6th International Workshop on Hybrid Systems and Biology - HSB'19
April 6-7, 2019 - Prague (Czech Republic)

Closed-loop neurohybrid interfaces: from in vitro to in vivo studies and beyond

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European Commission
SEVENTH FRAMEWORK PROGRAMME
THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION HORIZON 2020
Farnesina Ministero degli Affari Esteri e della Cooperazione Internazionale
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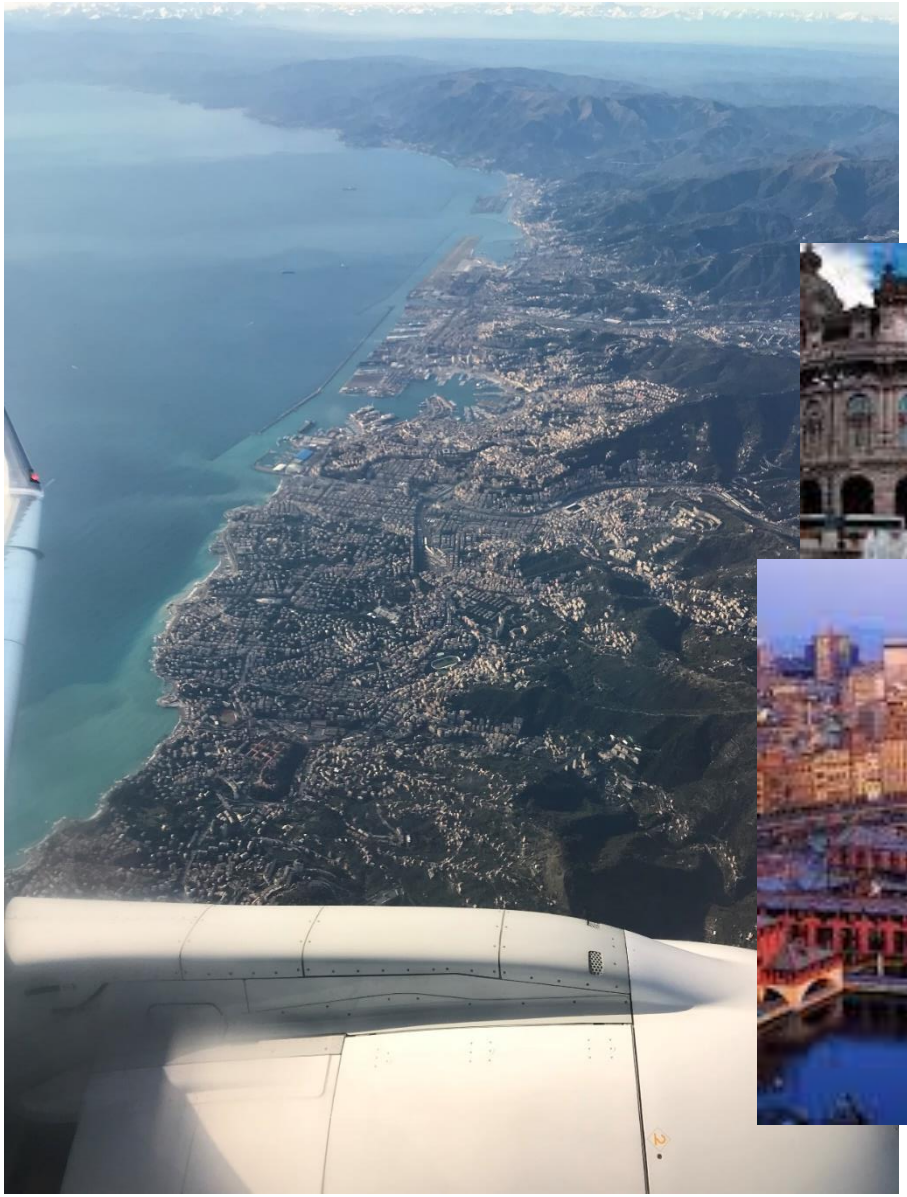

Disclaimer

I am not a Computer Scientist

I am a Biomedical Engineer… so maybe not even a ‘real’ engineer!

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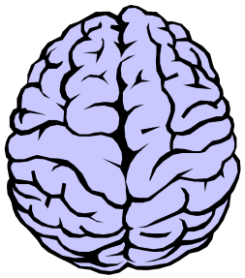
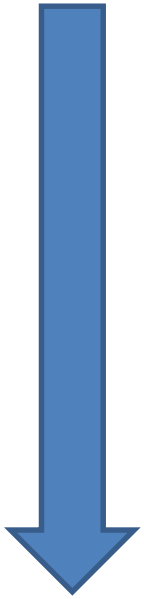
What is a hybrid system?

From hybrid to *neuro*hybrid



Why is it important to develop neurohybrid systems?

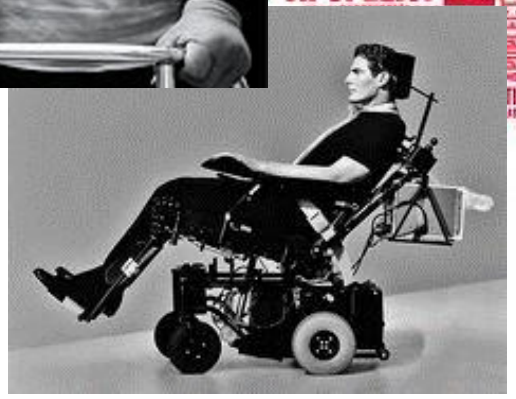
- Basic Neuroscience
- Brain Repair
- Neurorehabilitation
- …
- Wetware Technology
- New computational paradigms



Neuroscience
Neuroengineering

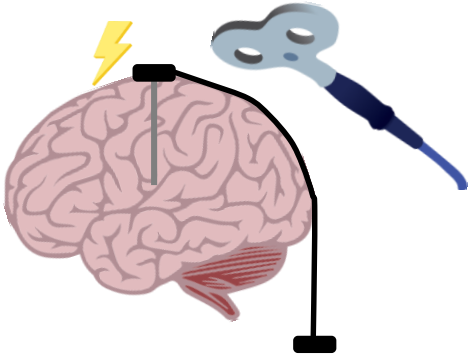
Computer Science
AI
Robotics

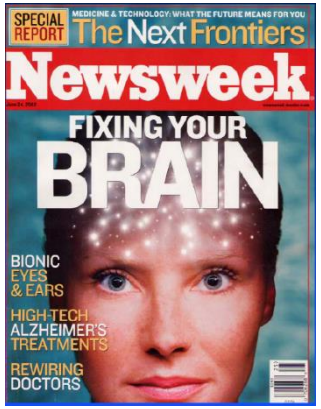
Diseases and injuries of the central nervous system affect more than one billion people worldwide



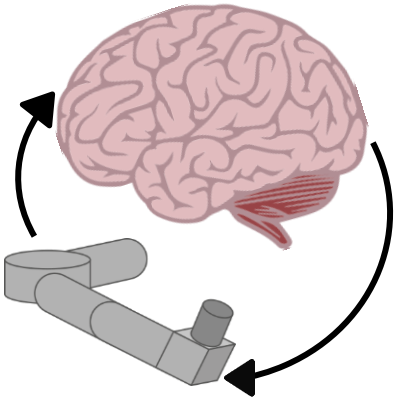
'Closed-loop' neurohybrid interfaces connecting neuronal and artificial systems can be used to **fix the brain**

- Brain Modulators (ICMS, DBS, NIBS)

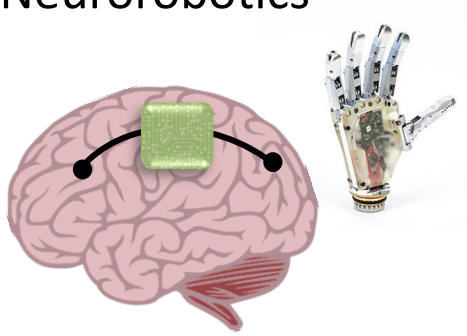




- BCI/BMI



- Neuroprosthetics & Neurorobotics



Special Collection on Emerging Experimental Methodologies in Translational Neuroscience

Brain and Neuroscience Advances

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Progress in Neuroengineering for brain repair: New challenges and open issues

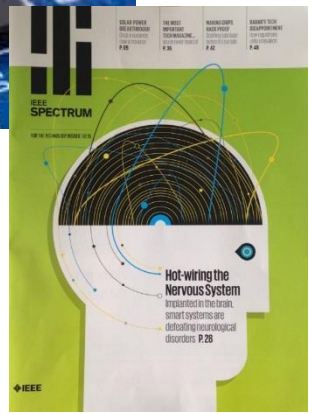
Gabriella Panuccio[1], Marianna Semprini[2], Lorenzo Natale[3], Stefano Buccelli[1,2,4], Ilaria Colombi[1,2,4] and Michela Chiappalone[2]

Brain modulators

- The '*electroceutical*' concept:

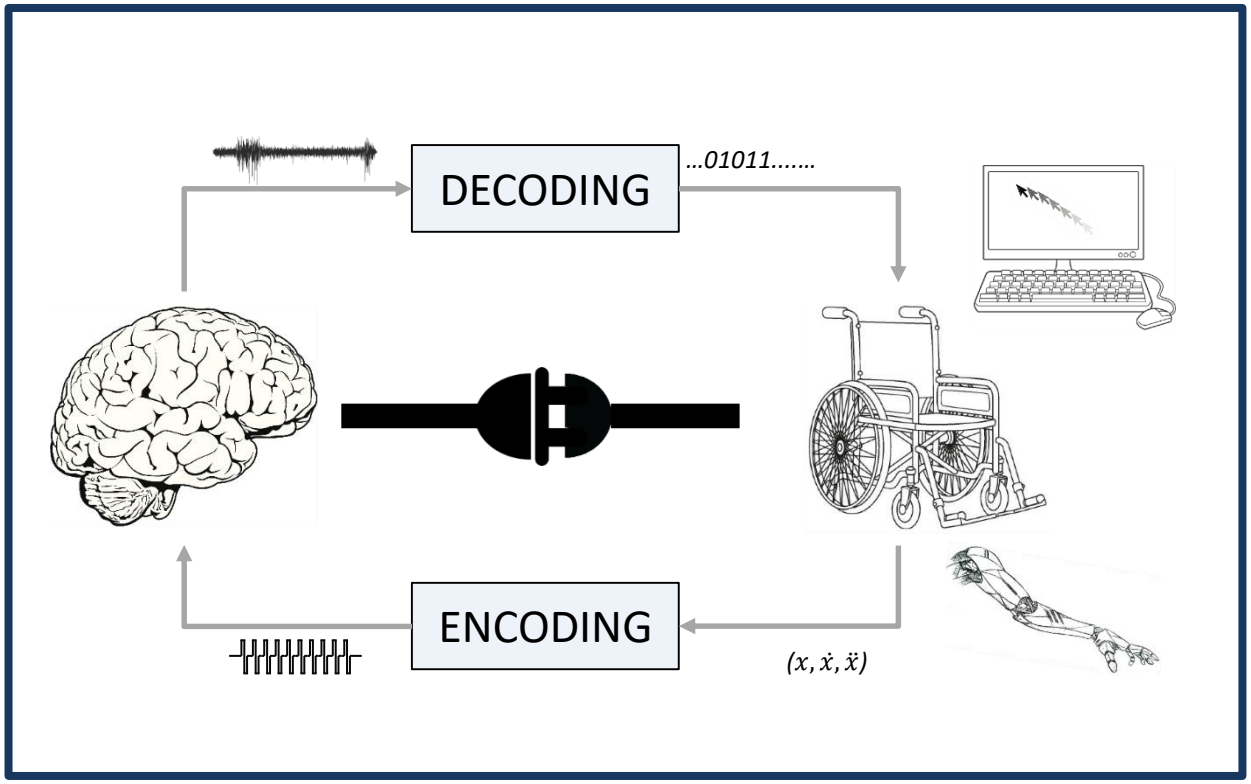
Replacing pharmaceutical interventions by **targeted electrical stimulation** delivered by smart microfabricated devices

'A jump start for electroceuticals', *Nature* April 2013
'Electroceuticals spark interest', *Nature* July 2014

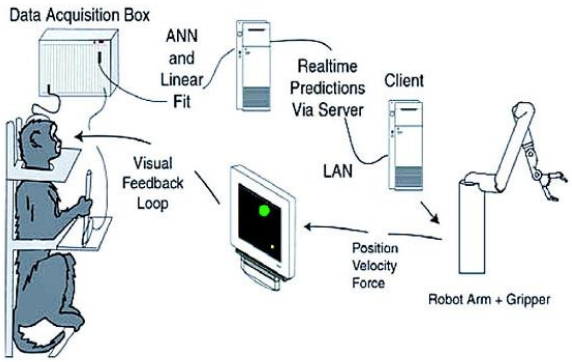


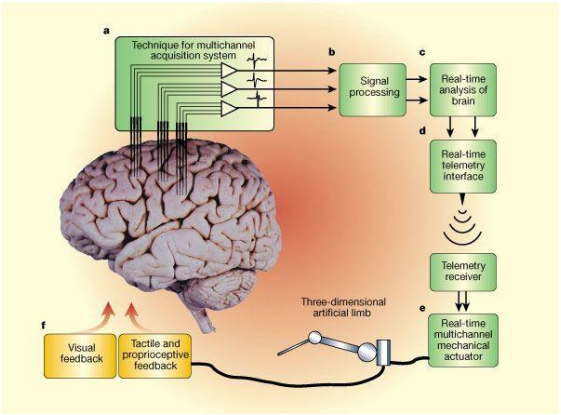
BCI/BMI

- Neural signals are recorded from the cortex using scalp or intra-cortical electrodes. Specific features are extracted from the signals (e.g. amplitudes of evoked potentials or sensorimotor cortex rhythms, firing rates of cortical neurons). The features are then translated into a pattern of commands for an output device (e.g. a simple word processor, a robot arm, a robotized wheelchair).



Invasive Brain Machine Interfaces - BMIs





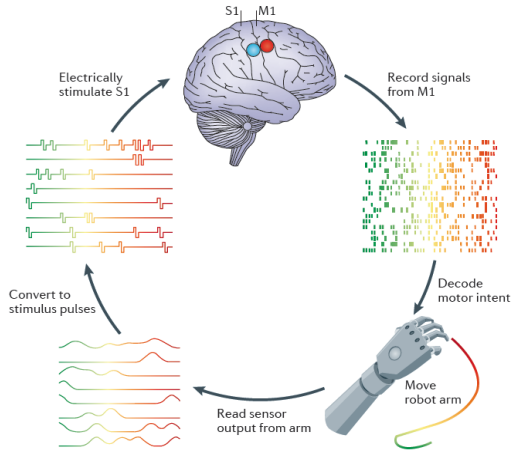
Chapin et al. ***Nature Neurosci,*** 1999; Wessberg et al. ***Nature*** 2000; **Action from thoughts**, MAL Nicolelis, ***Nature*** 2001

Neural signals recorded from the brain as input commands to control external devices

Hochberg et al. ***Nature***, 2006

Hochberg et al. ***Nature***, 2012

J. Donoghue's lab at Brown University
First implants on human subjects

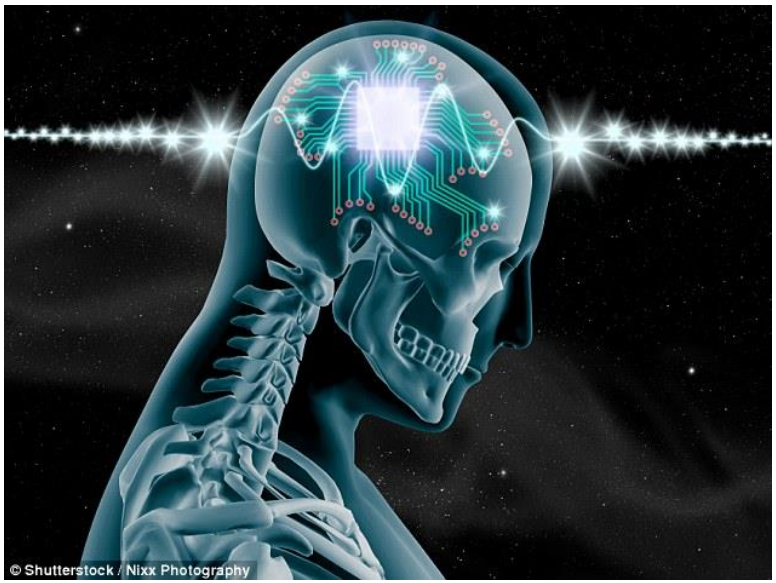


Bensmaia & Miller,
Nat Rev Neurosci, 2014

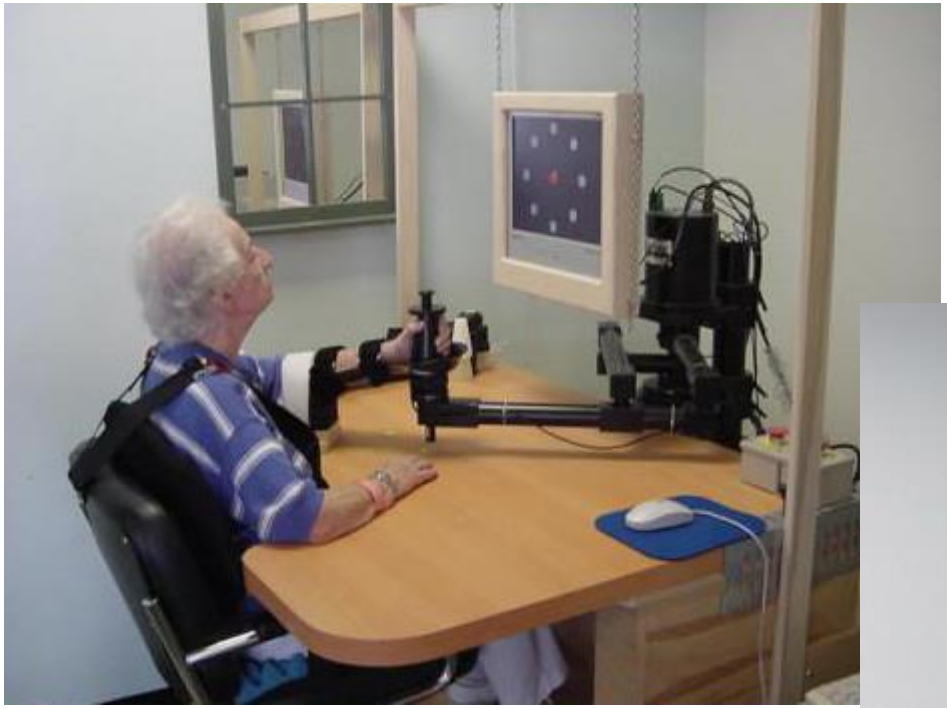
Neuroprosthetics

"a device or system that has an interface with the nervous system and supplements or substitutes functionality in the patient's body"

