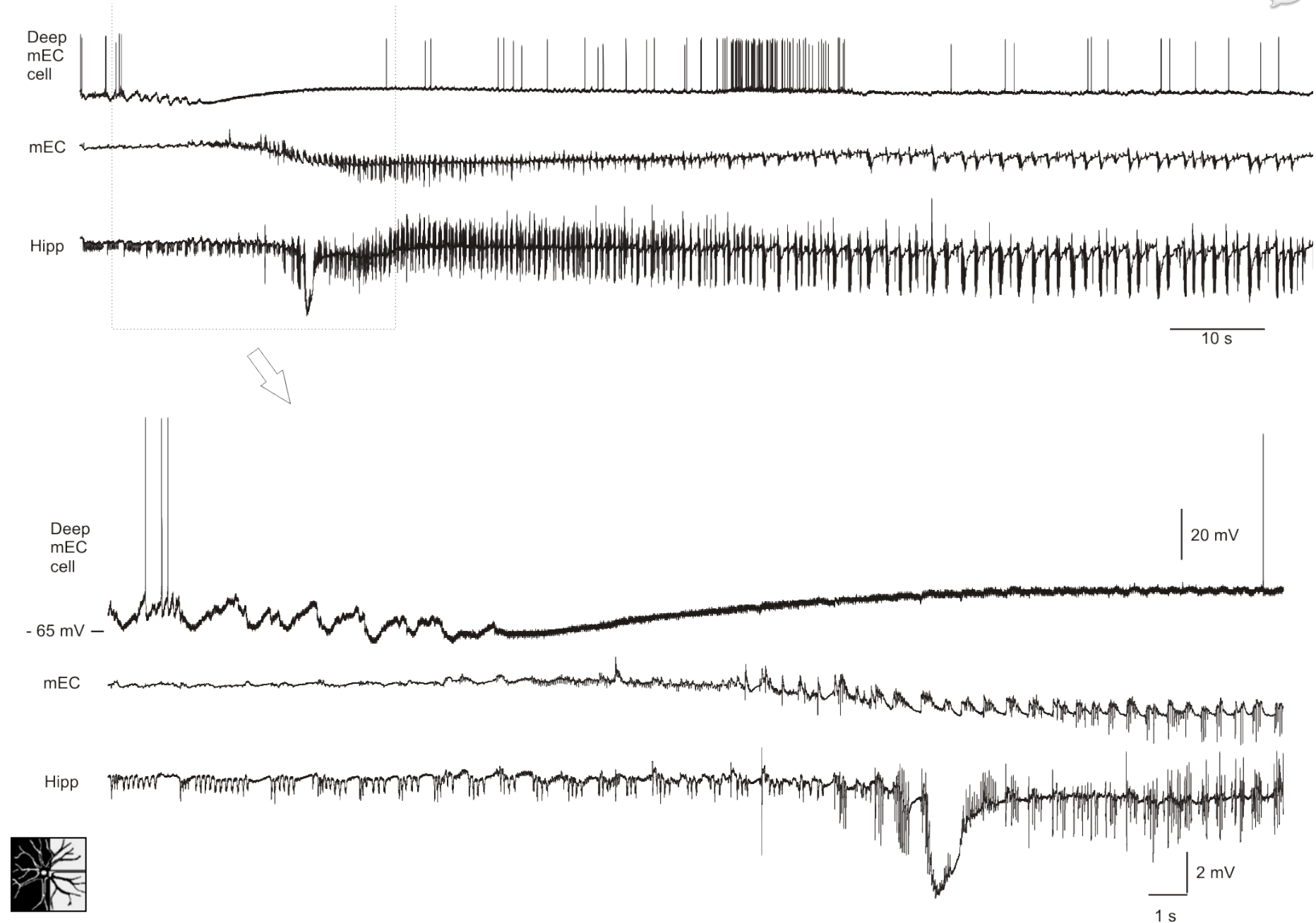
Superficial layers EC neuron



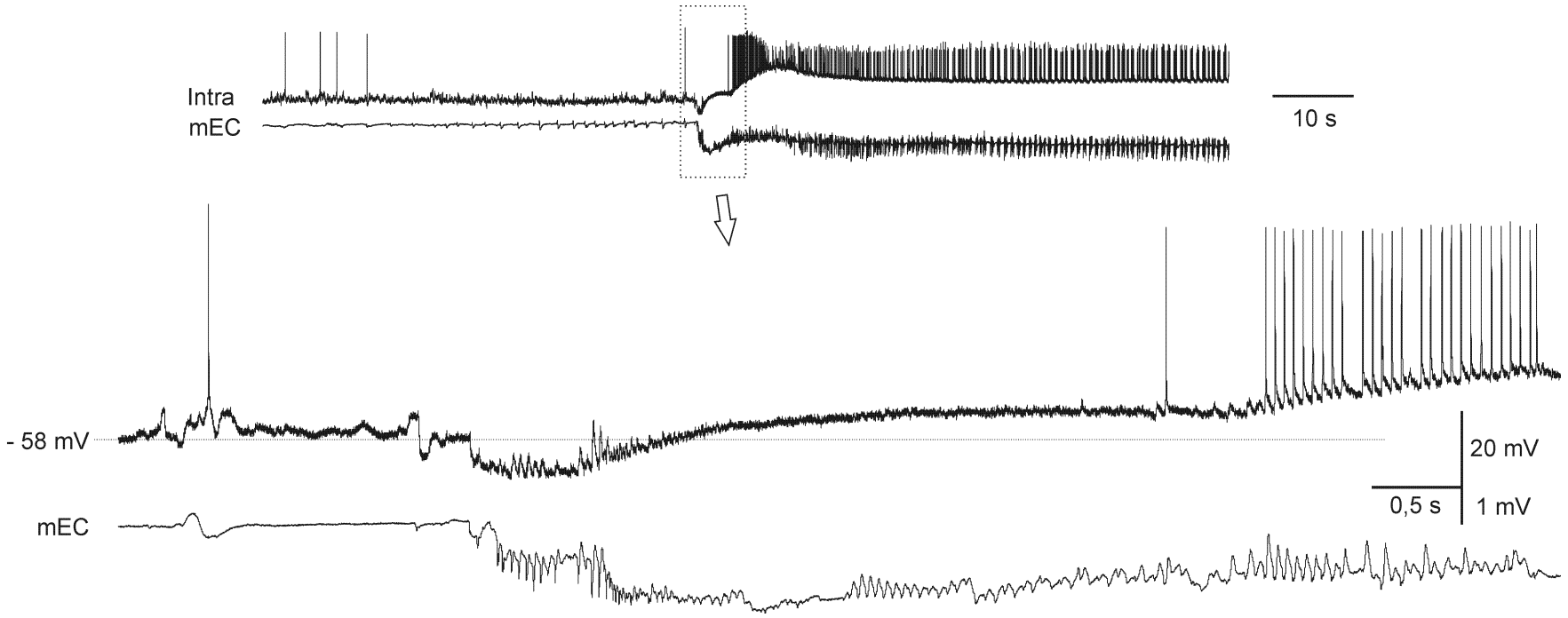
Superficial layers EC neuron



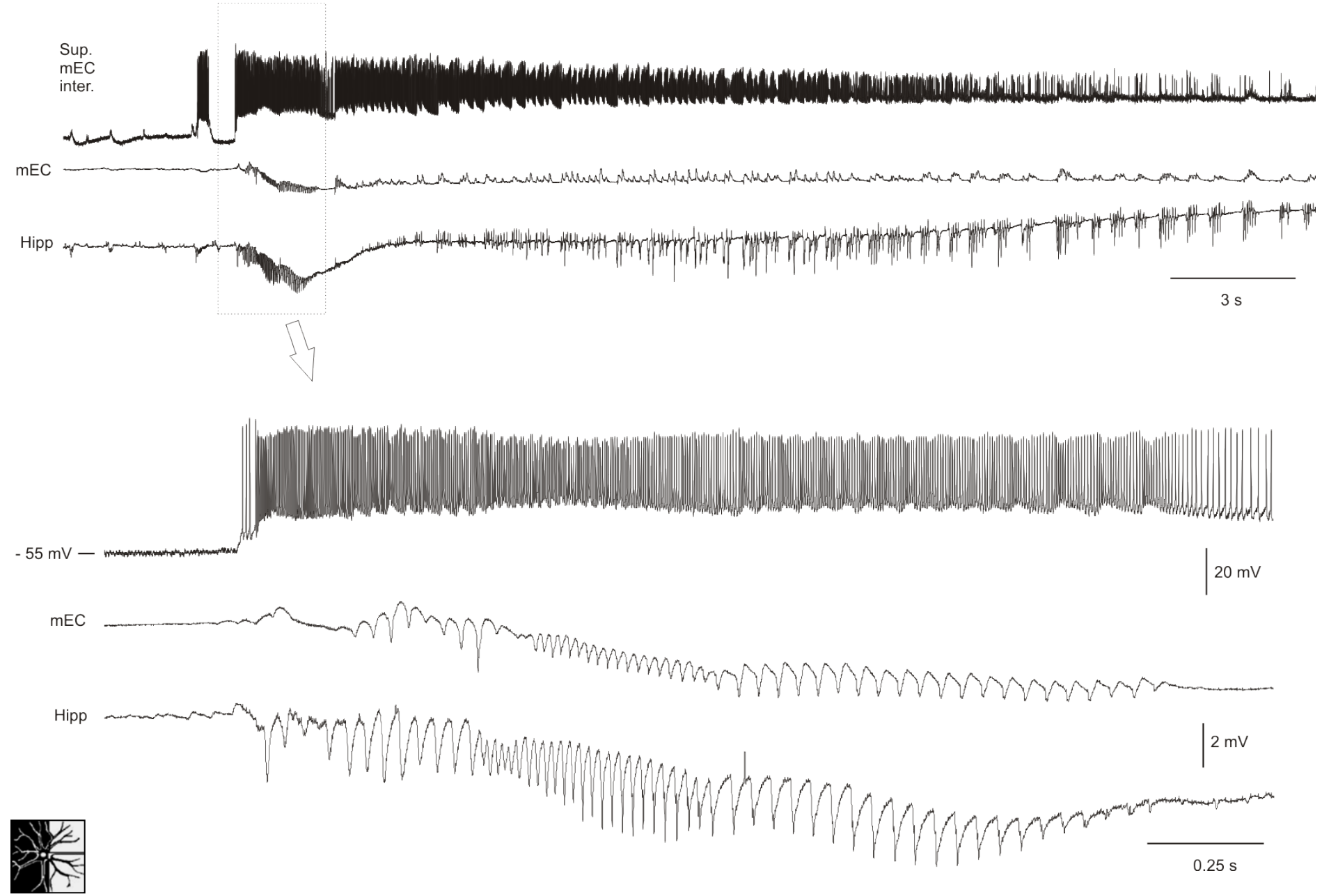
Deep layers EC neuron



Deep layers EC neuron



Putative EC interneuron



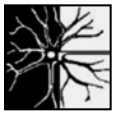
CONCLUSIONS (1)

- Transient disinhibition in the limbic region promotes seizure-like events that initiate with fast activity at 20-30 Hz in the EC and in the hippocampus

- This pattern is similar to the ictal discharges observed in human TLE

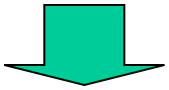
- Fast activity at seizure onset in the mEC correlates with
  - rhythmic IPSPs in superficial neurons
  - no activity in deep neurons
  - high rate firing in putative interneurons

- The study of fast activity at seizure onset may contribute to understand the mechanisms of interictal-ictal transition in human TLE