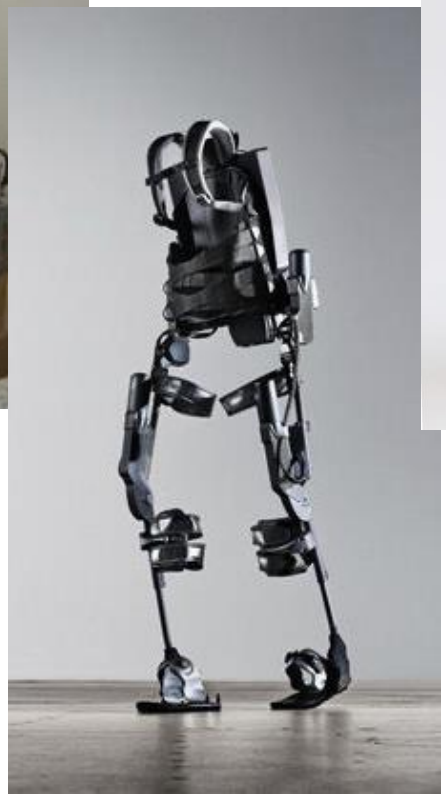
Wright et al, 2016



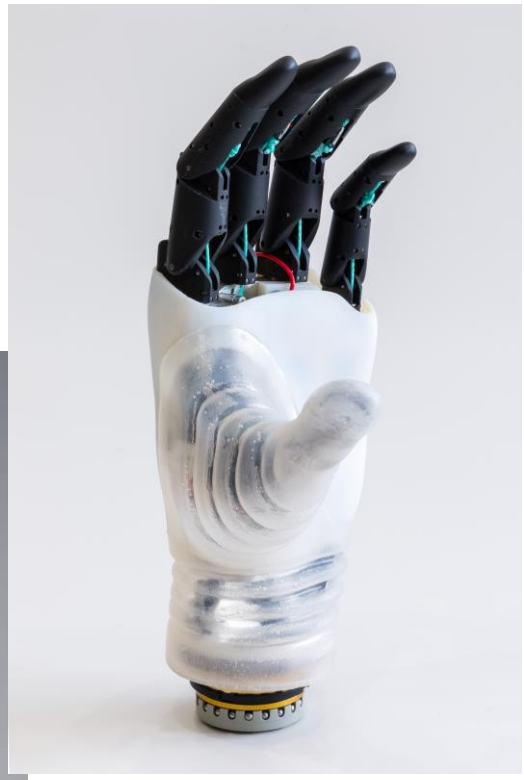
Neurorobotics



Robotic devices for stroke rehab



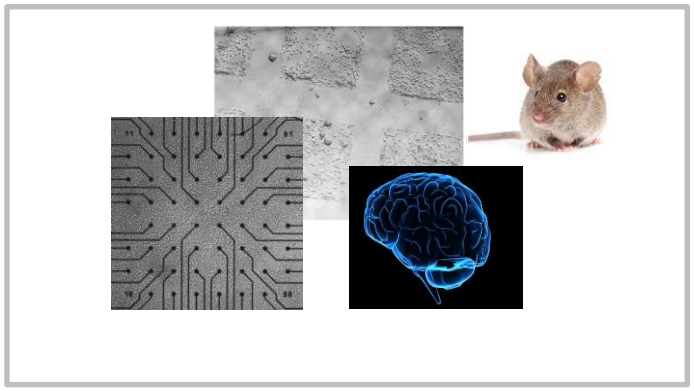
Wearable exoskeletons



Robotic limbs

Our research interests

neuronal system

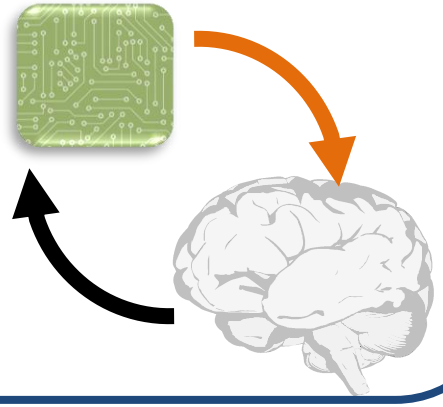


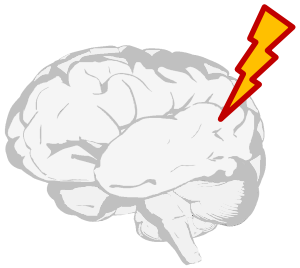
artificial system

- **METHOD** - Exploiting techniques and methodologies of engineering for biomedical applications
  - Understanding by building
  - Multi-scale experimental approach
  - Innovative 'experimental' models (*neurohybrid*)
- **FINAL GOAL** - Neurorehabilitation
  - **Neural Interfaces (including neuroprosthetics)**: interfacing neuronal circuits with artificial devices
  - **Neuromodulation**: drive neuronal dynamics
  - **Neurorobotics:** perform controlled training on patients and monitor recovery

Our multi-scale approach

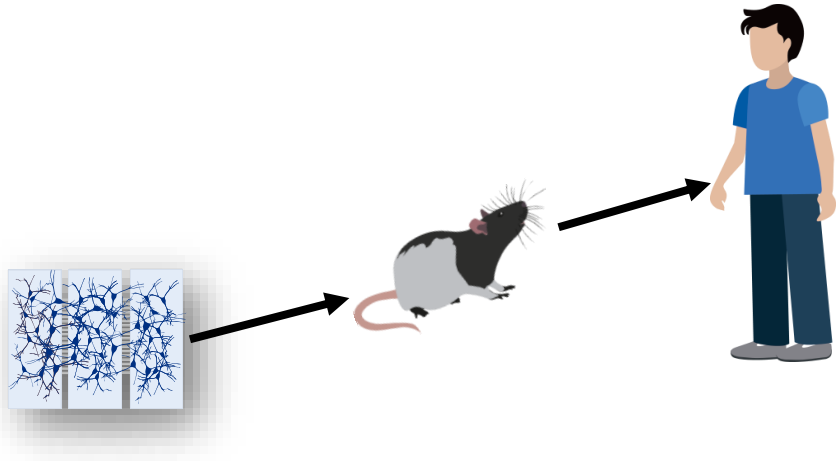
Neural Interfaces





Neuromodulation

Neurorobotics

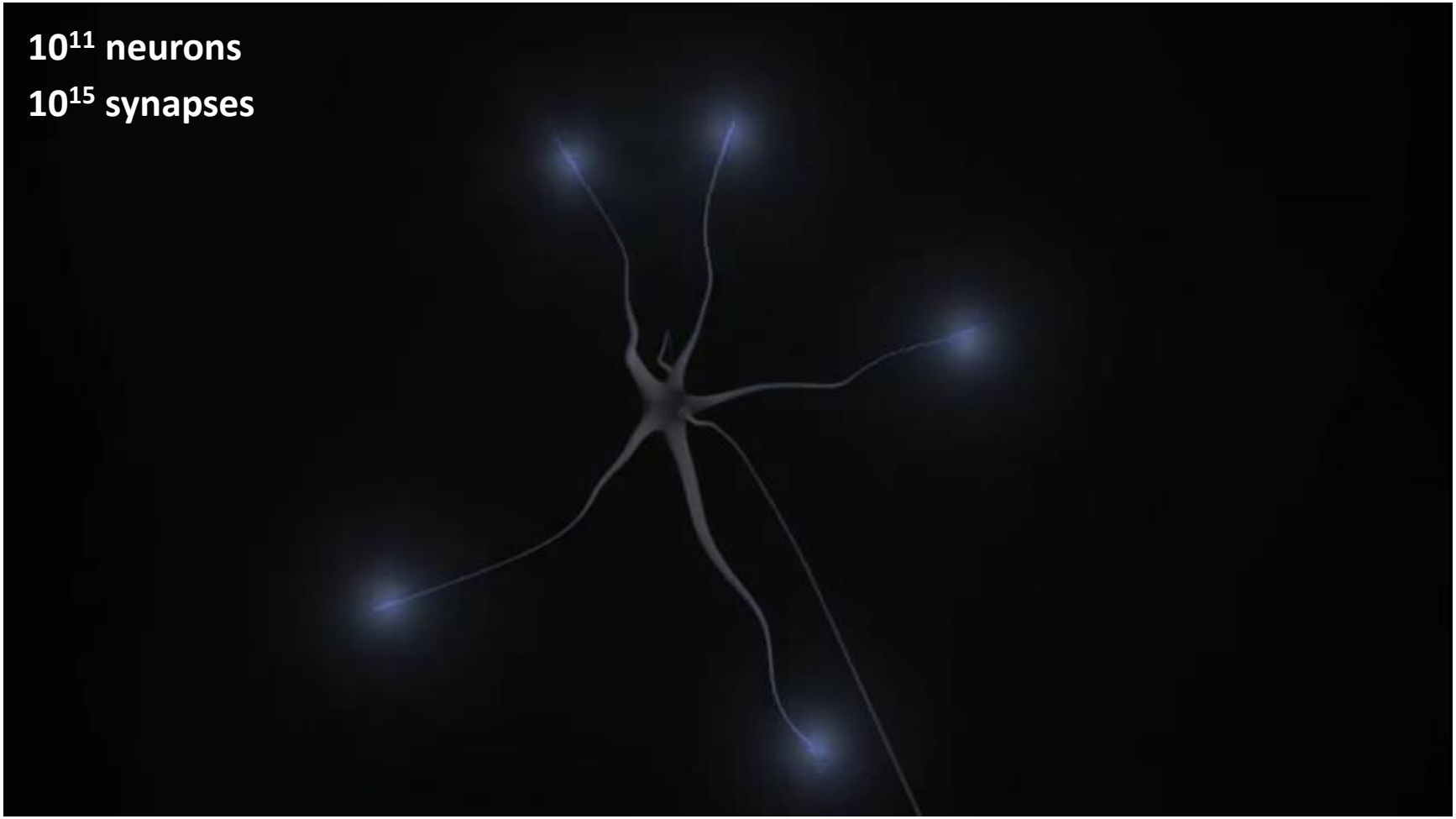


translational methodology

Our 'macro' scientific & technological questions

- How can we **interact** with a neuronal system and thus **modulate** its dynamics?
- How can we **interface** the neuronal element with an artificial one?
- How can we **restore** an injured or pathological communication through **an artificial device**?

The brain is one of the most complex system of the known Universe



The brain is a world consisting of a number of unexplored continents and great stretches of unknown territory

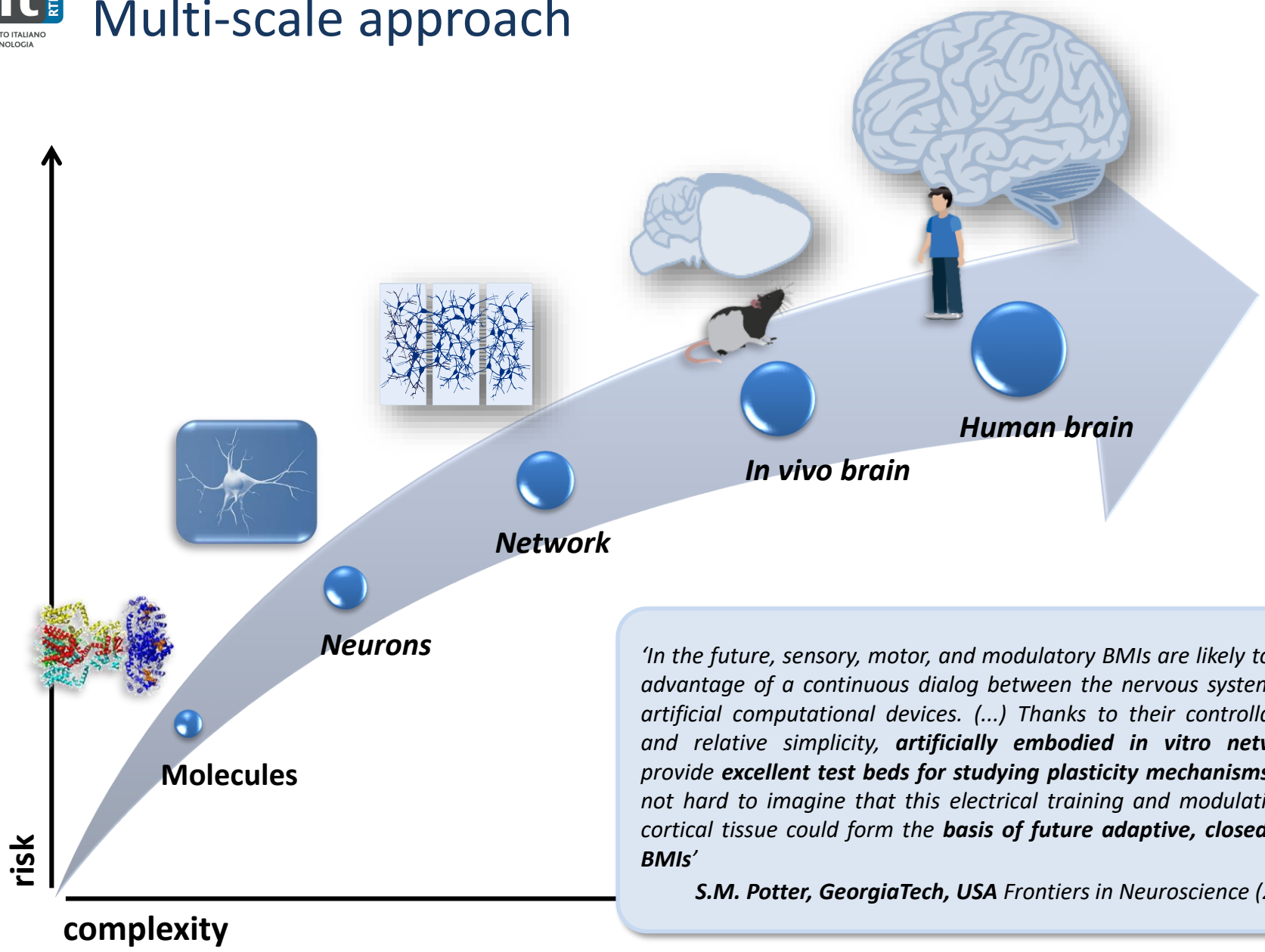
Santiago Ramón y Cajal

Lessons from Neuroengineering

- Reduce the complexity of the system by developing a simple experimental model

- Use the model to test technological solutions for brain repair

Multi-scale approach



'In the future, sensory, motor, and modulatory BMIs are likely to take advantage of a continuous dialog between the nervous system and artificial computational devices. (...) Thanks to their controllability and relative simplicity, ***artificially embodied in vitro networks*** *provide* ***excellent test beds for studying plasticity mechanisms****. It is not hard to imagine that this electrical training and modulation of cortical tissue could form the* ***basis of future adaptive, closed-loop BMIs****'*

S.M. Potter, GeorgiaTech, USA *Frontiers in Neuroscience (2010)*

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From in vitro…

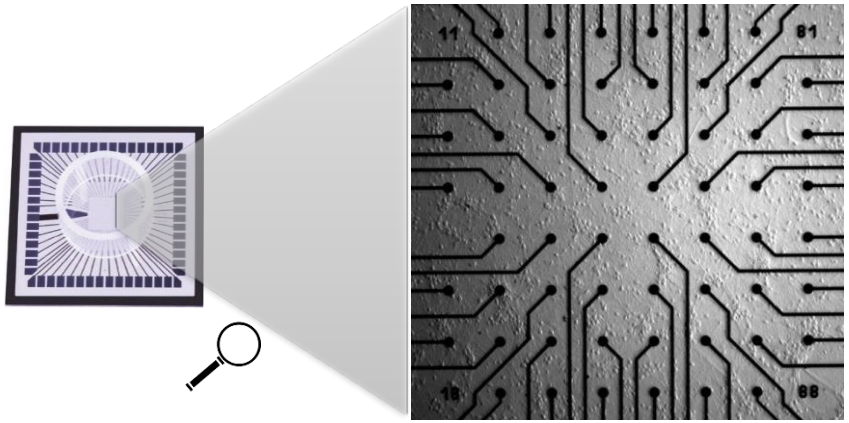
In vitro cortical cultures

Primary cultures of rat cortical neurons

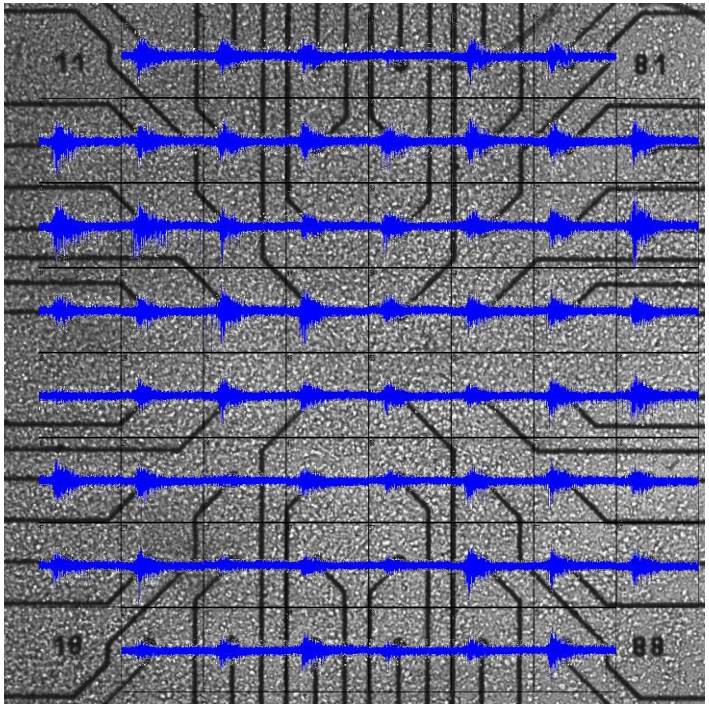
Rat embryos (E18)

Dissection
+
Enzymatic digestion
+
Mechanical dissociation

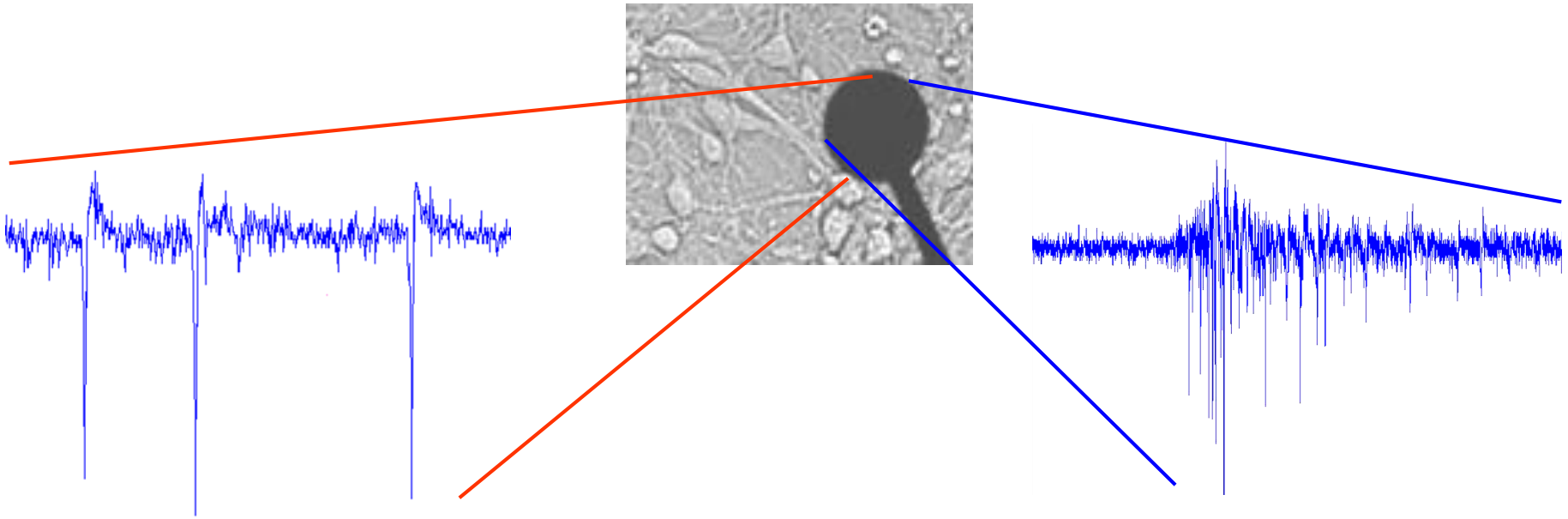
Micro-Electrode Arrays (MEAs)



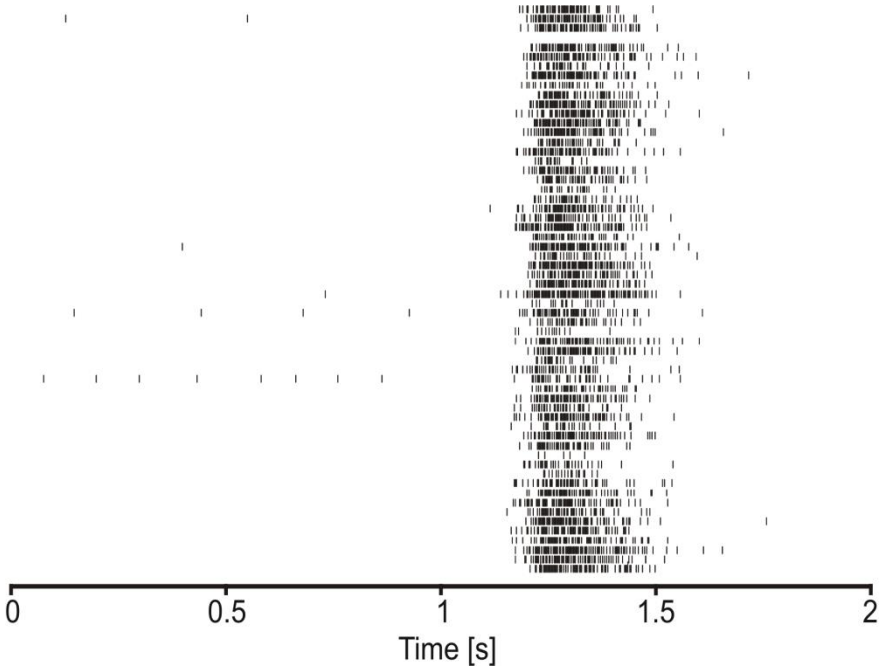
~ 50.000 cells

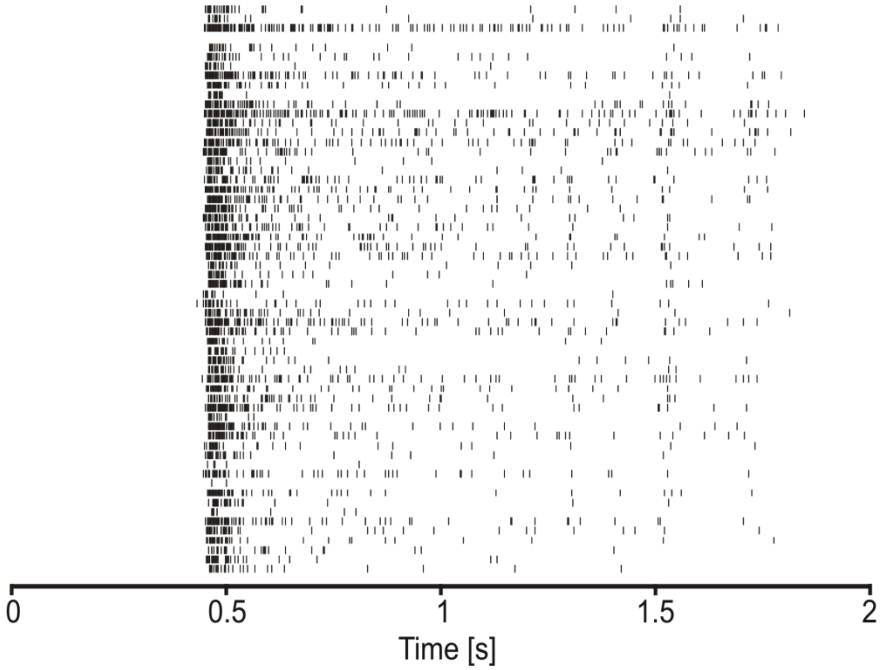


Spikes and Bursts in *electrophysiology*



- The **electrophysiological signal**, acquired from a single microelectrode is generally characterized by **two different patterns of activity**:
  - **Spike** – single over-threshold signal representing the electrical activity of one or more neurons (i.e. 1-3 cells).
  - **Burst** – sequence of highly packed spikes often occurring simultaneously on several channels and giving rise to a phenomenon generally known as '**network burst**'.



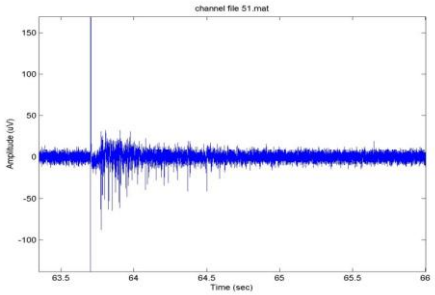


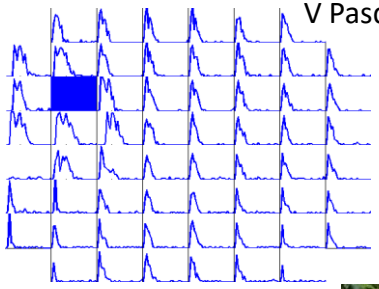
*How can we **interact** with a neuronal system and thus **modulate** its dynamics?*

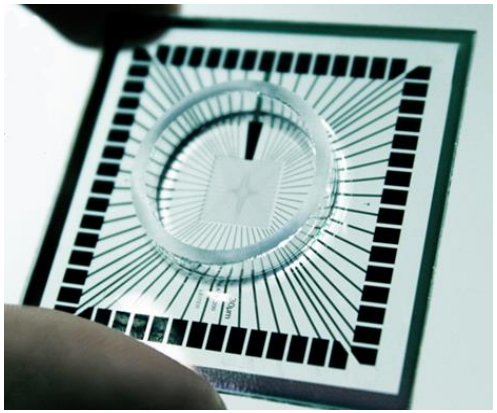
An in vitro model of neural dynamics

V Pasquale

Electrical modulation

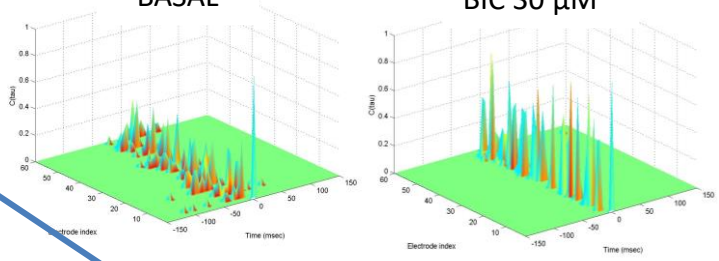


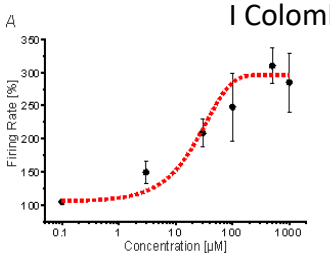




Pharmacological modulation

I Colombi

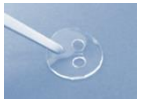


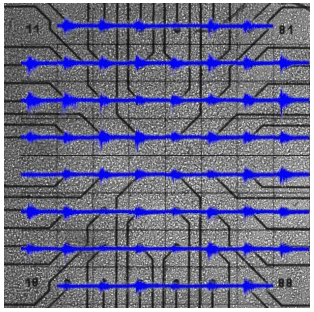


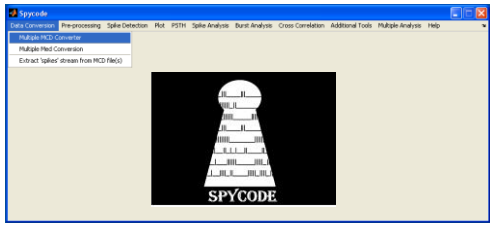
'In recent years, in vitro neuronal cultures have been recognized as a successful model system of neuronal activity'

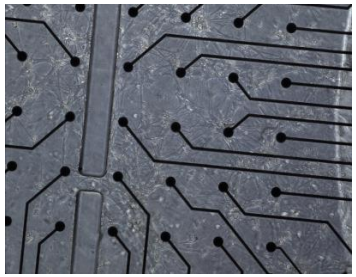
Orlandi JG et al. *Nature Physics*, 2013

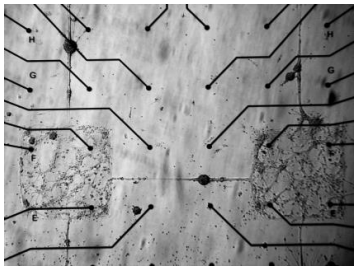
Network patterning







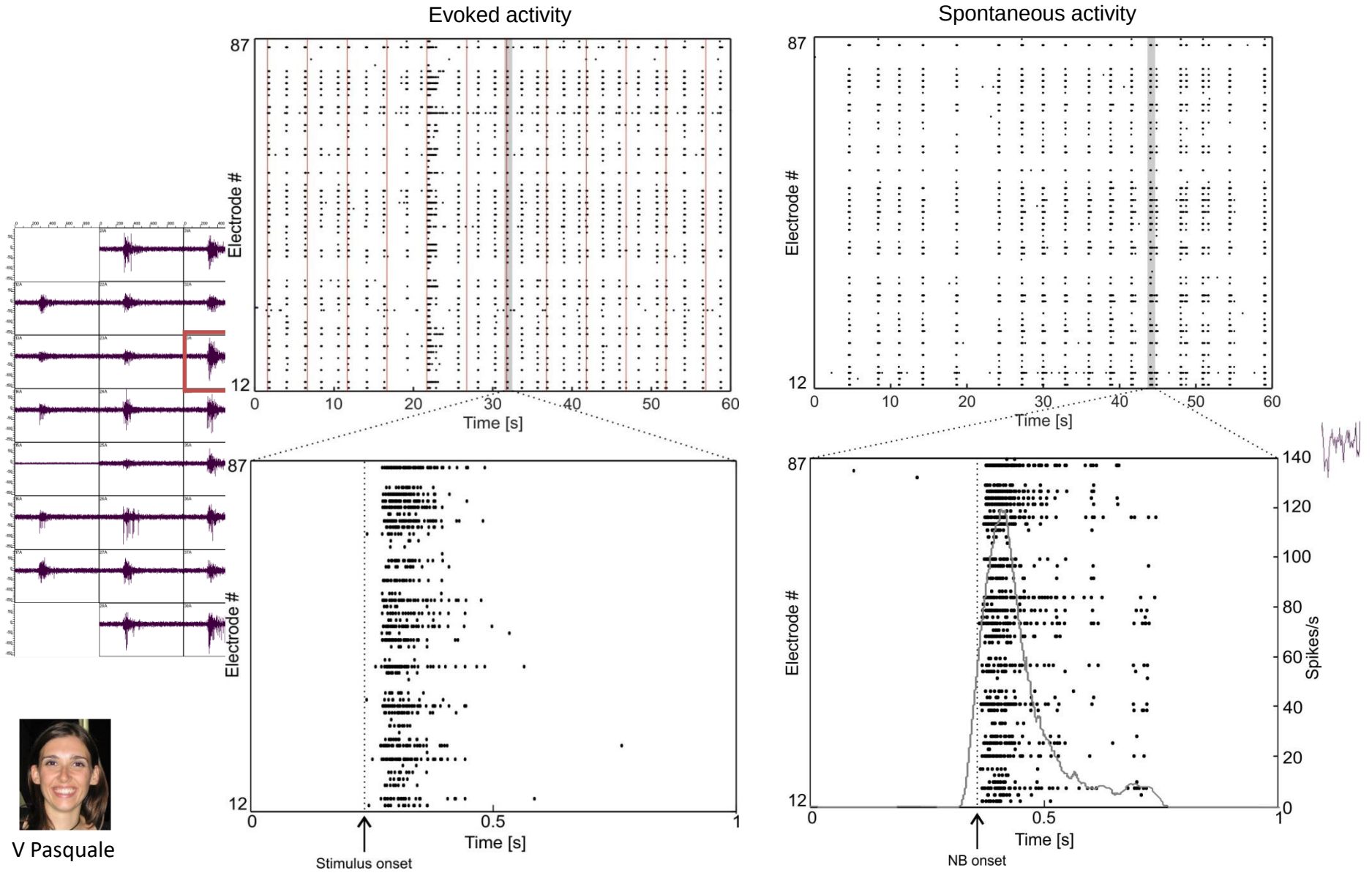




M Bisio

Chiappalone et al. ***Neurocomputing***, 2005; Chiappalone, et al. ***Brain Res***, 2006; Chiappalone, et al. ***Int J Neural Sys***, 2007; Maccione et al. ***J Neurosci Methods***, 2009; Bologna, et al. ***Neural Networks***, 2010; Pasquale et al. ***J Comput Neurosci***, 2010; Bisio et al, ***PLoS One***, *2014;* Kanner et al, ***JoVE***, 2015; Pasquale et al. ***Scientific Reports*** 2017

Network bursts are typical features of in vitro neuronal cultures

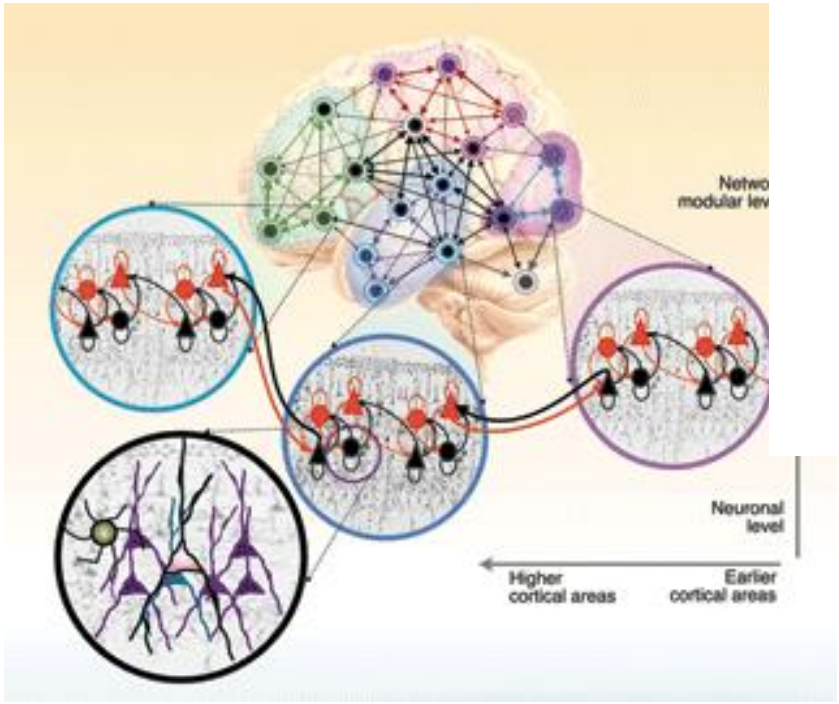


V Pasquale

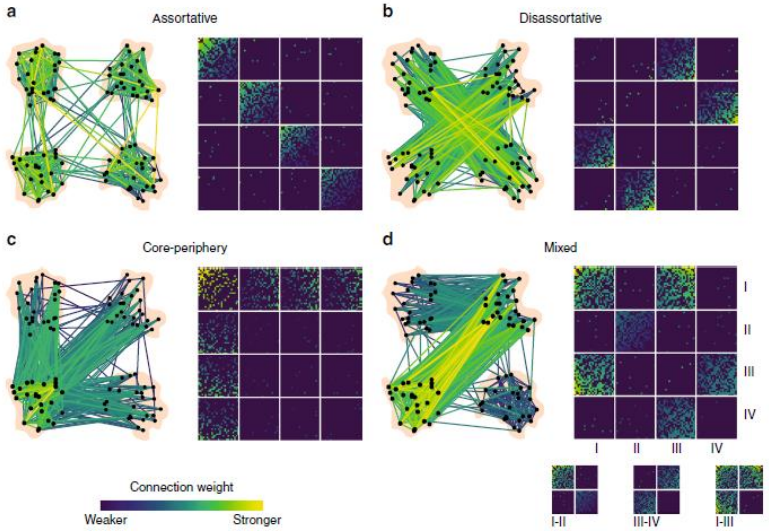
Pasquale, et al. ***J Comput Neurosci***, 2010; Pasquale, et al. ***Scientific Reports***, *2017*