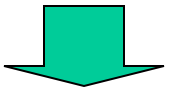


human EEG interictal-ictal EC pattern during TLE seizures
is similar to
guinea pig interictal-ictal EC pattern in acute TLE seizures

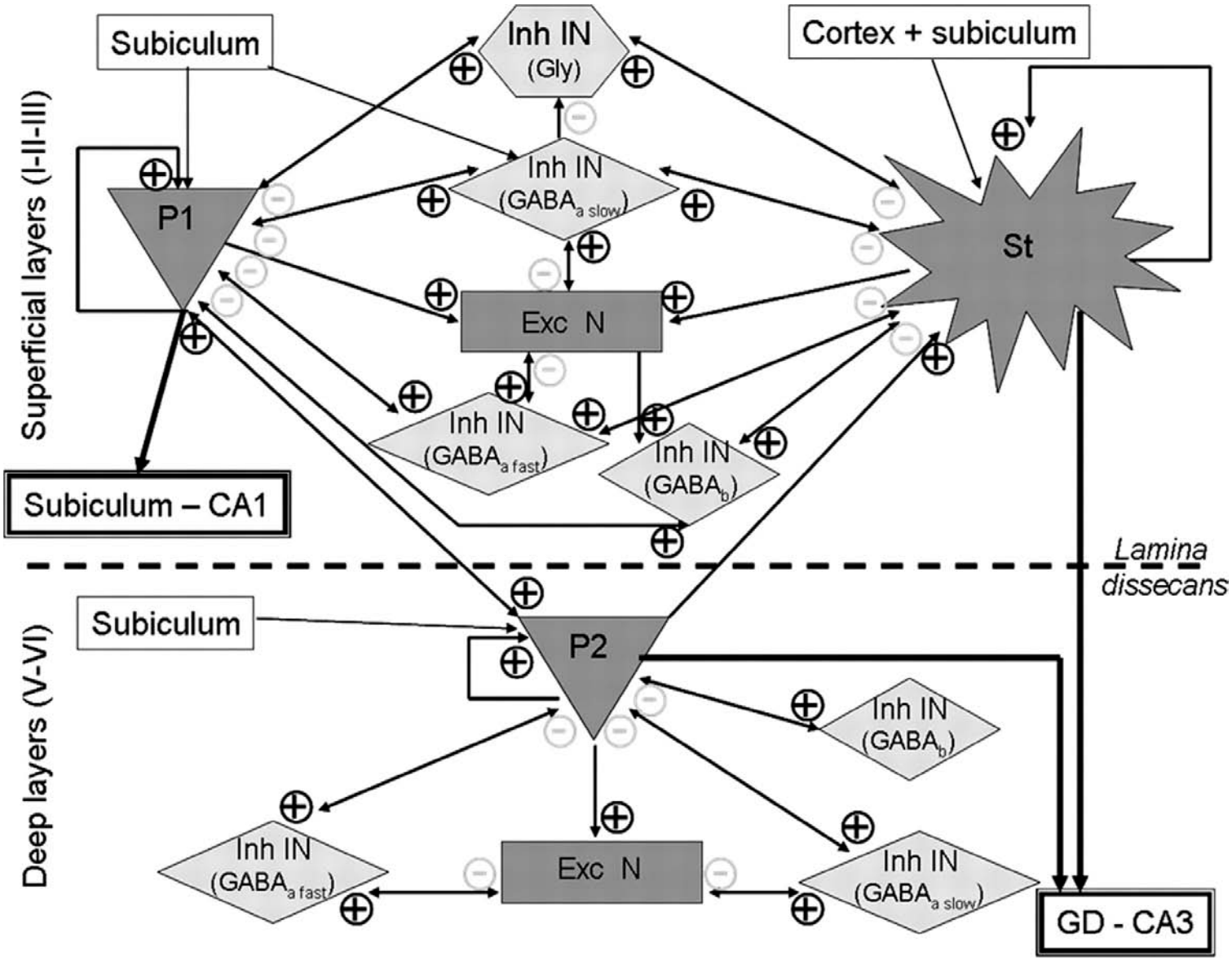
reproduction of the pattern by a model of Entorhinal Cortex



analysis of the network determinants responsible
for the interictal-ictal-postictal transition
in the EC model



predictions to be tested in the guinea pig isolated brain



Labyt, Wendling, Uva, de Curtis 2006

Real field potentials

Simulated signals

Superficial EC

Deep EC

Superficial EC model

Deep EC model

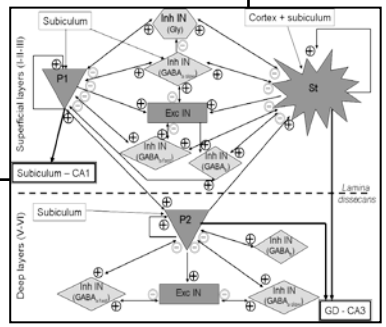
Connectivity

Parameter modifications

Comparison

- Visual inspection of temporal dynamics
- Spectral analysis (PSD, time-frequency)
- Nonlinear correlation coefficient h^2 and time delays between deep & sup. EC activity