The concept of brain modularity

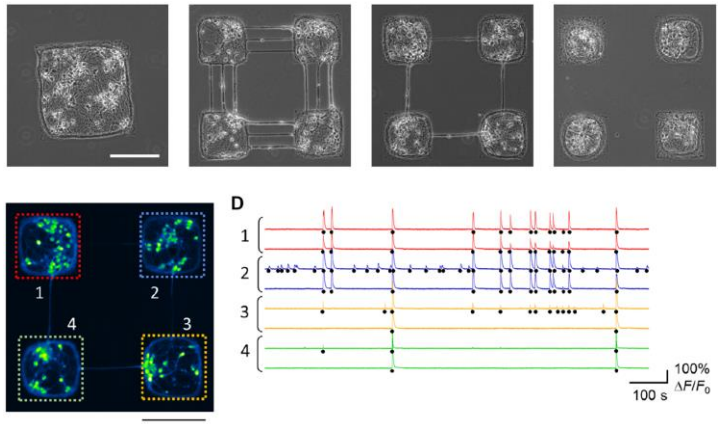
- Brain is redundant and intrinsically modular, being composed of local networks that are embedded in networks of networks (*Meunier et al., 2009; Levy et al, 2012)*



Ref: Park & Friston, Science 2013

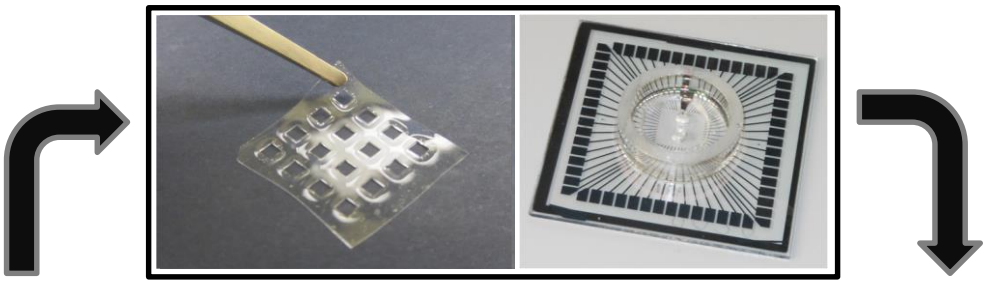


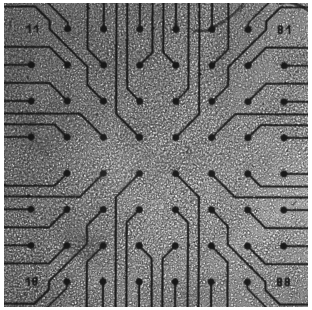
Ref: Betzel et al, Nat Communications 2018

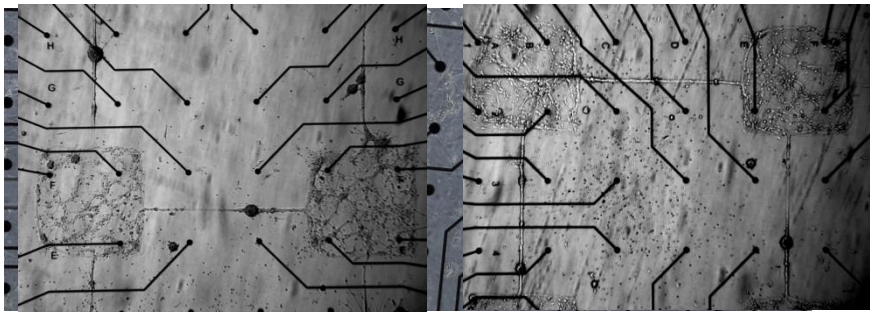


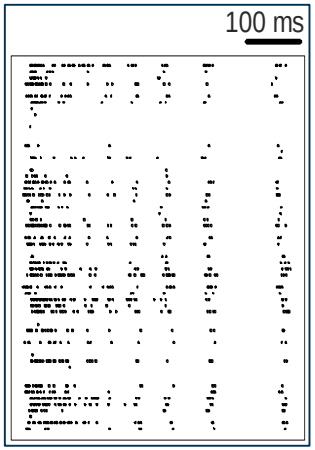
Ref: Yamamoto et al, Science Advances 2018

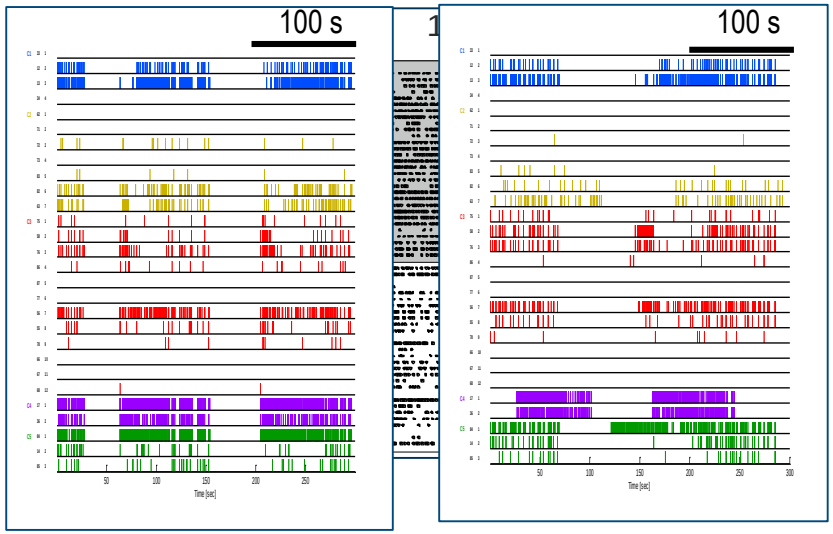
Brain modularity in vitro: network patterning







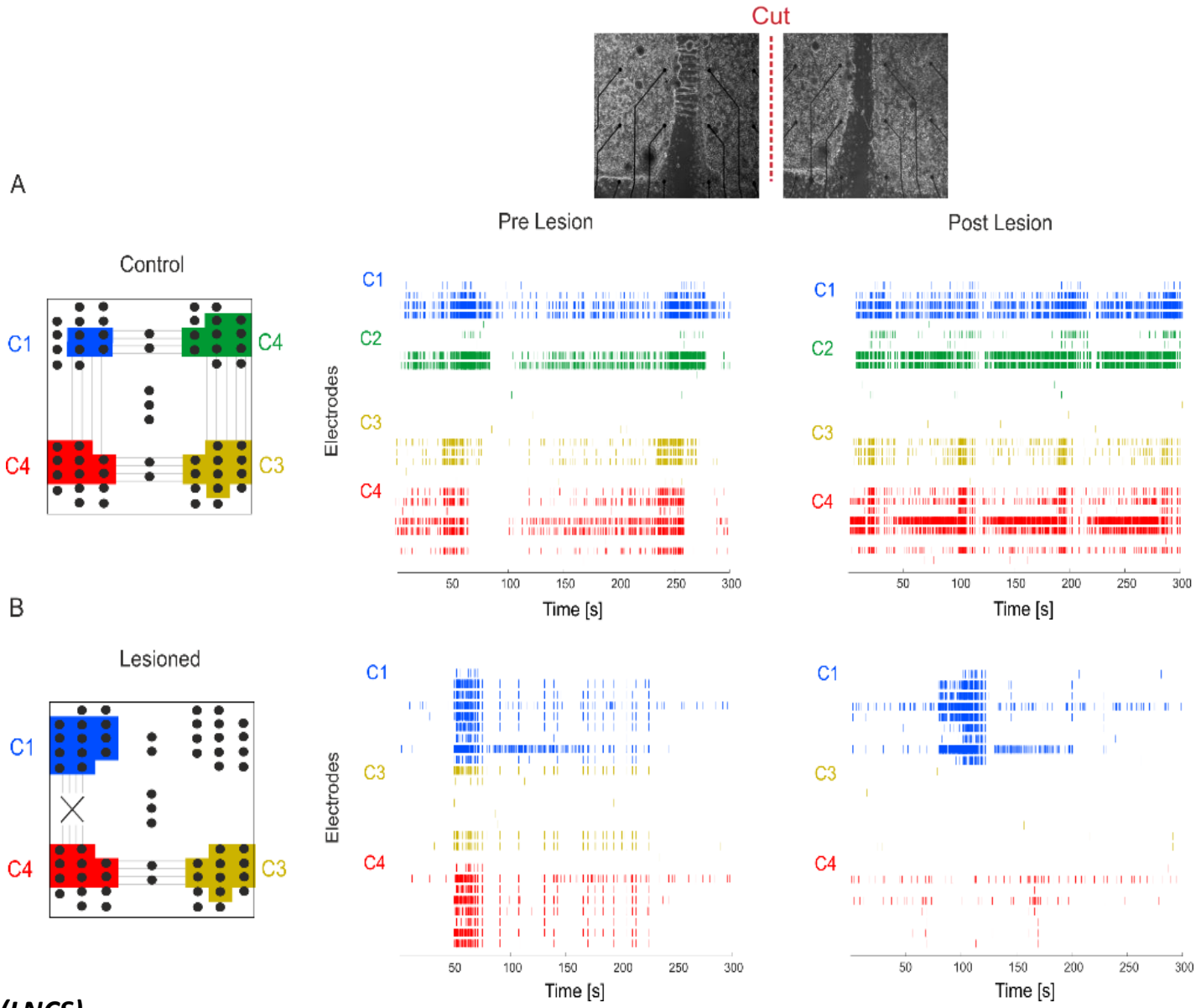




M Bisio, in collaboration with TAU (S. Kanner, P. Bonifazi)

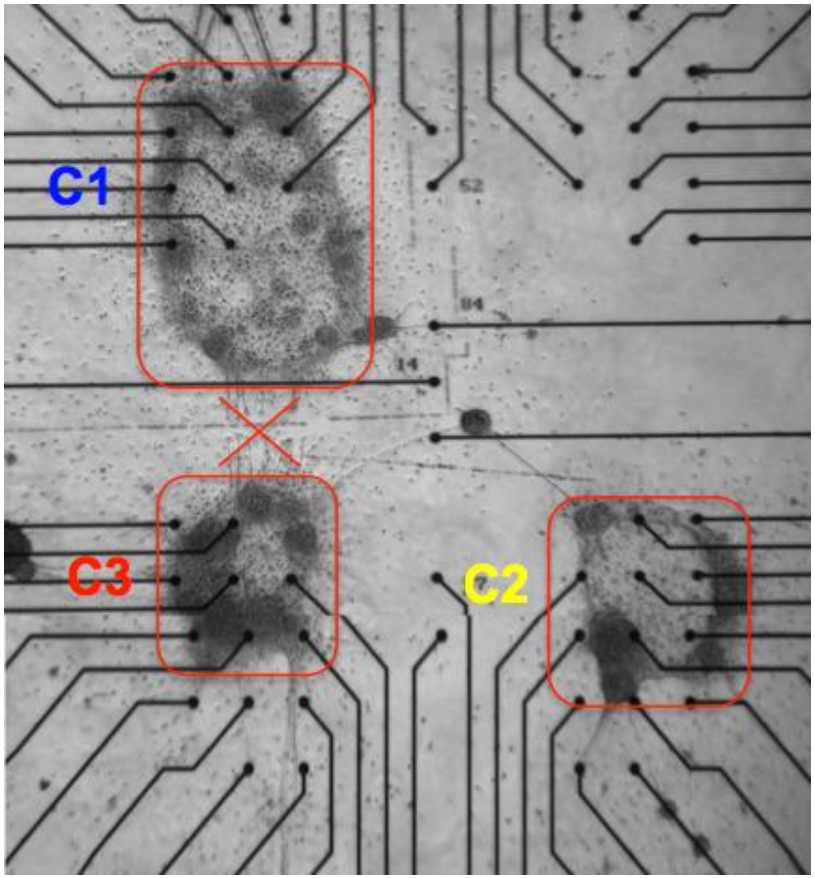
*Bisio et al, **PLoS One**, 2014; Kanner et al, **JoVE**, 2015*

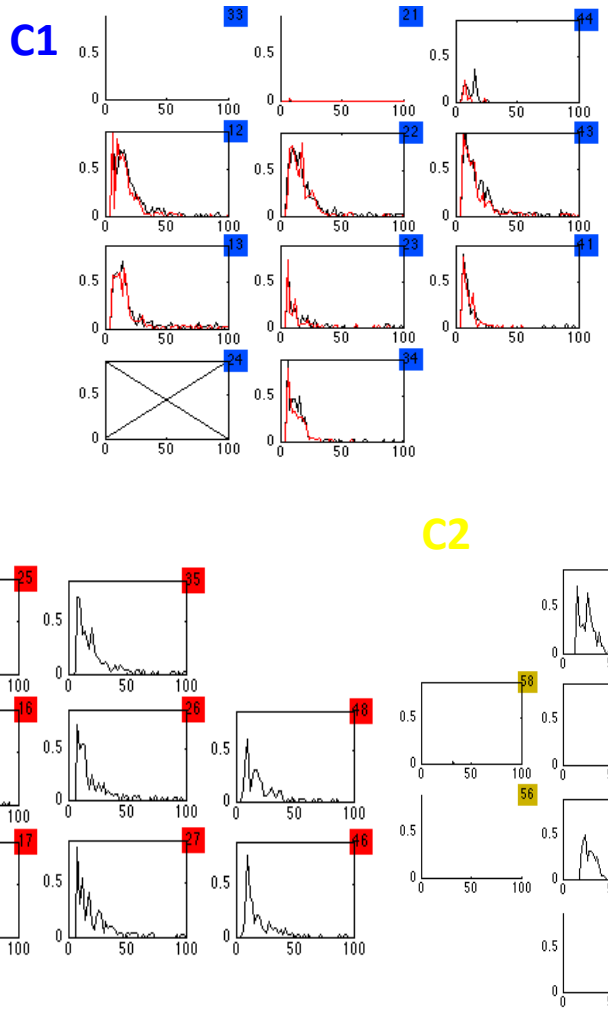
Multimodular systems (electrophysiology)



Averna et al, ***submitted (LNCS)***

Multimodular systems (electrophysiology)



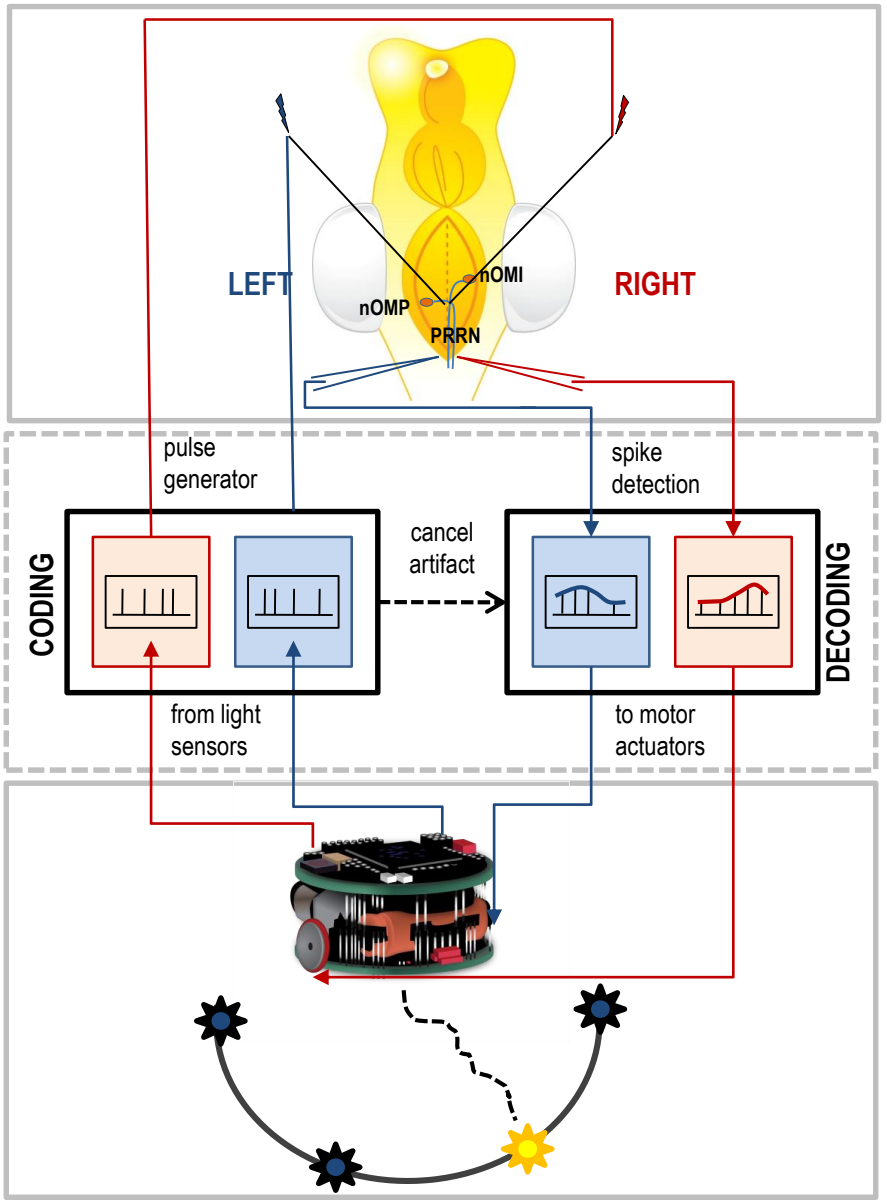


Averna et al, ***submitted (LNCS)***

*How can we **interface** the neuronal element with an artificial one?*

The first closed-loop system

- **A brain with a body**, i.e. a brain with an artificial sensory system and an artificial motor system
- First example of a **closed-loop system**: an in vitro brain of a sea lamprey bidirectionally connected to a mobile robot.