Low similarity

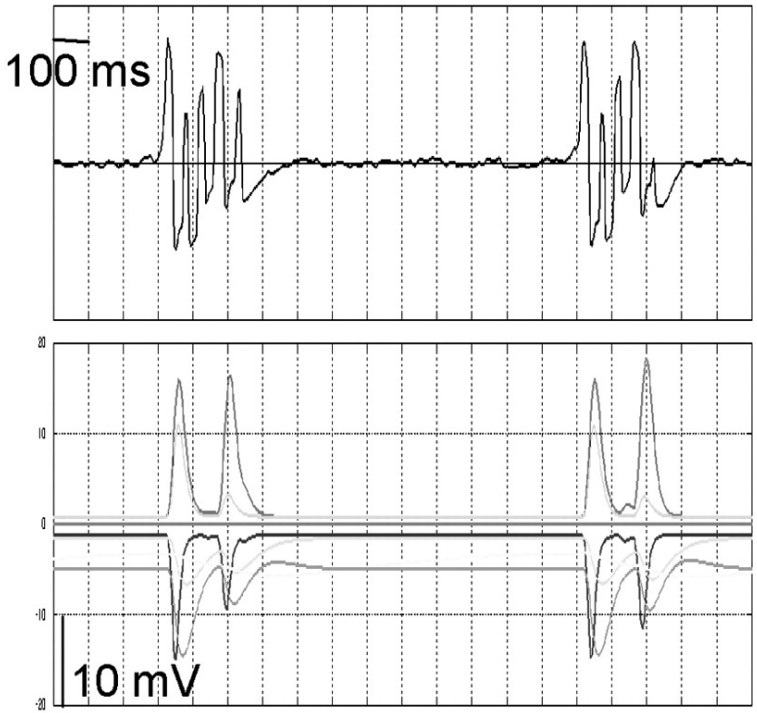


High similarity

Model-based interpretation

Labyt, Wendling, Uva, de Curtis 2006

Superficial layers



Pyramidal N (Glu)

Stellate N (Glu)

GABAa fast

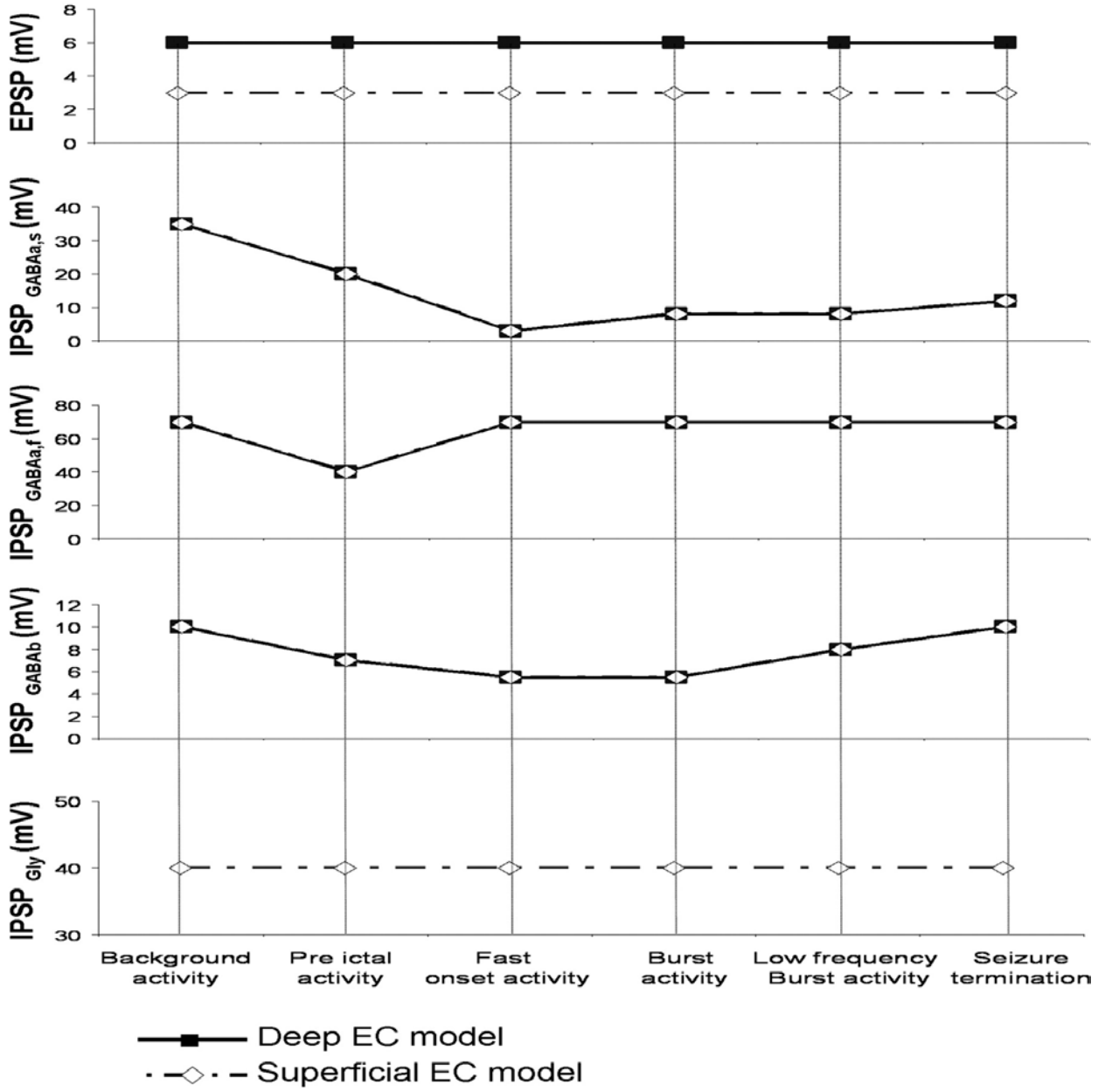
GABAa slow

GABAb

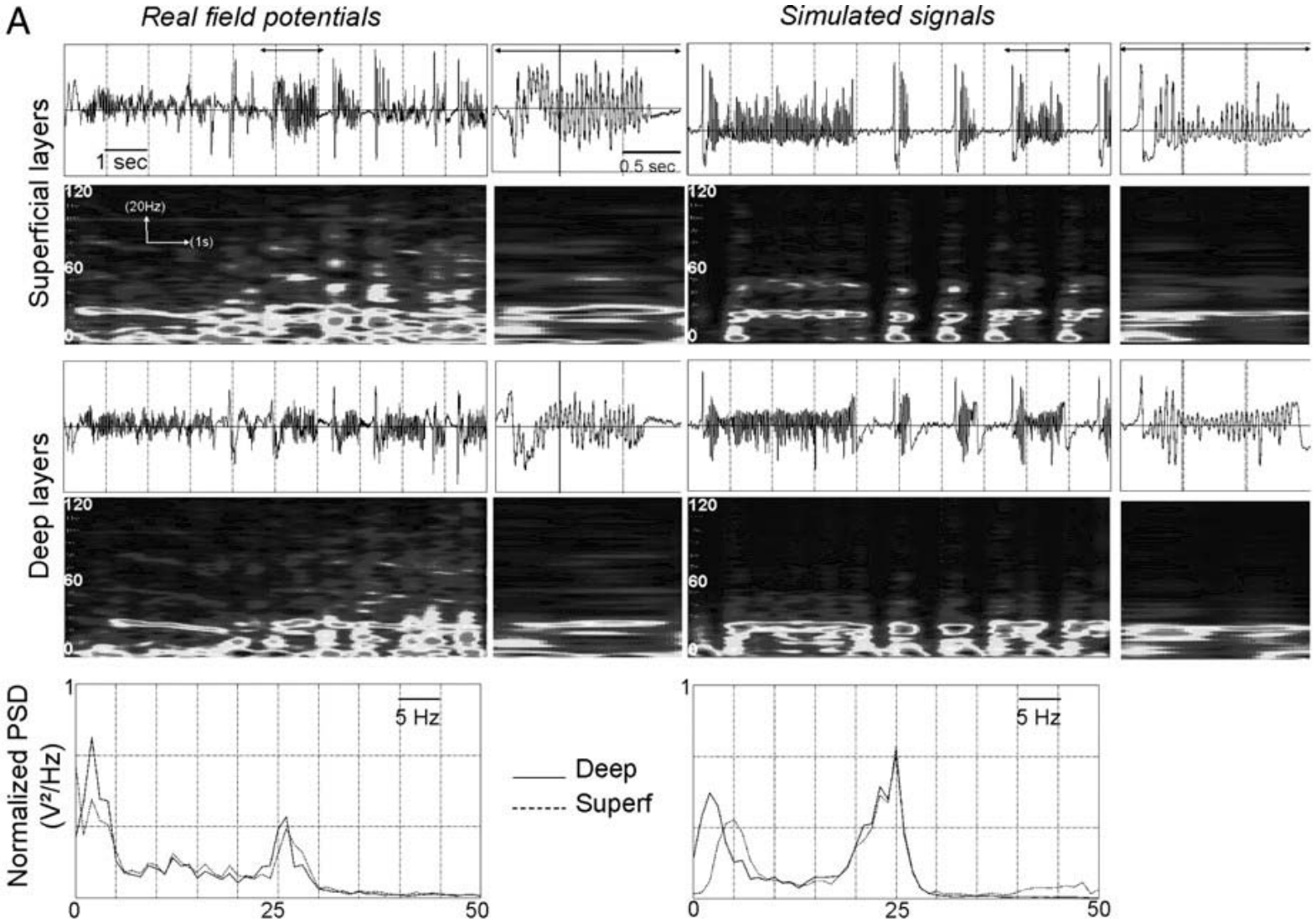
Glycine

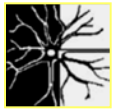
Excitatory IN (Glu)

Labyt, Wendling, Uva, de Curtis 2006



Labyt, Wendling, Uva, de Curtis 2006





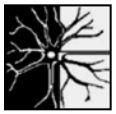
Labyt, Wendling, Uva, de Curtis 2006

CONCLUSIONS (2)

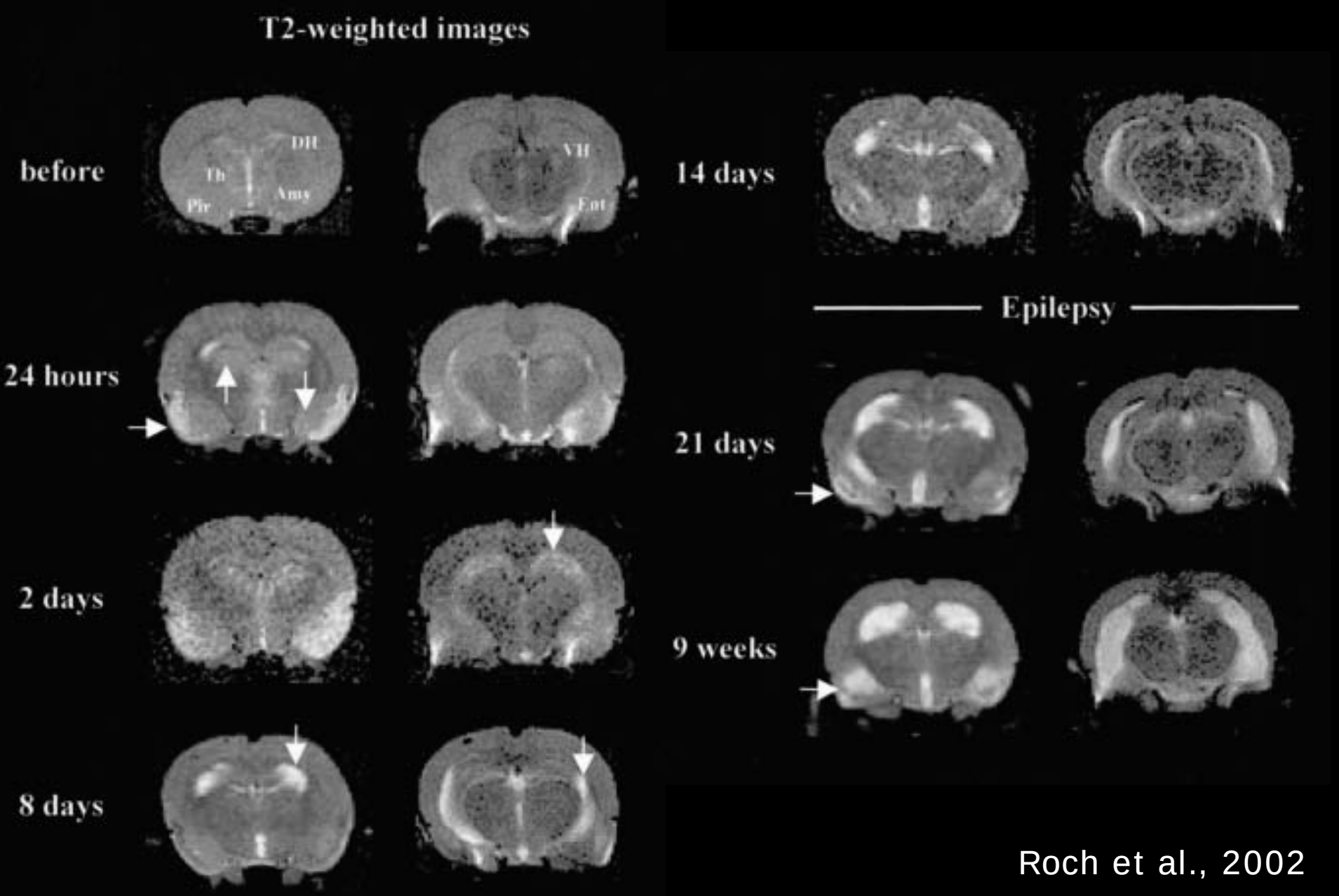