Karniel A, et al. ***J Neural Eng***, 2005
Kositsky, Chiappalone et al. ***Front Neurorobotics***, 2010
Mussa-Ivaldi FA, et al. ***Front Neurosci***, 2010

NORTHWESTERN UNIVERSITY

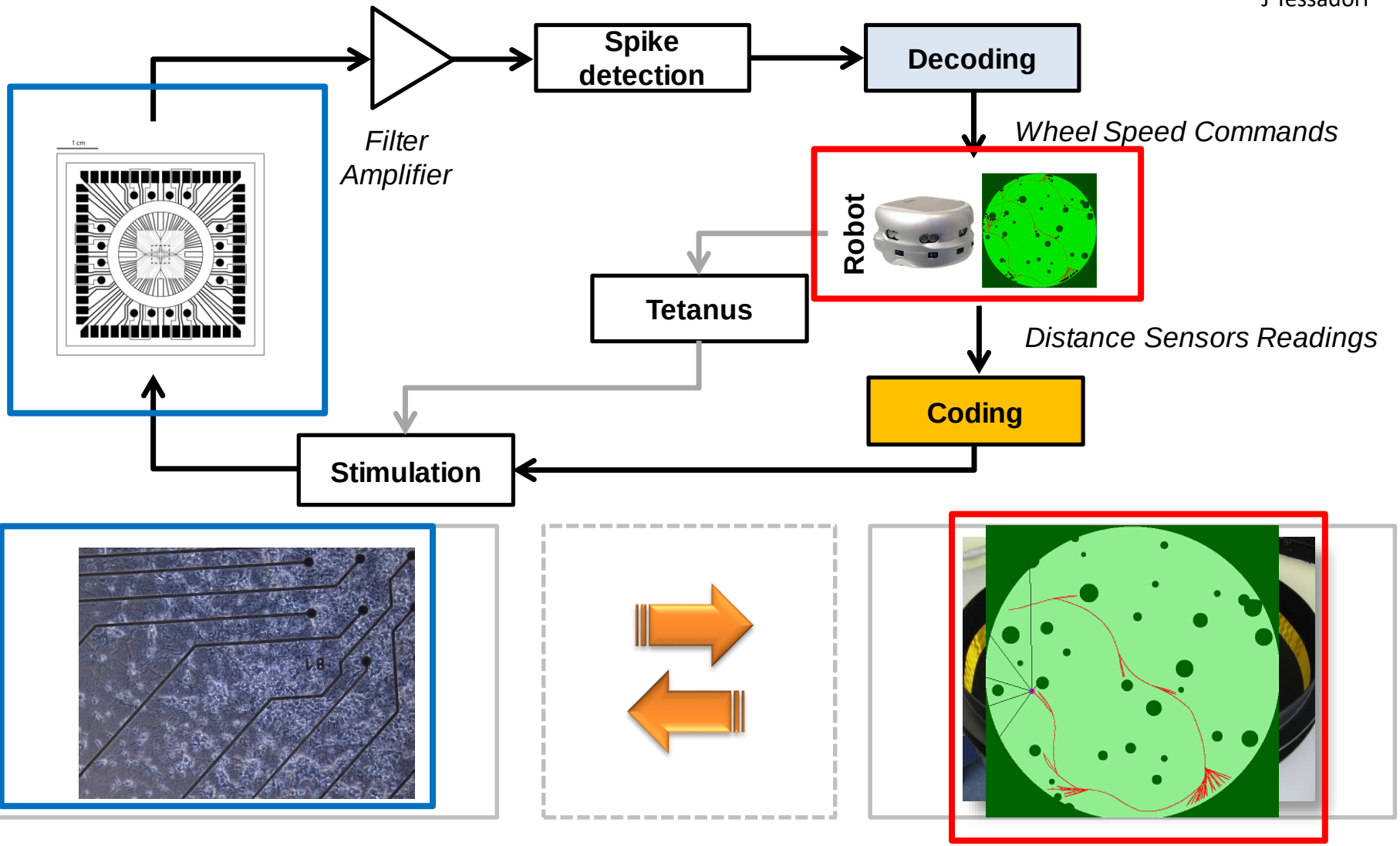

FA Mussa-Ivaldi


M Kositsky


V Sanguineti

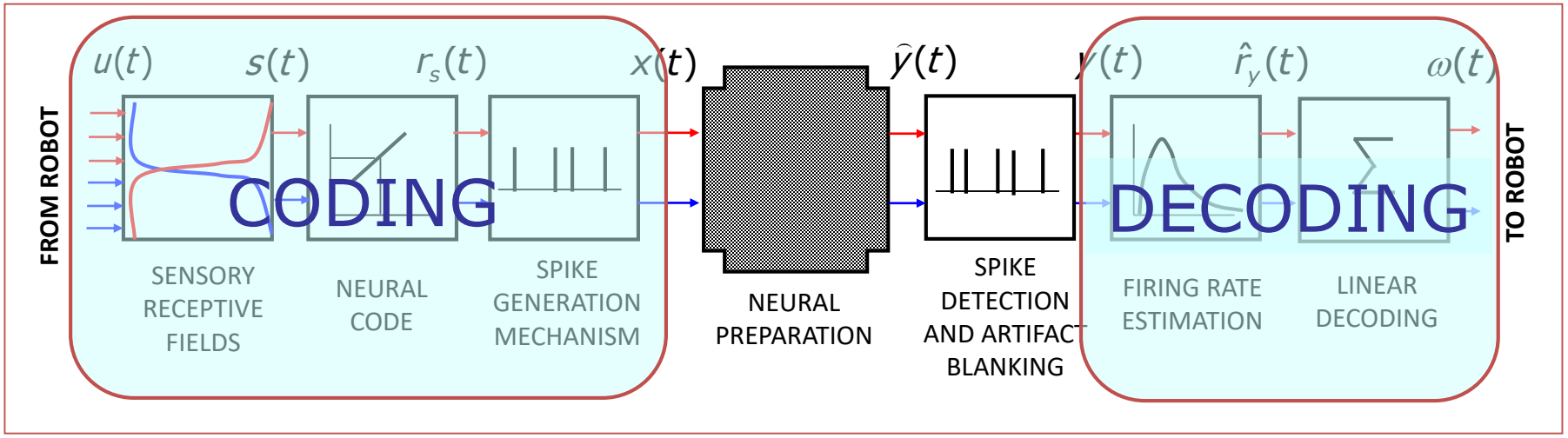
Our neurorobotic system

J Tessadori

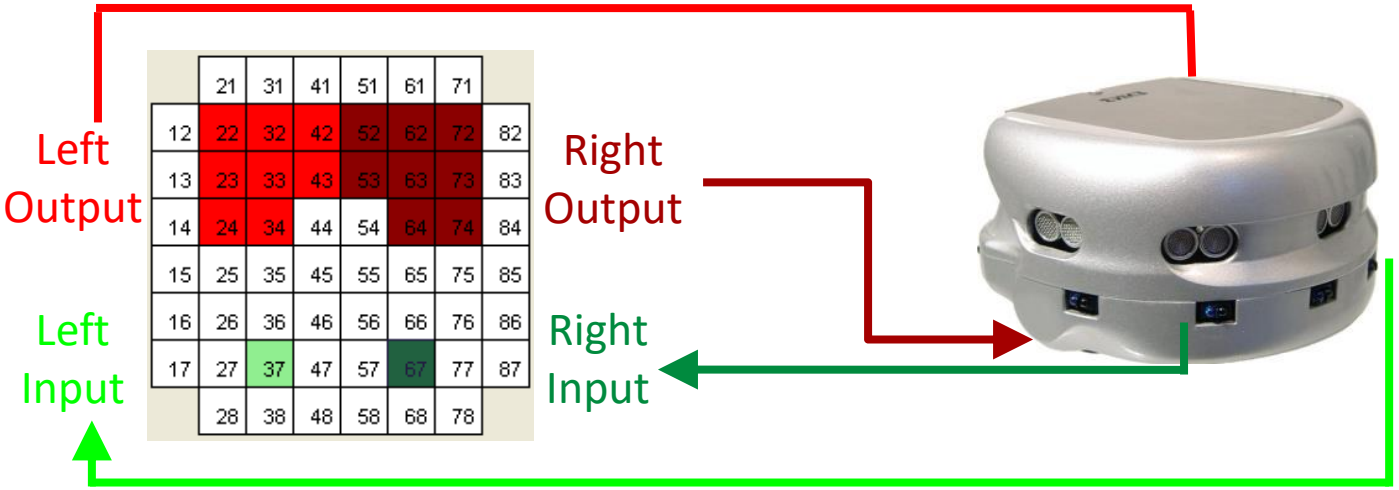


Tessadori et al. ***Living Machines*** 2013; Tessadori and Chiappalone ***JoVE***, 2015

Hybrid communication in neurorobotics experiments



Target behavior: 'Braitenberg vehicle' which (learns to) avoids obstacles



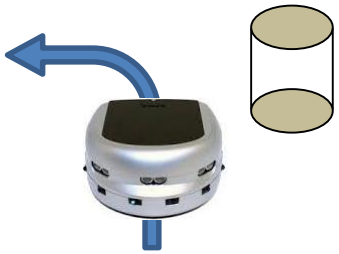
J Tessadori

Tessadori et al. ***Living Machines*** 2013; Tessadori and Chiappalone ***JoVE***, 2015

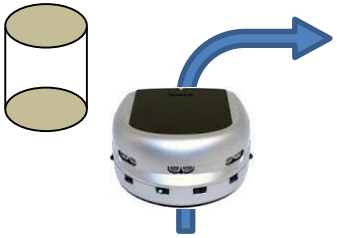
Robot navigation paradigms

- If activity is (close to) equal in the **Right** and **Left** area
  - ➢ the robot goes **straight**

- If the activity on the **Right** area is higher than the activity in the **Left** area
  - ➢ the robot turns **left** (the obstacle was on its right side)



- If the activity on the **Left** area is higher than the activity in the **Right** area
  - ➢ the robot turns **right** (the obstacle was on its left side)

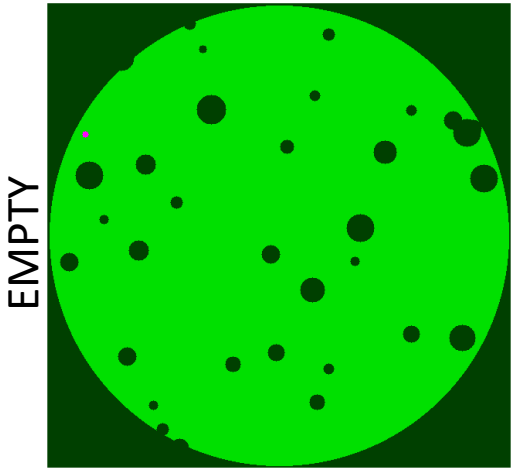


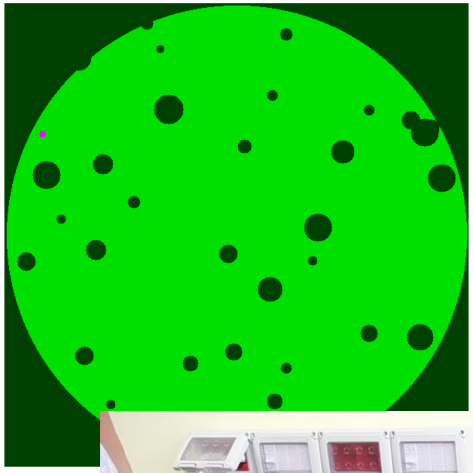
J Tessadori

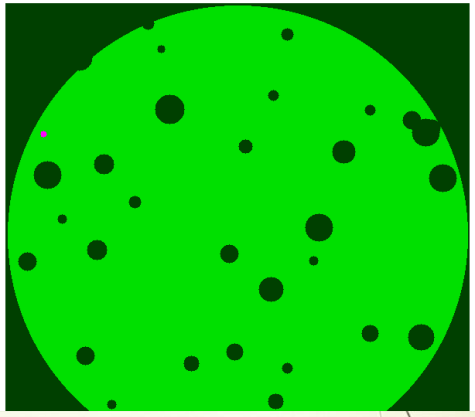
Tessadori et al. ***Living Machines*** 2013; Tessadori and Chiappalone ***JoVE***, 2015

Is there any exchange of information?

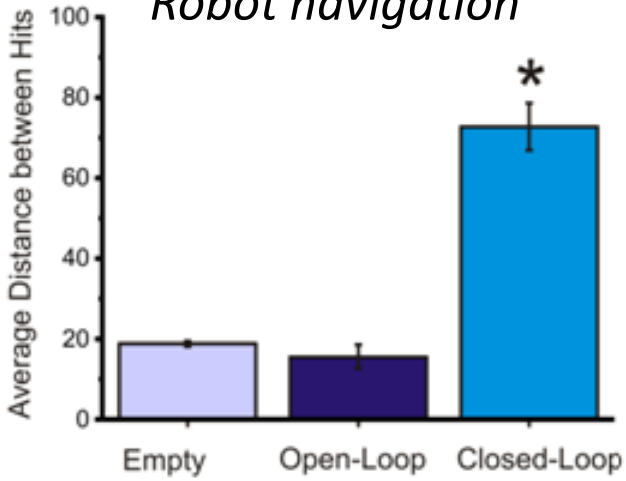
J Tessadori

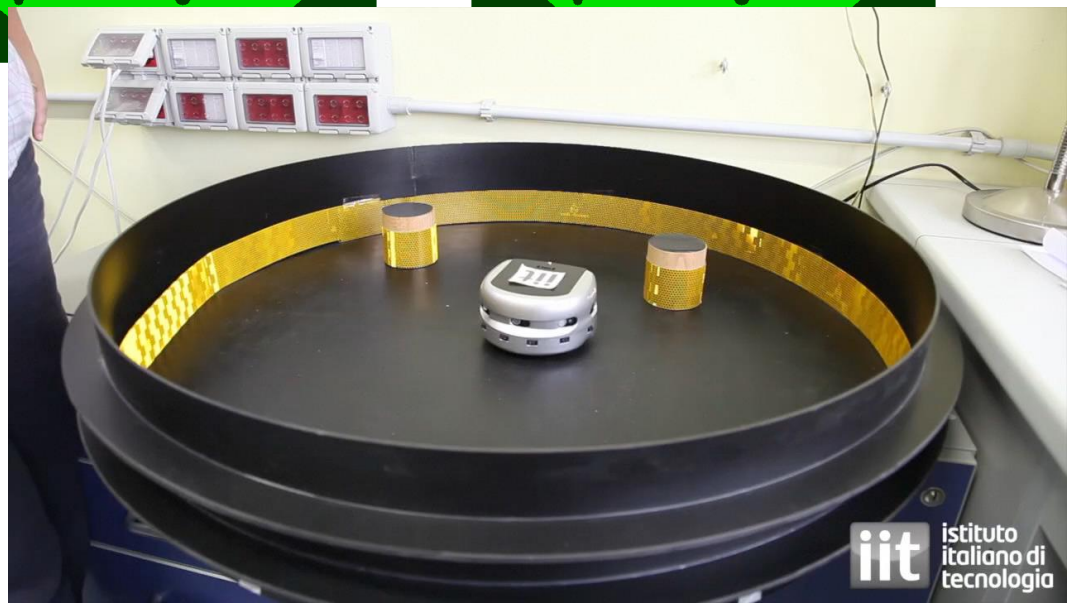






Robot navigation

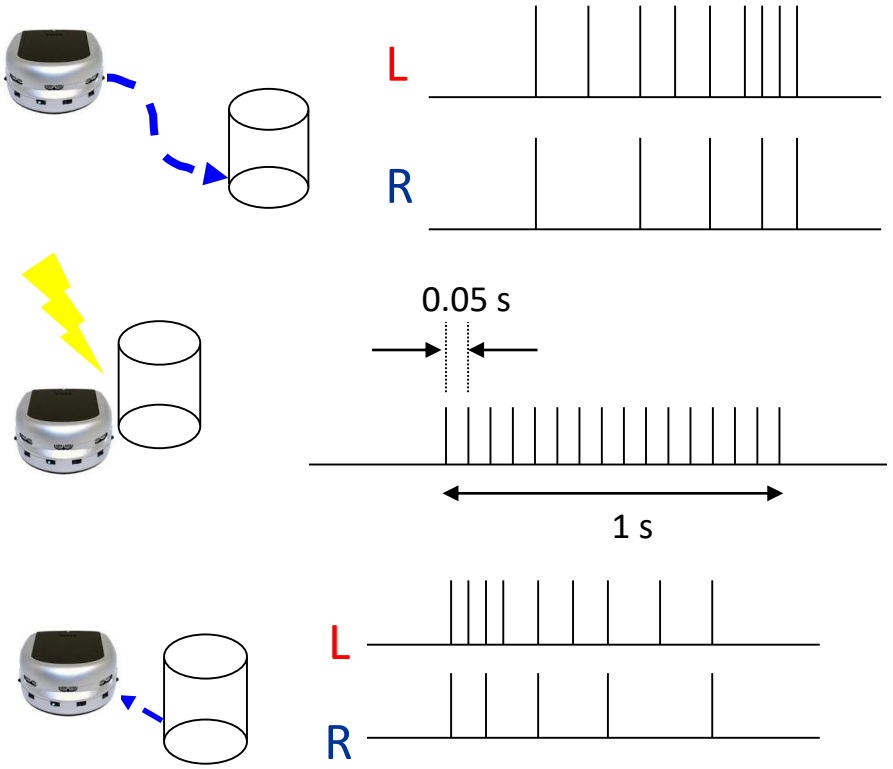




Tessadori et al. *IEEE-BioRob*, 2012; Tessadori et al. ***Front. Neural Circuits***, 2012; Nava et al. ***Living Machines*** 2014

Adding (some kind of) training for inducing learning

- Localized tetanic stimulus affects the network response to activation stimulus (Jimbo et al. *Biophys J*, 1999; Chiappalone et al. *Eu J Neurosci*, 2008; Le Feber et al. *PLoS One*, 2010)
- **Tetanic stimulation**: when the robot hits an obstacle a short tetanic burst is delivered from the collision side



Obstacle hit:

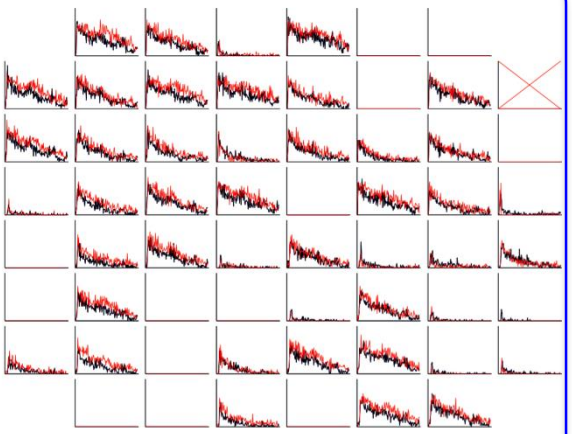
- Still for 2 s
- Tetanic stimulation (20 Hz, 2s)
- Step back to a previous position

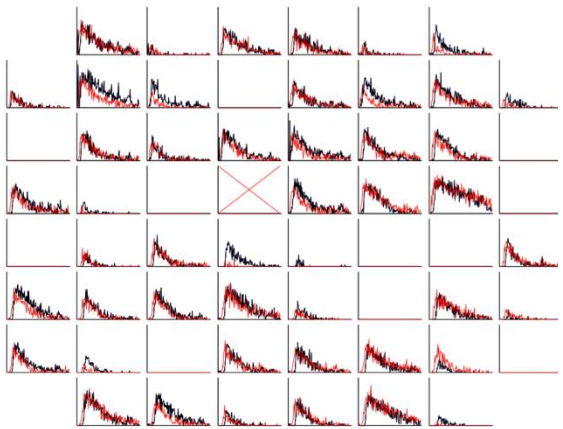
Changes in the network activity

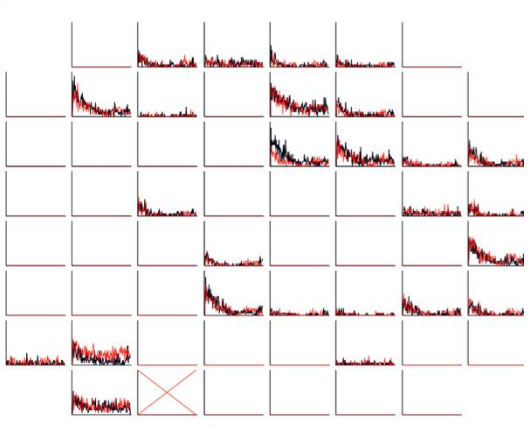
D Ito

Tetanus (closed-loop) | **No Tetanus** | **Sham tetanus (open-loop)**

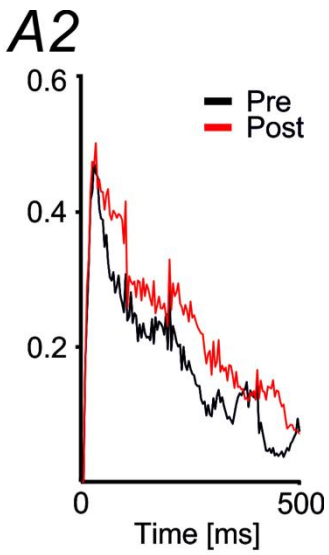
8 x 8 PSTH map

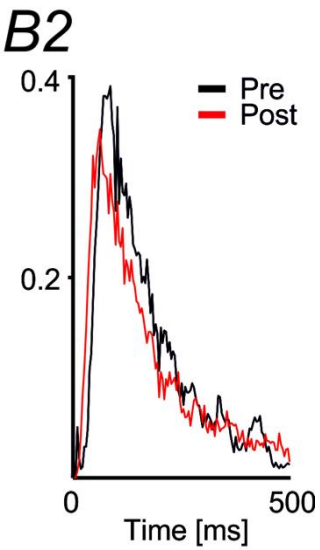


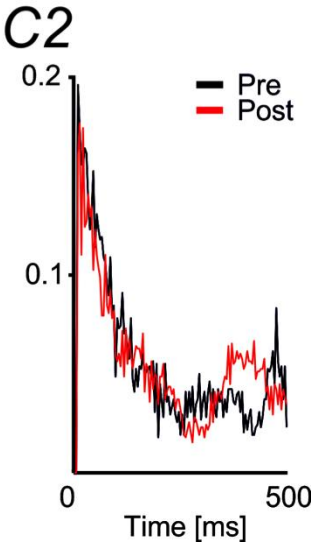




Averaged PSTH profile



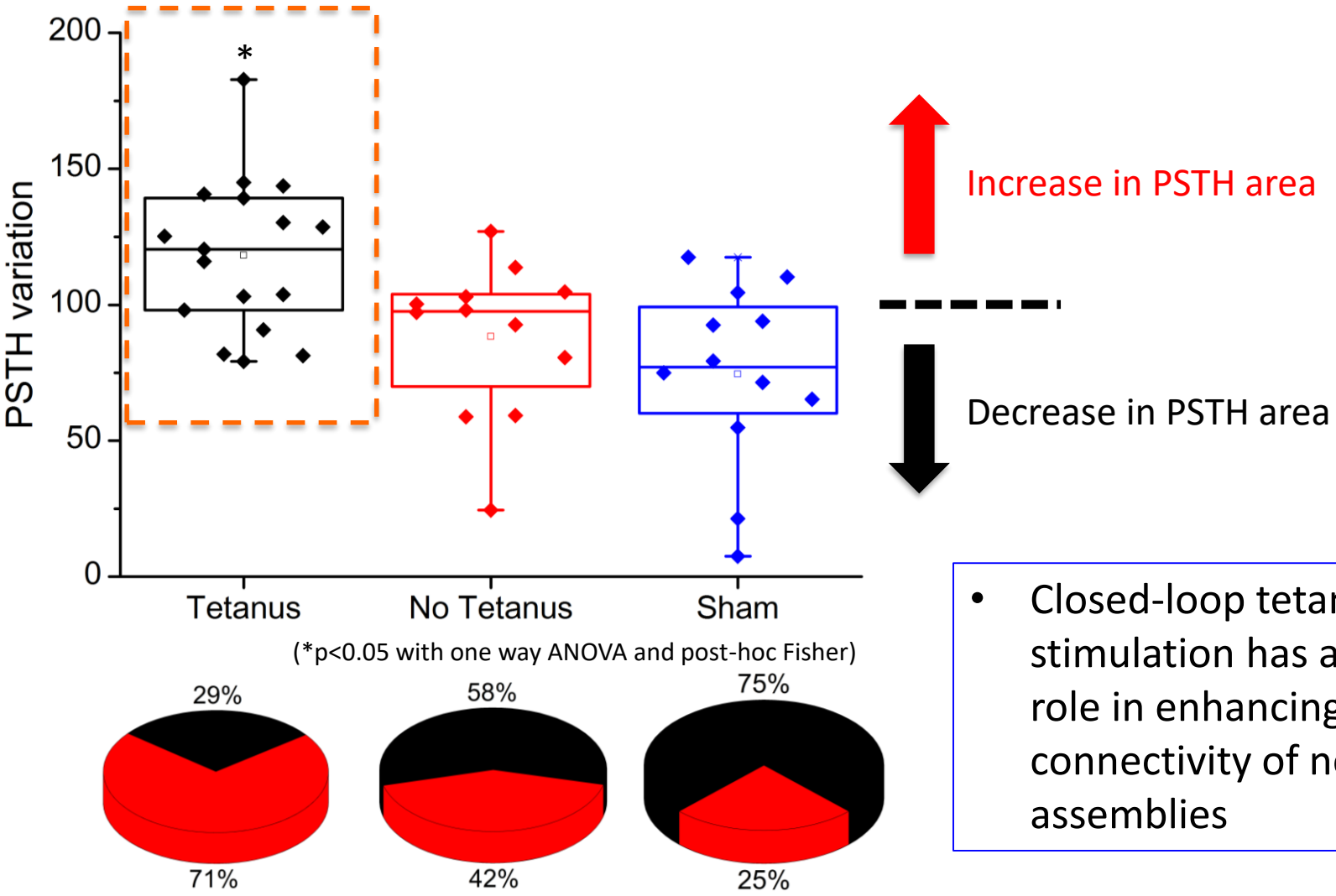




Ito el al., ***EMBEC '17 & NBC '17***, 2017

Changes in the network activity

D Ito



- Closed-loop tetanic-stimulation has a critical role in enhancing connectivity of neuronal assemblies

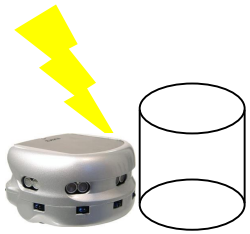
Red: increase in PSTH area, Black: decrease in PSTH area

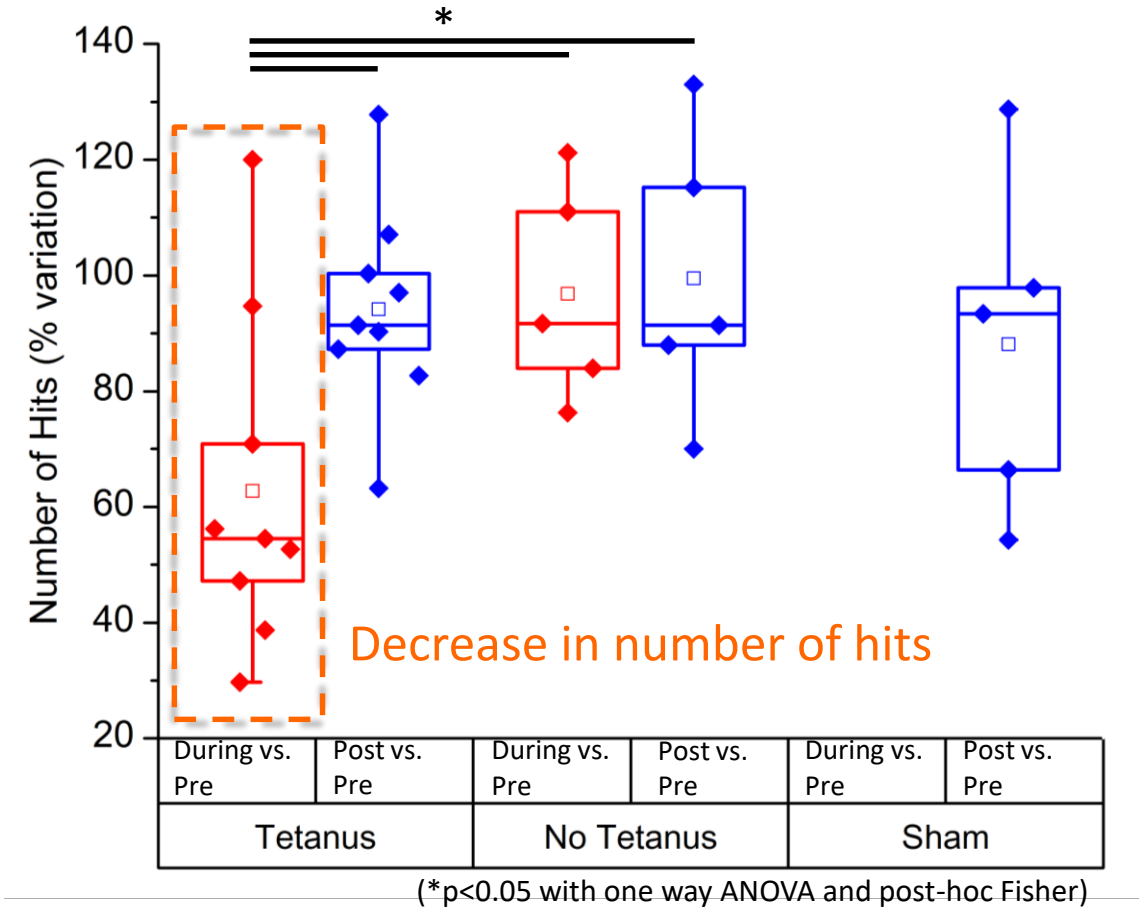
Ito el al., ***EMBEC '17 & NBC '17***, 2017

Changes in robotic performances


D Ito

Variation of number of hits





(*p<0.05 with one way ANOVA and post-hoc Fisher)

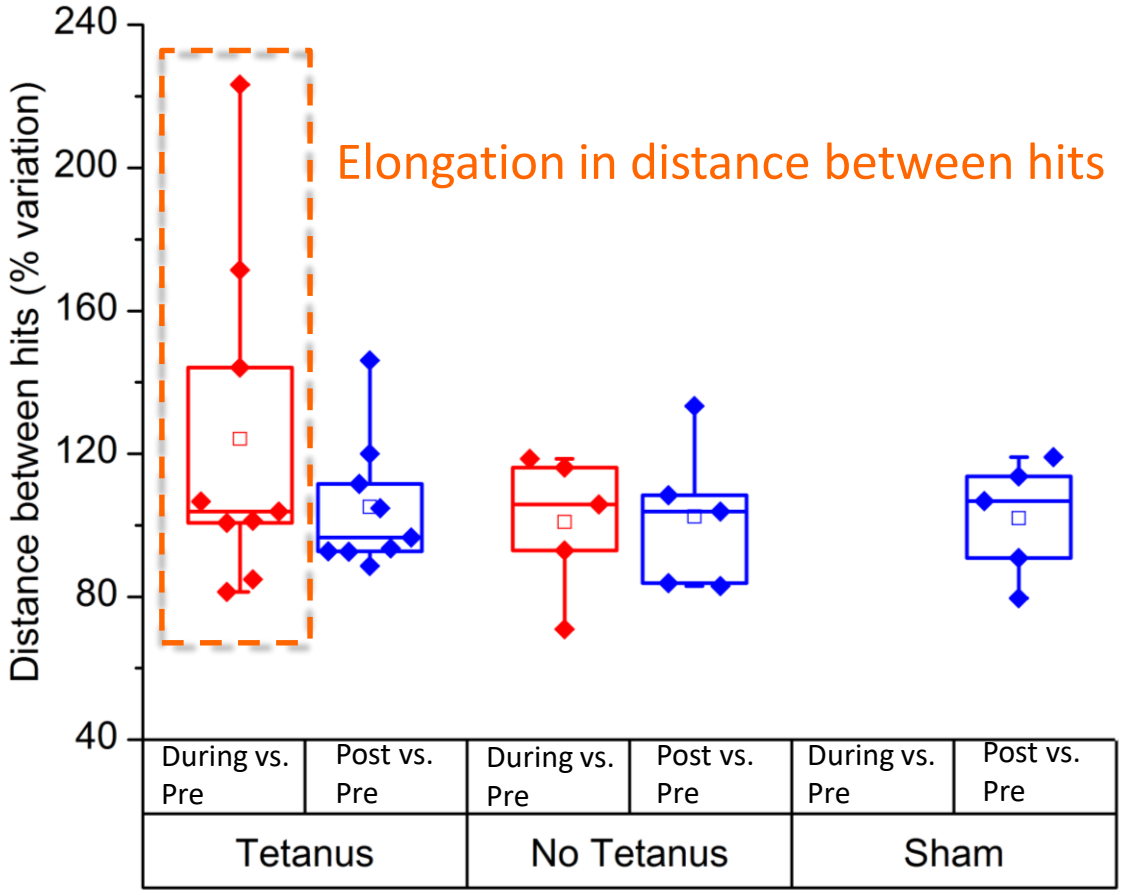
- Robot performance was improved during Tetanic stimulation robot run
- In no tetanus experiment the improvement was not found.

Ito el al., ***EMBEC '17 & NBC '17***, 2017

Changes in robotic performances

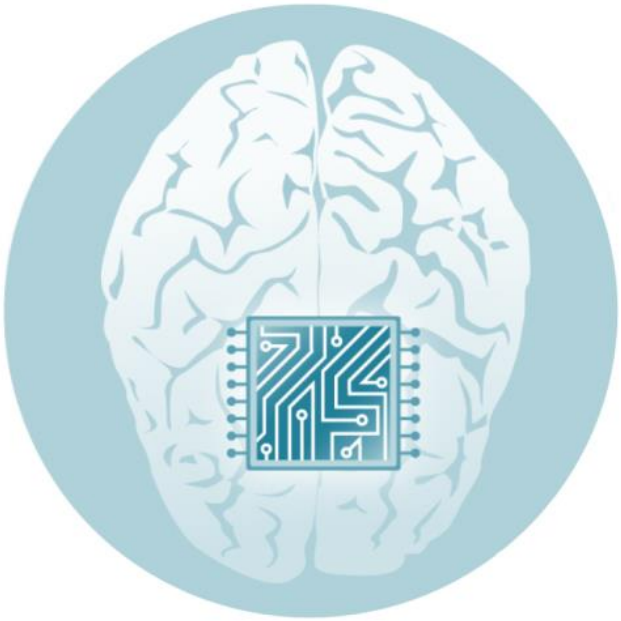
D Ito

Variation of distance between hits



(No significant differences among each experimental condition)

Ito el al., ***EMBEC '17 & NBC '17***, 2017



*How can we **restore** an injured or pathological communication through **an artificial device**?*

Future and Emerging Technologies
FET Open

S. Micera

G. Ruffini

"… jump on the way towards future European scientific and industrial leadership in areas that today simply do not exist yet..."