- Seizure-like events that initiate with fast activity at 20-30 Hz can be reproduced in a computer “lumped” model of the EC

- The computer model allows to predict possible mechanisms responsible for the initiation and the termination of ictal discharges

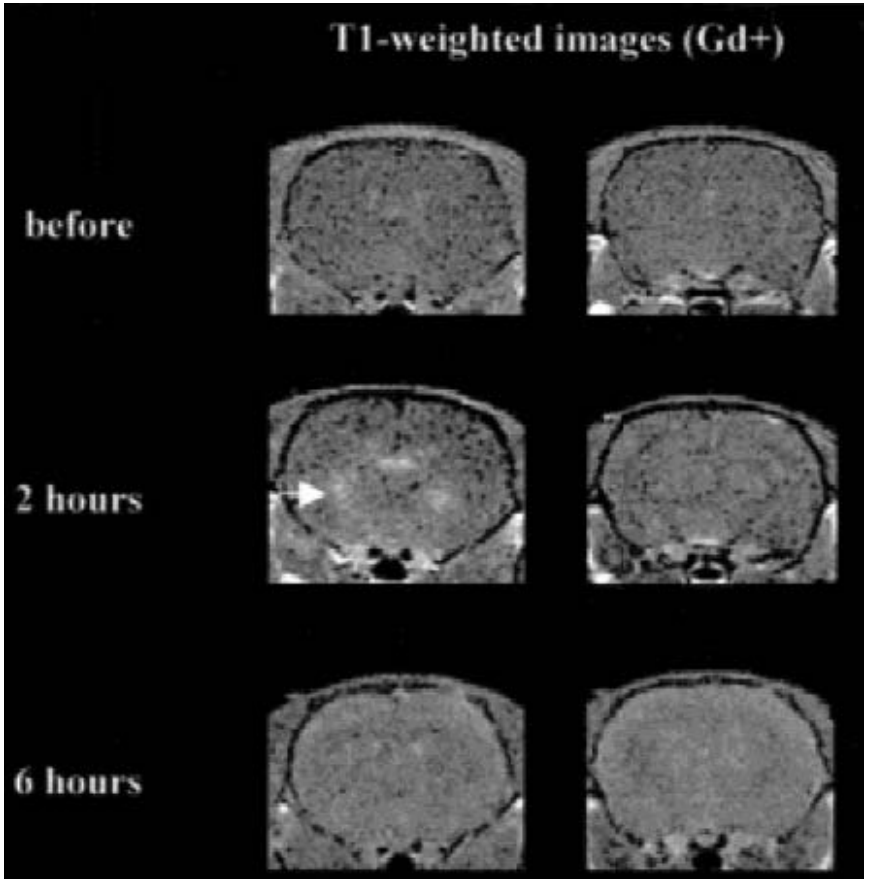
- In the model:
  - the onset of fast activity in the model is generated by a transient reduction of GABAa-mediated transmission in superficial neurons
  - seizures are terminated by recovery of GABAb inhibition

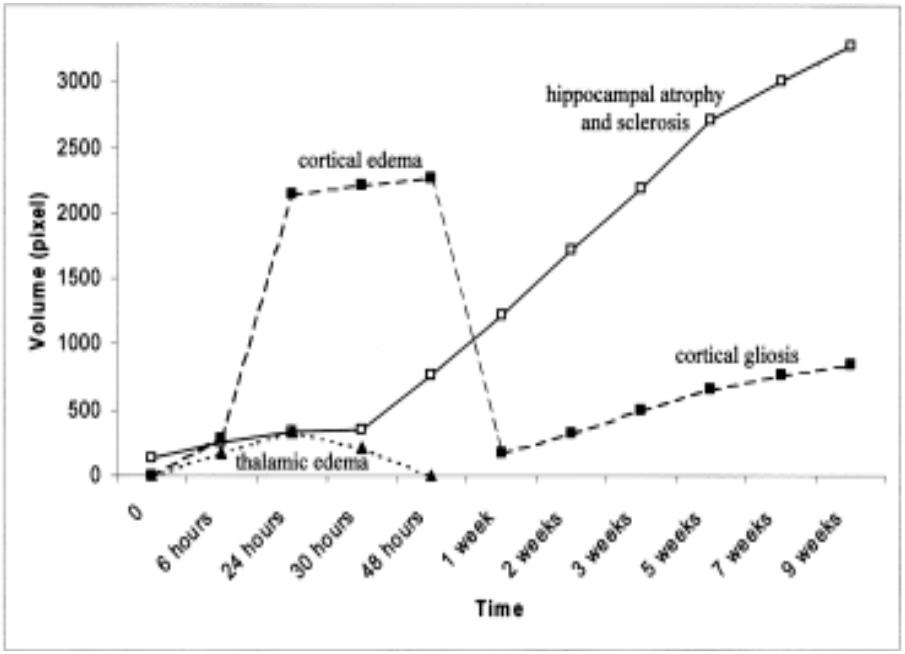


Ischemic-like alterations during pilo-induced status epilepticus



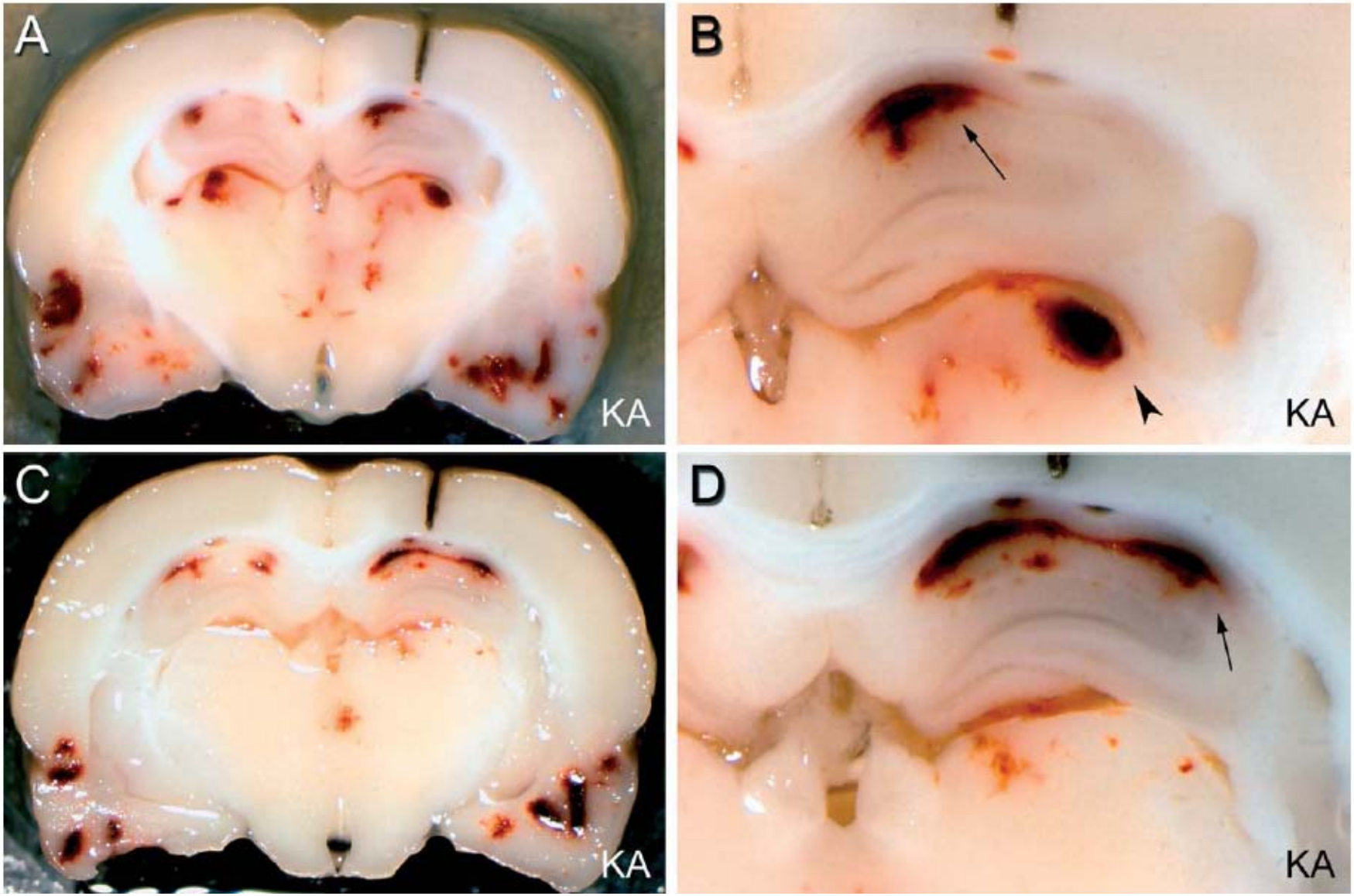
Roch et al., 2002



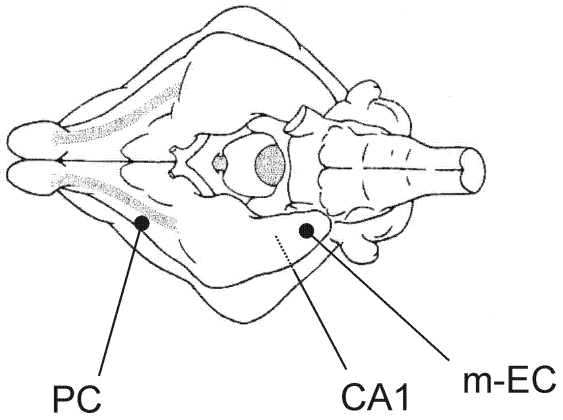


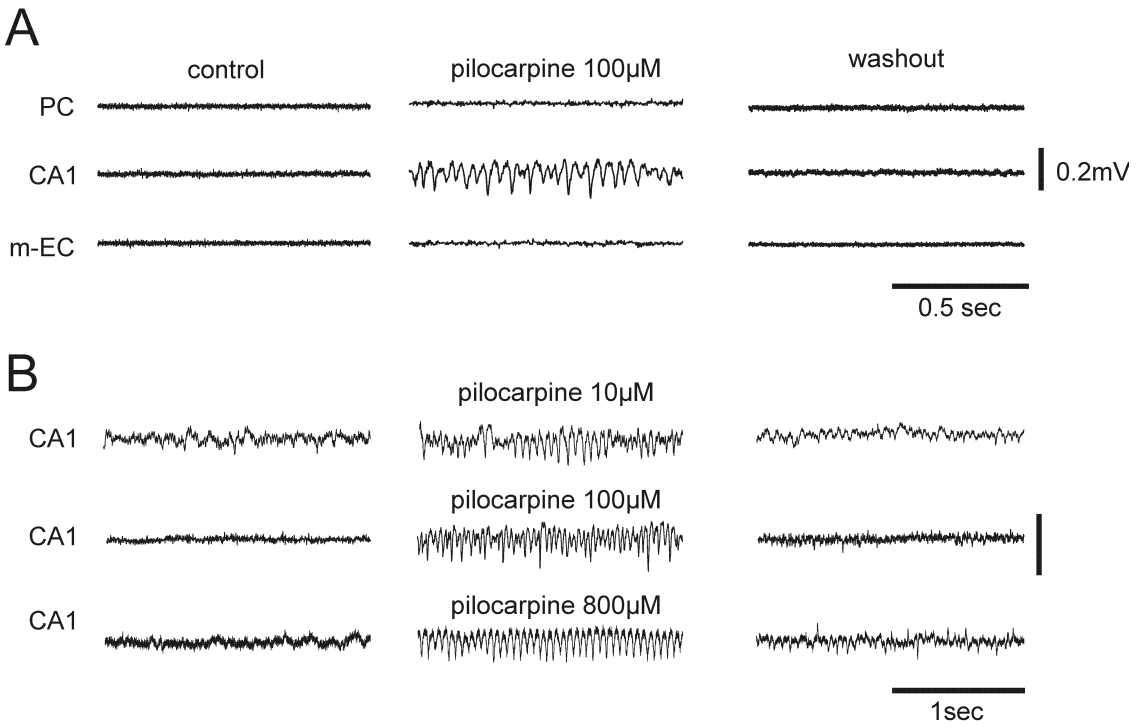
Roch et al. (2001)

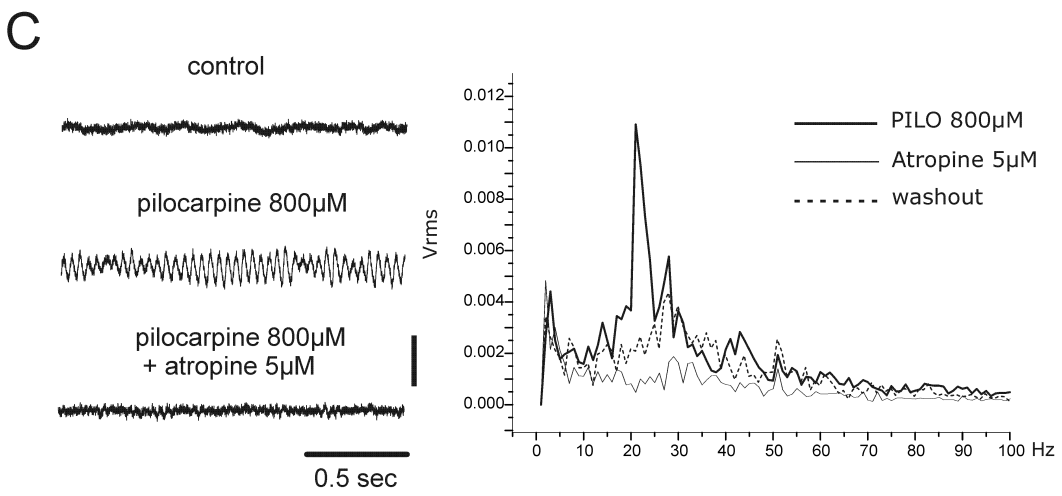
Ischemic-like alterations after KA-induced status epilepticus