BRAIN BOW

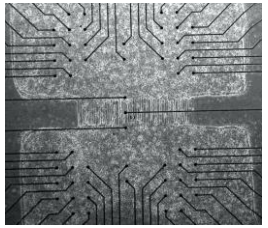
New Knowledge

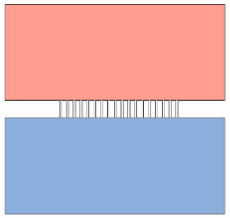
New Technologies and their Applications

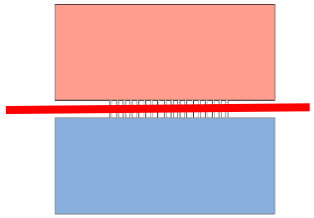
BrainBow's experimental framework

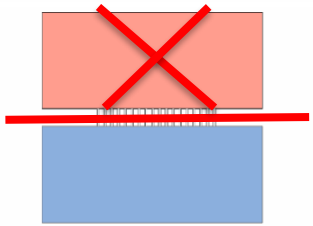
Provide the **technological tools** to design **next-generation neuroprostheses** aimed at restoring injuries at the level of the brain ('**brain-prostheses**')

Develop a **proof of principle** with ***in vitro*** **systems**



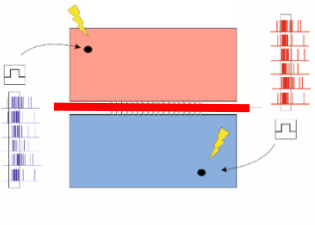


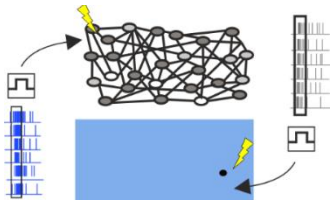




Bidirectional Bridging - BB

Hybrid Bidirectional Bridging - HBB

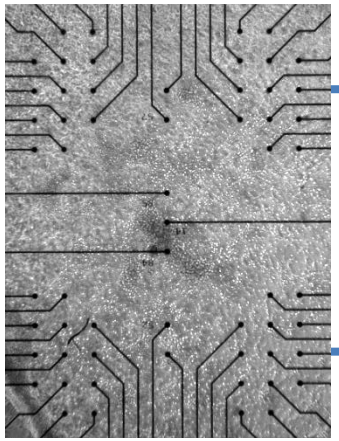




Real-time closed-loop system


Y Bornat

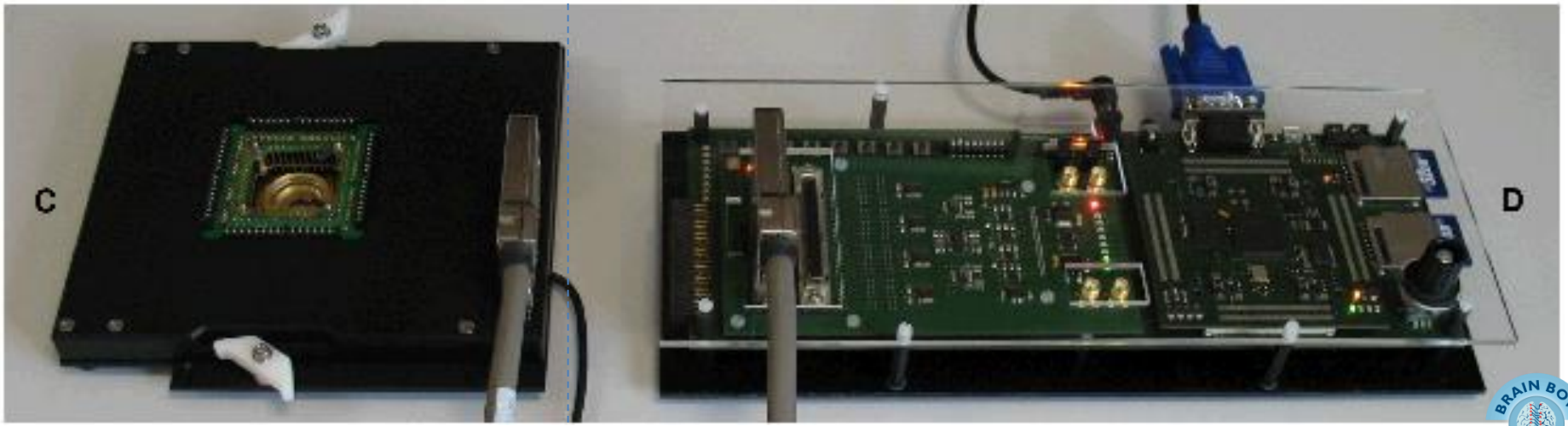

T Levi



Event Processing

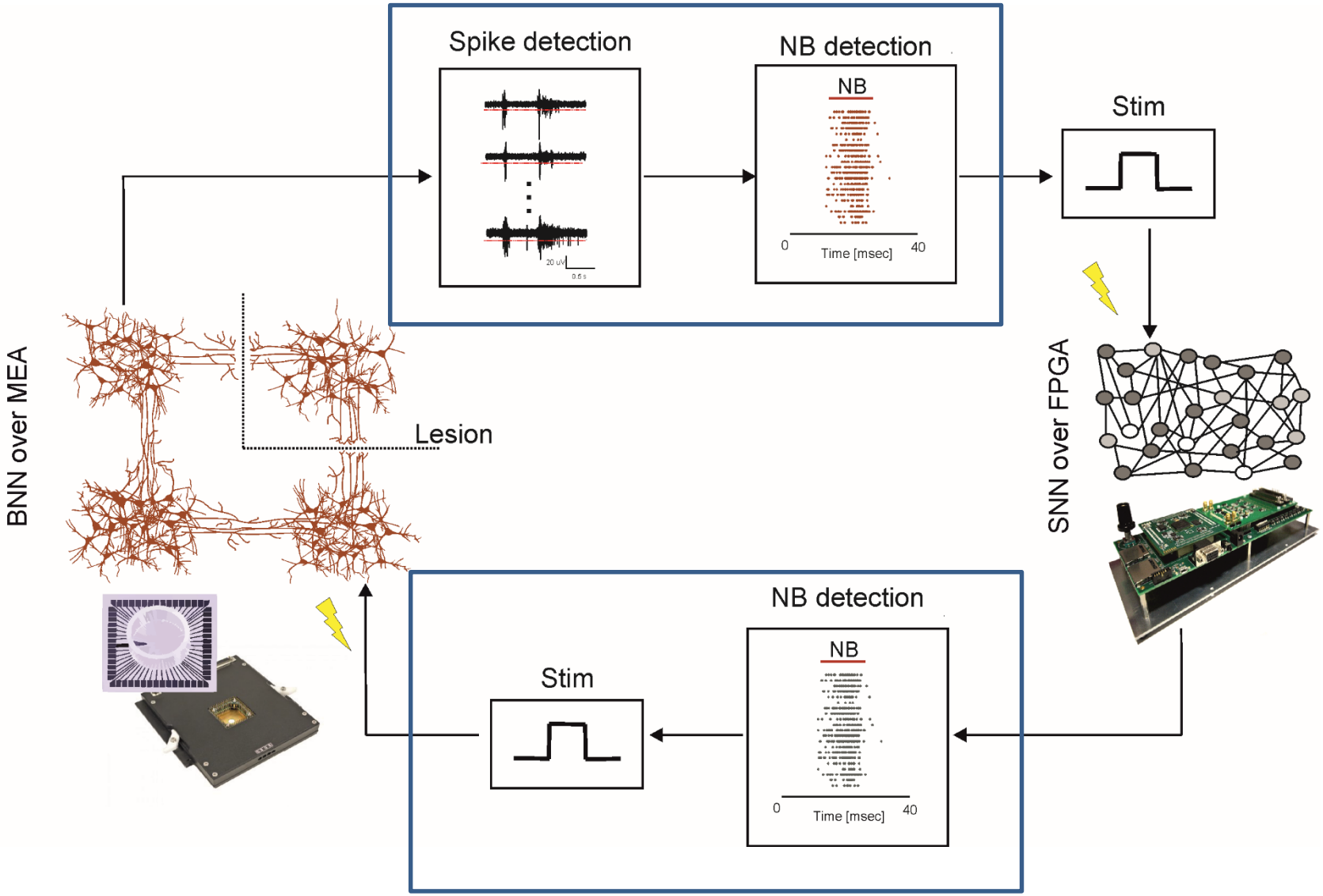
Event detection

Trigger generator

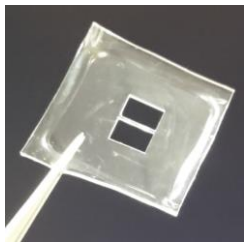


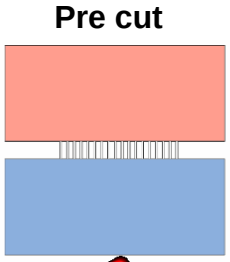
Bonifazi et al., ***Front Neural Circuits*** (2013); *Bonifazi et al.* ***IEEE NER Conference****, 2013*

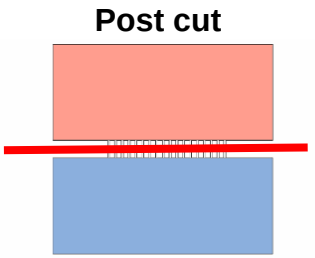
Real-time detection, processing, triggering



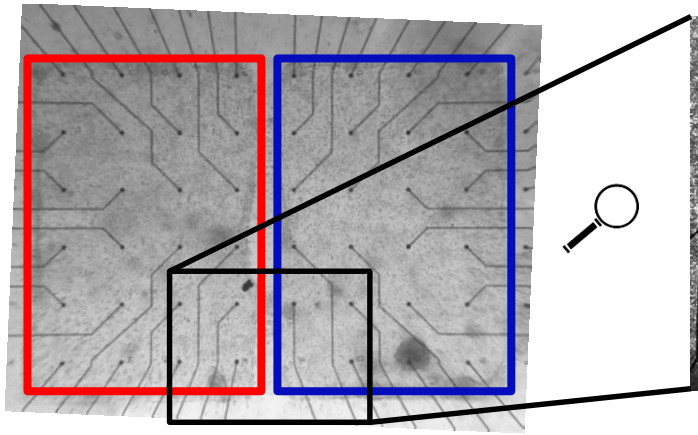
Experimental framework

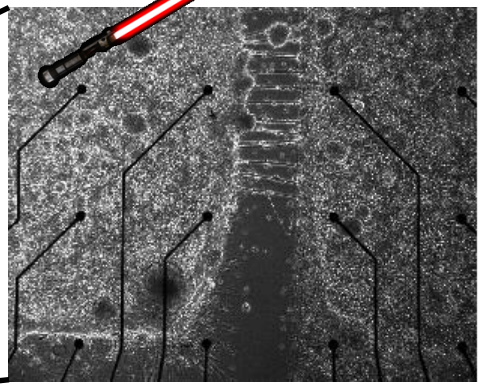




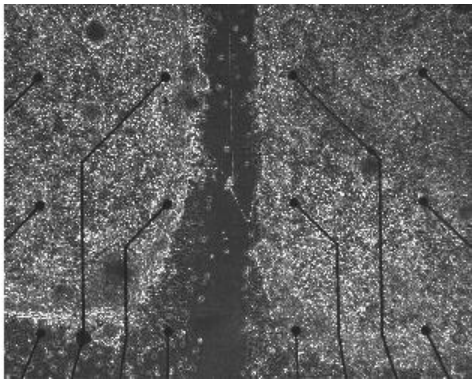


Laser-cut performed



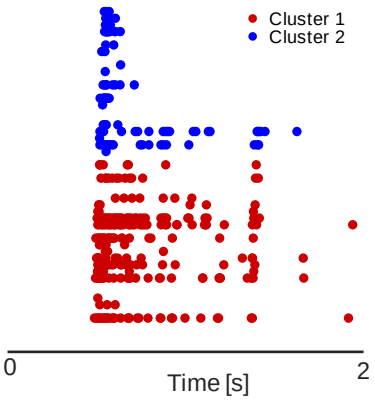


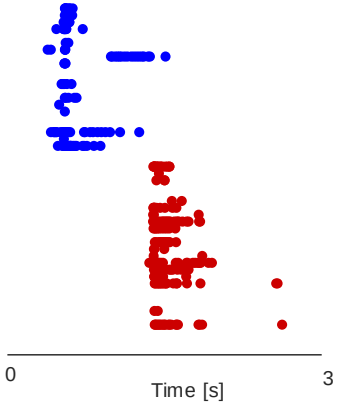
Pre-lesion



Post-lesion

Bimodular cultures





S Buccelli

L Martines

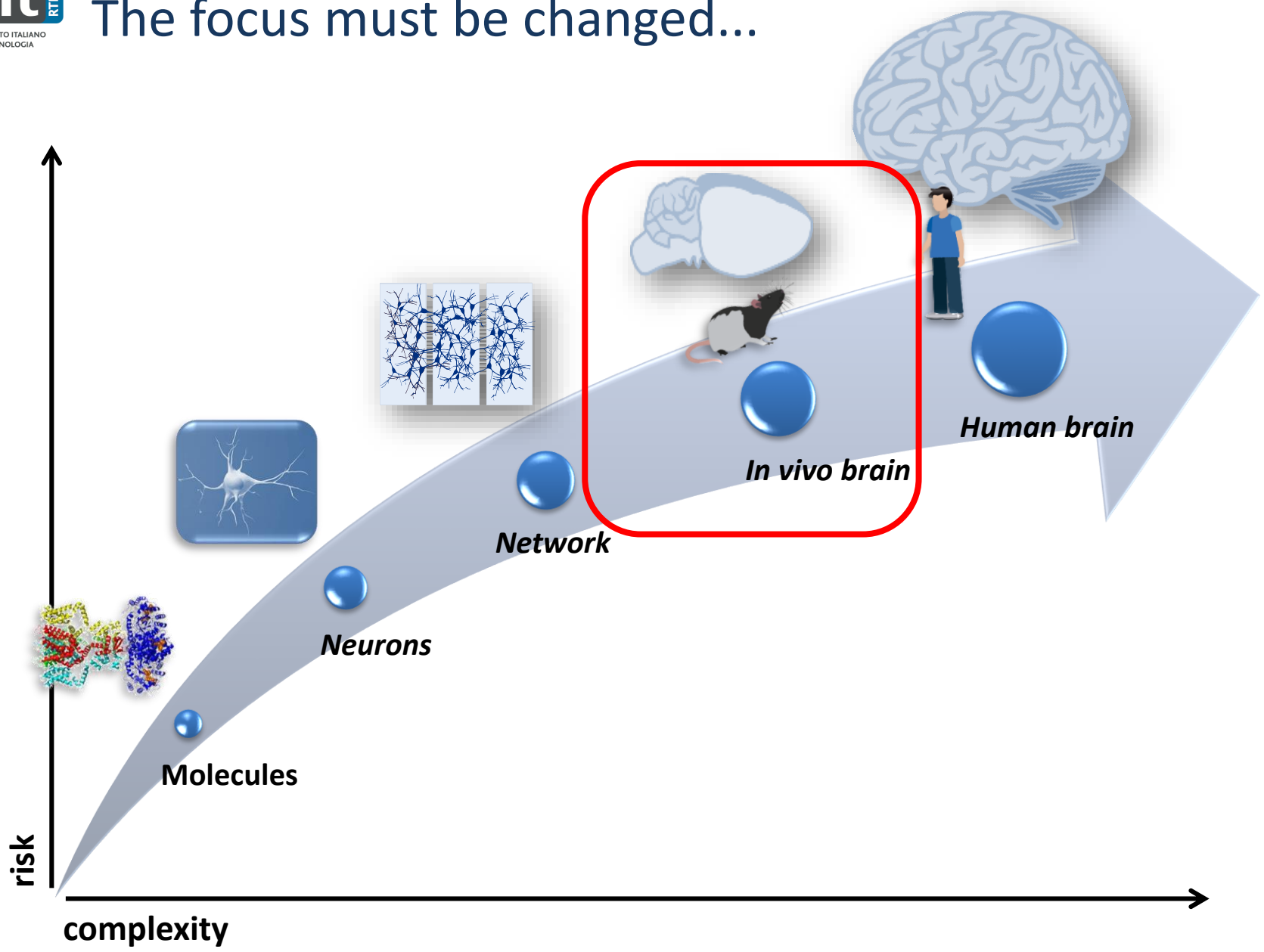
A Averna

I Colombi

F Difato

Buccelli et al., *submitted*; Soloperto, Bisio et al., ***Molecules*** 2016

The focus must be changed...