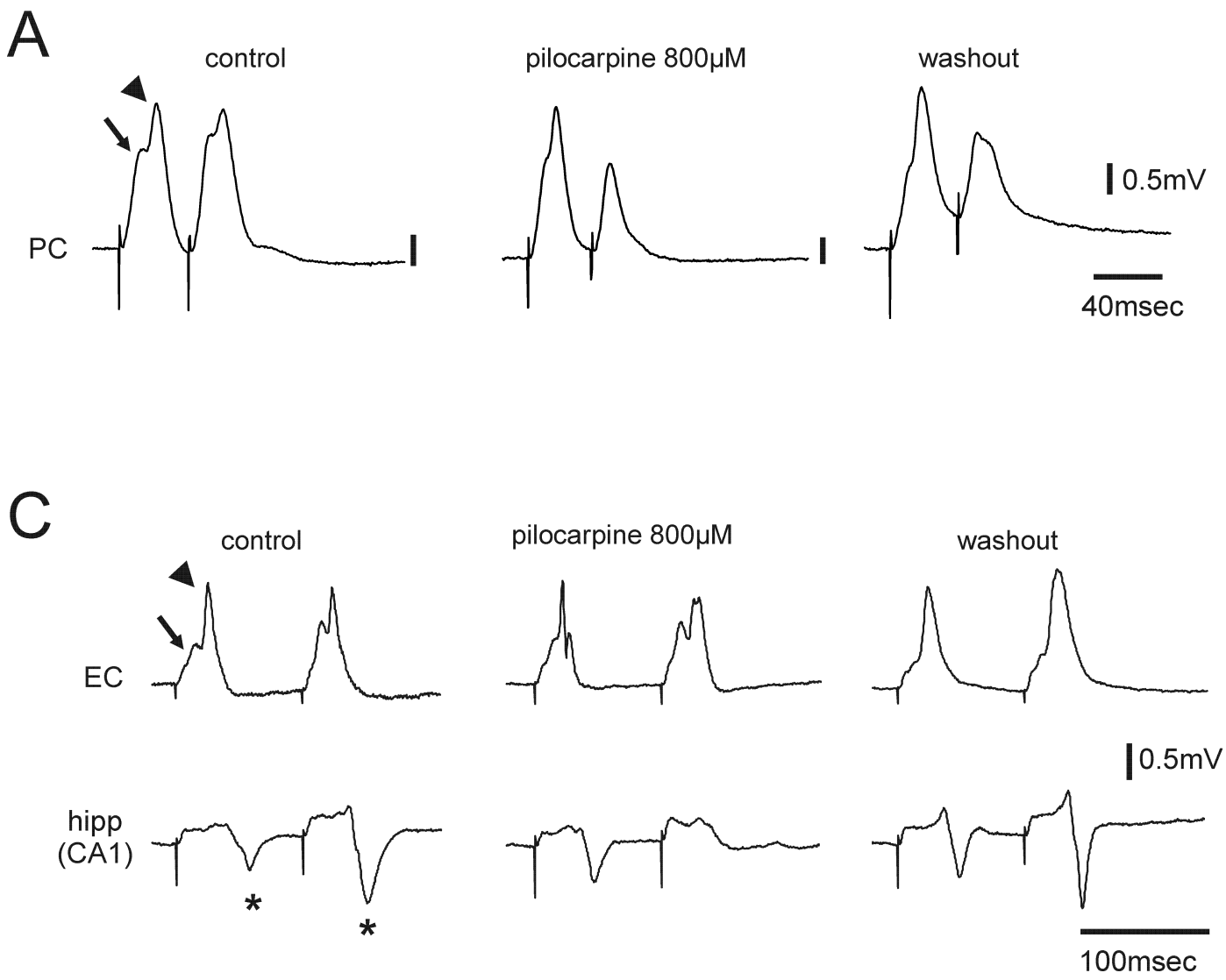


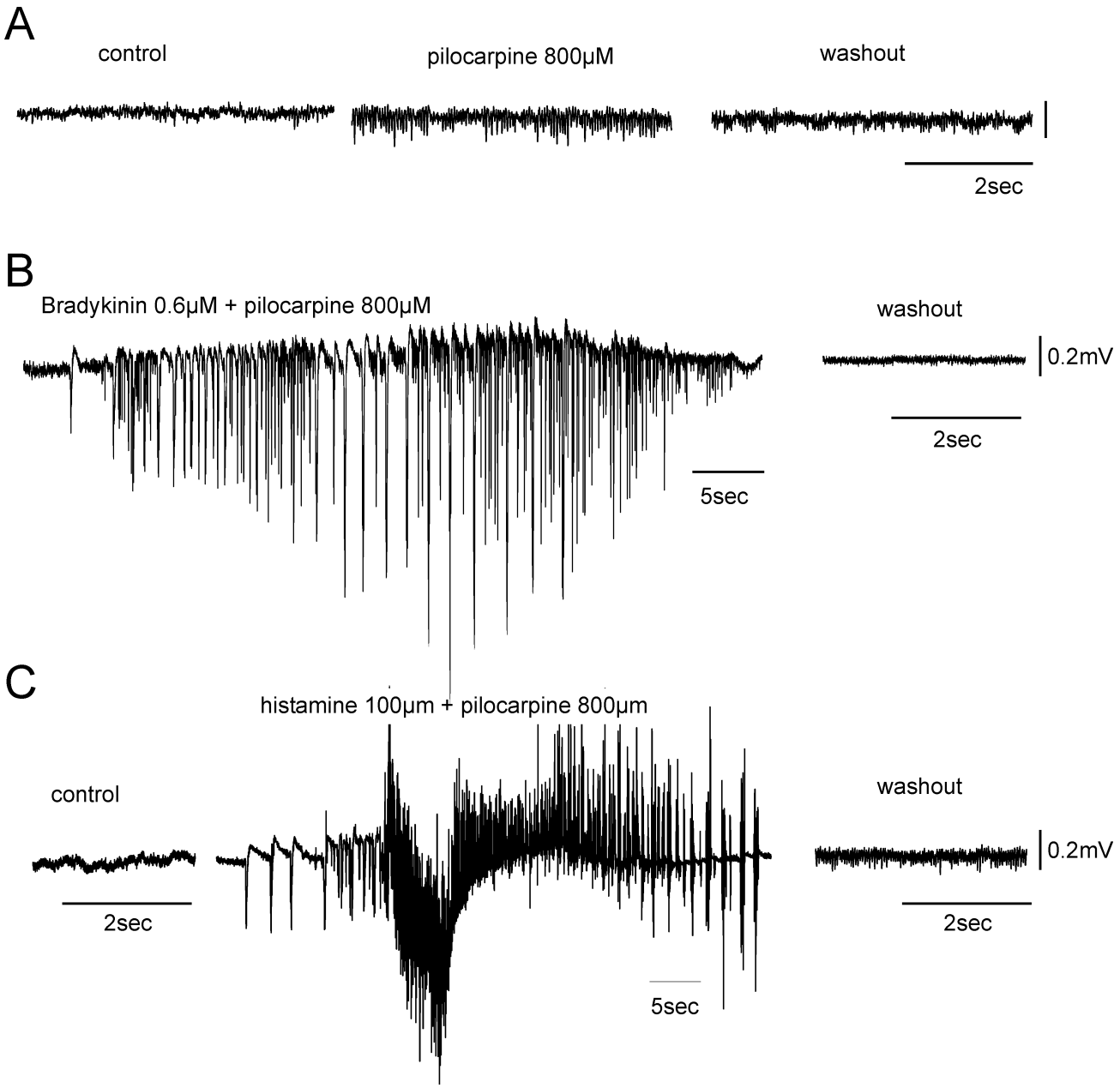
Sloviter 2005

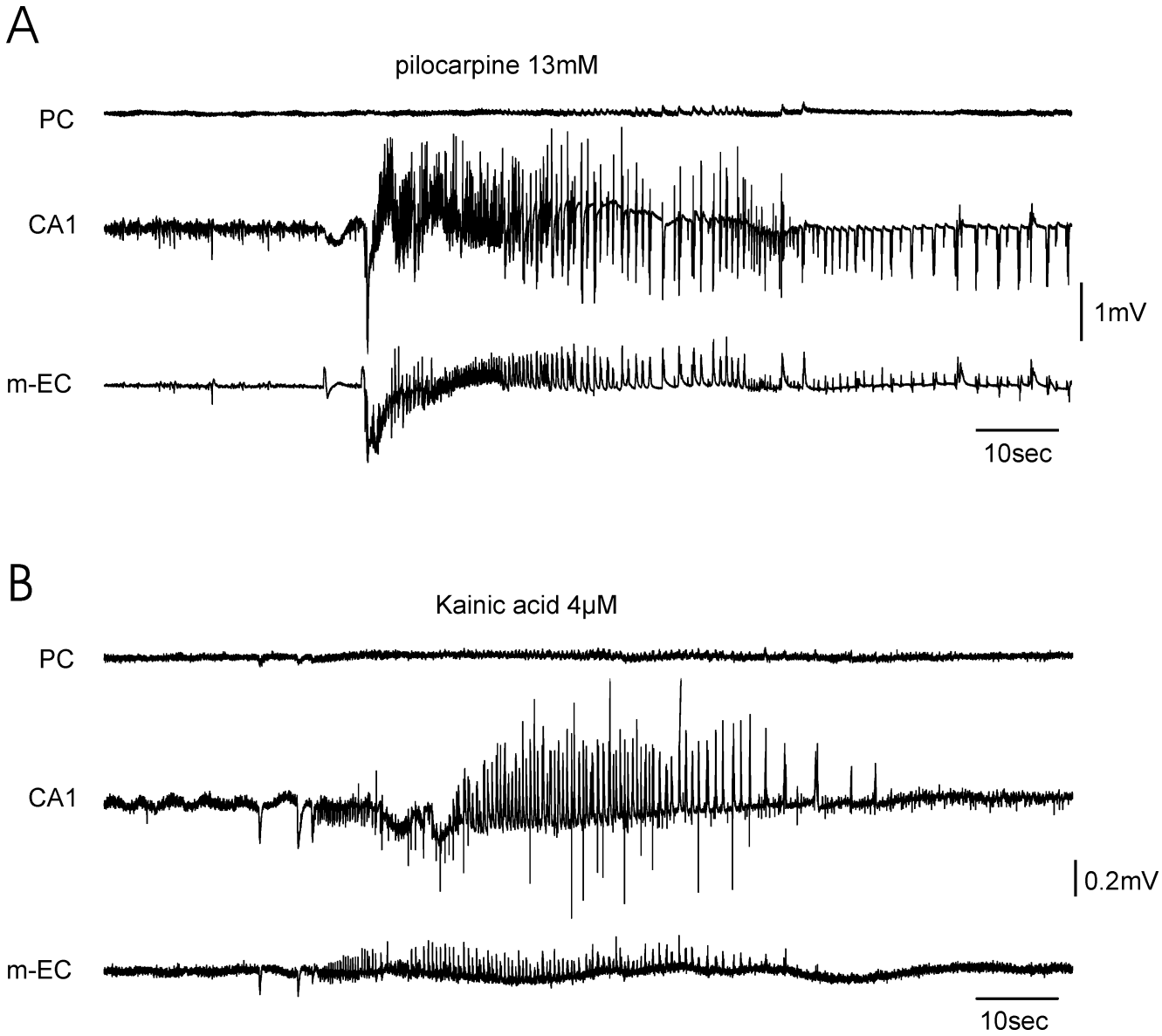

PC
CA1
m-EC

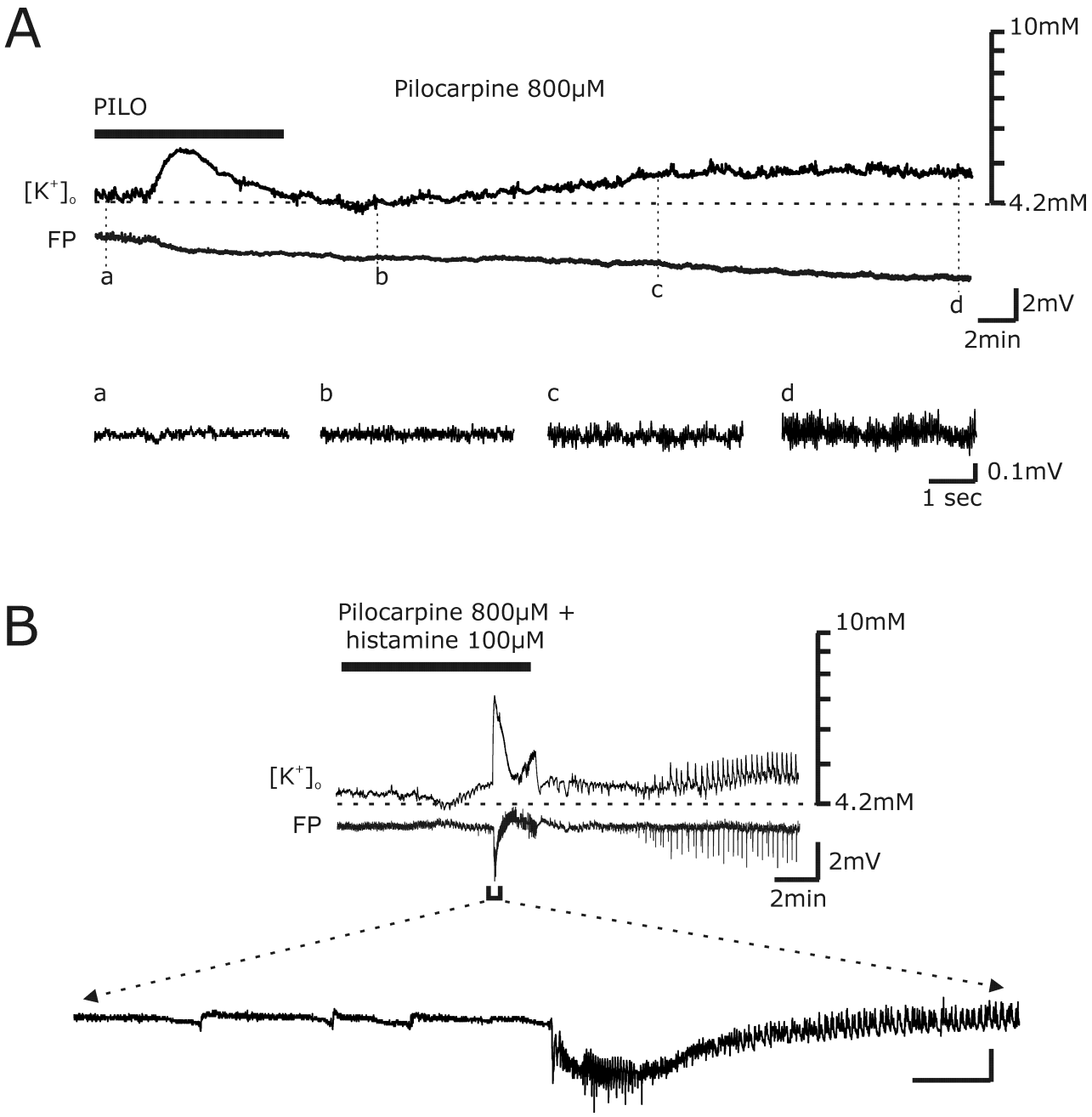

A
control
pilocarpine 100µM
washout
PC
CA1
m-EC
0.2mV
0.5 sec
B
pilocarpine 10µM
CA1
pilocarpine 100µM
CA1
pilocarpine 800µM
CA1
1sec


C
control
pilocarpine 800µM
pilocarpine 800µM
+ atropine 5µM
0.5 sec
Vrms
0.012
0.010
0.008
0.006
0.004
0.002
0.000
0
10
20
30
40
50
60
70
80
90
100 Hz
PILO 800µM
Atropine 5µM
washout


A
control
pilocarpine 800μM
washout
PC
0.5mV
40msec
C
control
pilocarpine 800μM
washout
EC
0.5mV
hipp
(CA1)
*
*
100msec


A
control
pilocarpine 800μM
washout
2sec
B
Bradykinin 0.6μM + pilocarpine 800μM
washout
0.2mV
2sec
5sec
C
histamine 100μm + pilocarpine 800μm
control
washout
0.2mV
2sec
2sec
5sec


A
pilocarpine 13mM
PC
CA1
m-EC
1mV
10sec
B
Kainic acid 4μM
PC
CA1
m-EC
0.2mV
10sec

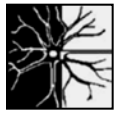

A
Pilocarpine 800μM
PILO
10mM
4.2mM
[K+]o
FP
a
b
c
d
2mV
2min
a
b
c
d
0.1mV
1 sec
B
Pilocarpine 800μM +
histamine 100μM
10mM
4.2mM
[K+]o
FP
2mV
2min

Conclusions (3)

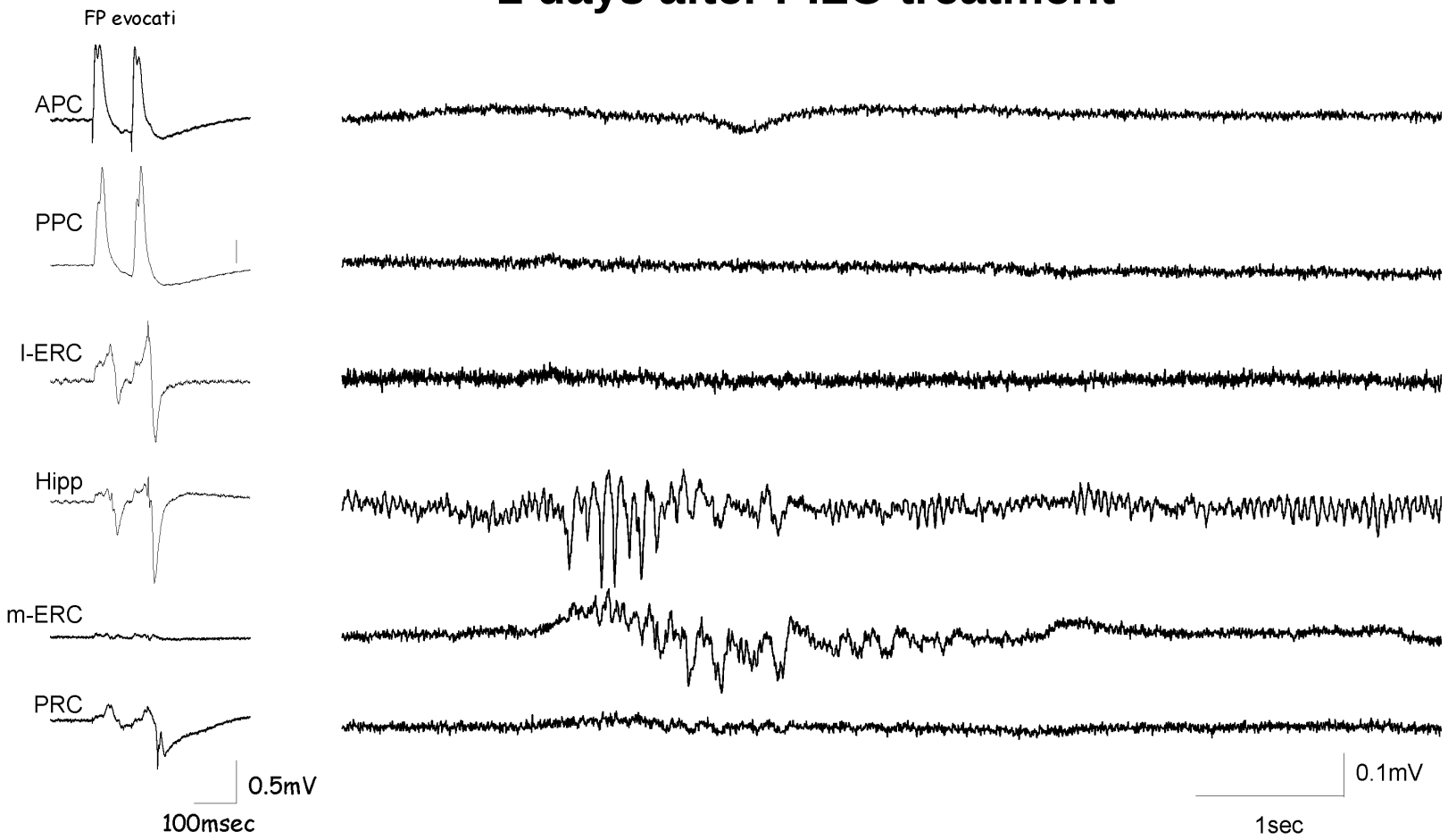
- Perfusion with PILO (10-800 µM) in the guinea pig brain isolated and maintained in vitro does not induce epileptiform activity, but promotes:
    - oscillations in the gamma range,
    - depression of paired pulse stimulation.

- Co-perfusion of PILO and mediators that cause the opening of the blood brain barrier leads to epileptiform activity.

- Our data suggest that:
    - pilocarpine alone is not able to induce epileptiform activity
    - BBB breakdown may contribute to the precipitation of seizures.



Recordings from isolated guinea pig brain in vitro
2 days after PILO treatment



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