ISTITUTO ITALIANO
DI TECNOLOGIA

To in vivo…

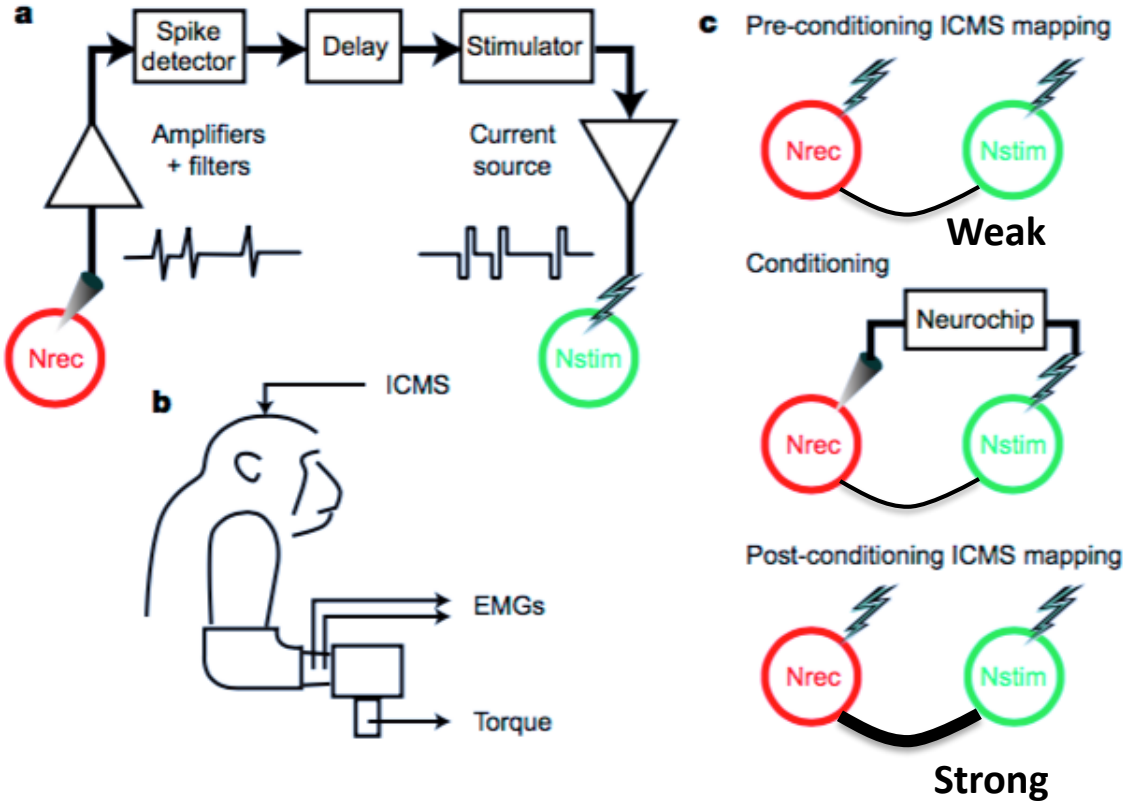
Exploiting Hebbian Conditioning

When one cell repeatedly assists in firing another, the axon of the first cell develops synaptic knobs… in contact with the soma of the second cell'

Donald Hebb (Wiley, New York) 1949
The Organization of Behavior

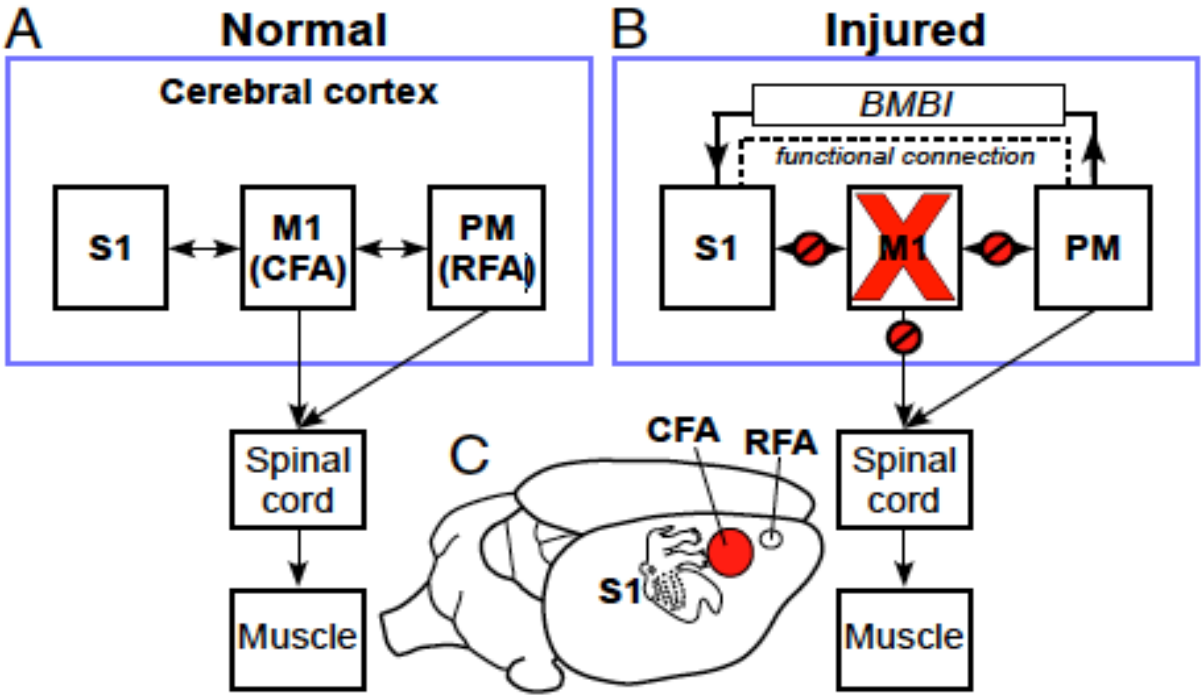
'Cells that fire together, wire together'

Carla Shatz 1992
The developing brain, Scientific American 267



Jackson et al. *Nature* 2006

Exploiting Hebbian Conditioning In Vivo



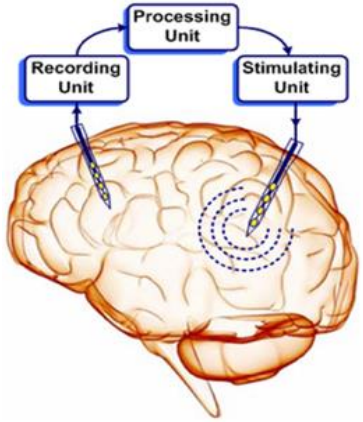
Restoration of function after brain damage using a neural prosthesis
(Guggenmos et al., PNAS – Dec 24th, 2013)

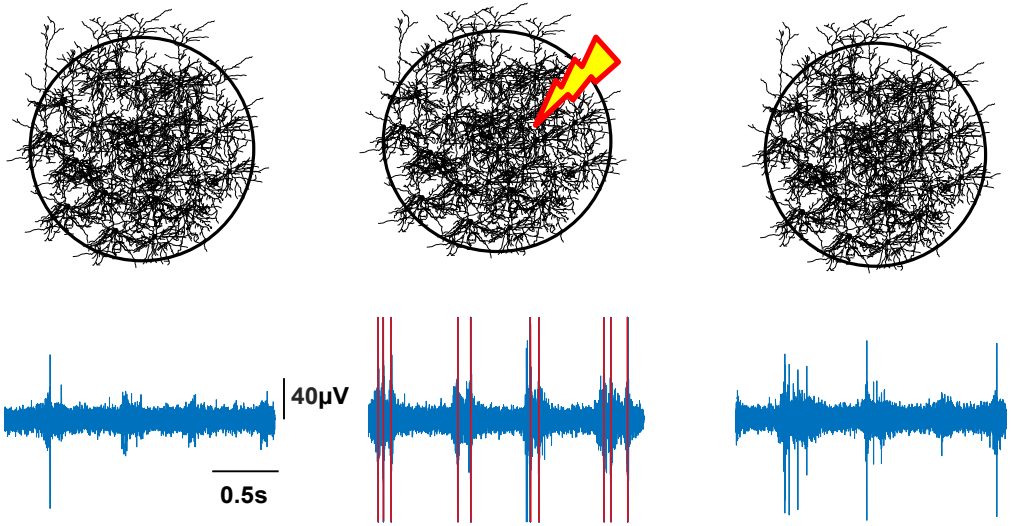
Investigating neural correlates of behavioral improvement

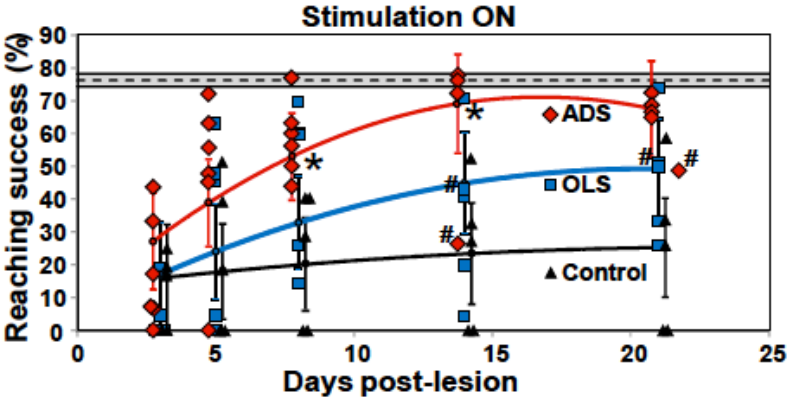
RJ Nudo

D Guggenmos

KU MEDICAL CENTER
The University of Kansas







Restoration of function after brain damage using a neural prosthesis (Guggenmos et al., PNAS 2013)

Promote recovery of functions after injury by stimulating neurons in the brain thanks to innovative protocols (closed loop ADS vs open loop RS) and technologies

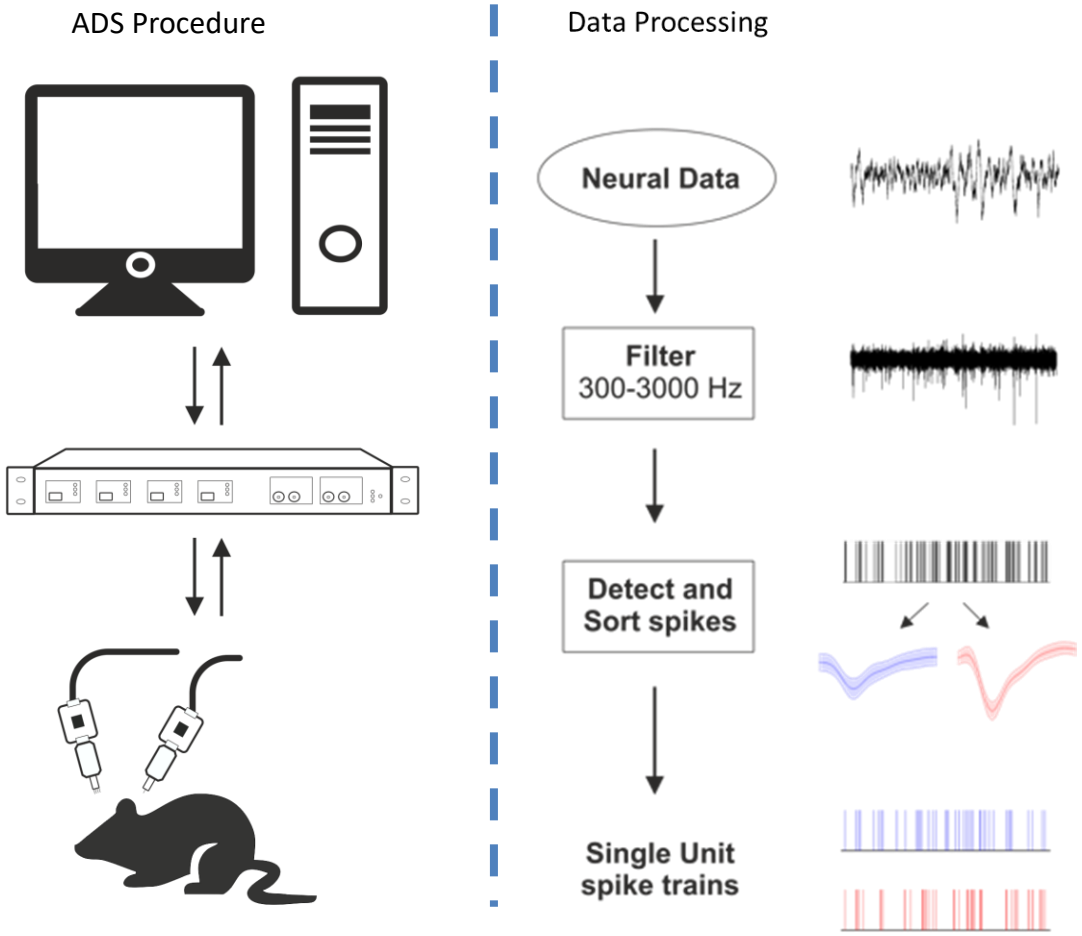
A Averna

ISTITUTO ITALIANO DI TECNOLOGIA

Farnesina
Ministero degli Affari Esteri
e della Cooperazione Internazionale

Averna A, Pasquale V, Van Acker G, Murphy M, Rogantin MP, Nudo RJ, Chiappalone M* and Guggenmos D*. **Intracortical microstimulation induces changes on firing patterns of distant cortical areas**. *(submitted)*

Investigating neural correlates of behavioral improvement




A Averna


F Barban


M Murphy

Experimental protocols & scientific questions

*Characterize electrophysiological effects of intracortical microstimulation on both **healthy** and **injured** cortical networks in rodent models*

Healthy Anaesthetized

Can ICMS change in INTRA-cortical activity?

Is the response to ICMS dependent on the temporal distribution of the stimuli?

Healthy Chronic

How persistent is the effect of stimulation? What is its extinction rate?

Injured Anaesthetized

What is the electrophysiological effect of a focal lesion?

What is the ability of ADS to modulate such effect?

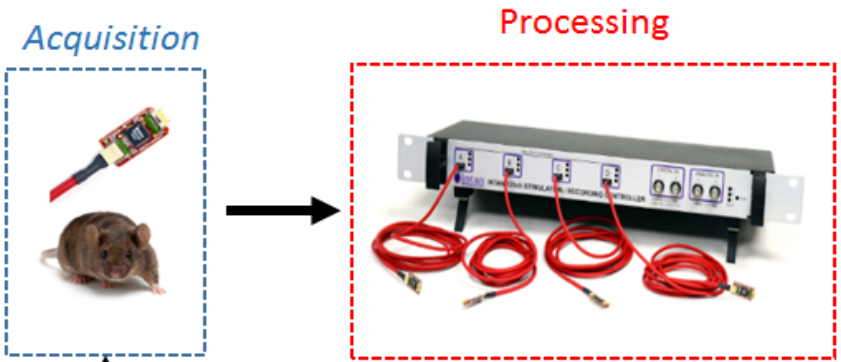
D Guggenmos

A Averna

Averna A, Guggenmos D, Pasquale V, Semprini M, Nudo R, and Chiappalone M. **Neuroengineering tools for studying the effect of intracortical microstimulation in rodent models**. *40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC'18)*. Honolulu (HW, USA), July 18-21, 2018. ***Selected as oral contribution***

Technological improvements: real time data processing

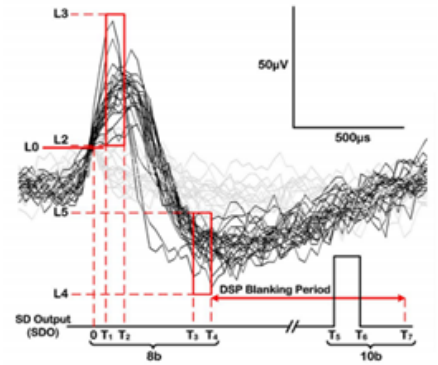
Improving commercial **low-cost** setup



Original Spike detection:
single hard threshold

Stimulation

Implemented spike detection algorithm



Reduced **false positive** spike detection thanks to multiple windows discriminator

S Buccelli

M Murphy

Murphy*, Buccelli* et al. ***In preparation***

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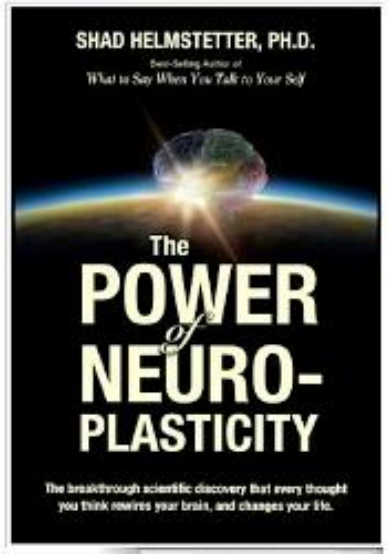
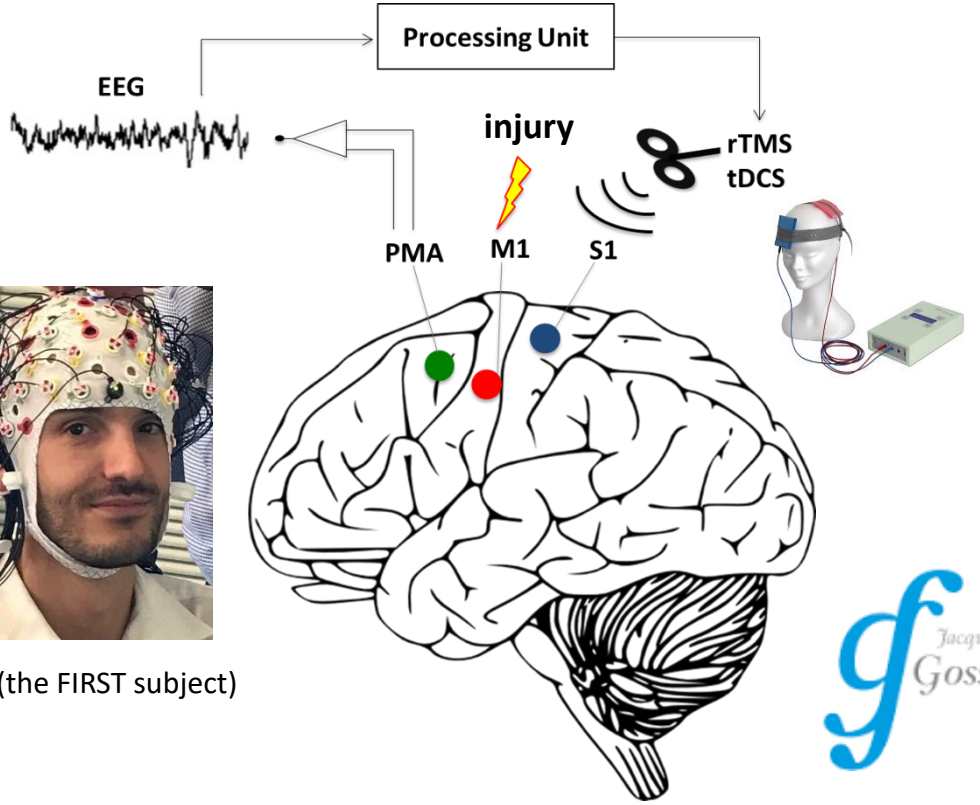
…And beyond!

Neuromodulation and Neurorehabilitation

- Understand the **principles underlying neuroplasticity** by developing novel **stimulation** strategies for **controlled neuromodulation** of brain activity to enhance rehabilitative processes.
  - Experimental protocols for **invasive and non-invasive stimulation** could be investigated and exploited for brain rehabilitation and repair.





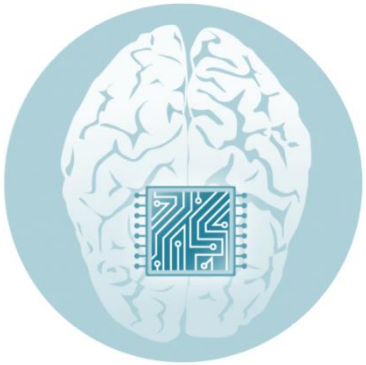
S Buccelli (the FIRST subject)

M Semprini

F Barban

Jacques & Gloria Gossweiler Foundation

*How can we **restore** an injured or pathological communication through **an artificial device**?*



...developing **innovative devices** that can communicate with the nervous system

...developing **personalized interventions (closed-loop)** suited to the patient and to a specific disease

...**robotic devices** able to dialogue with the nervous systems

Beyond Neuroengineering…

Is the brain a good model for machine intelligence?

To celebrate the centenary of the year of Alan Turing's birth, four scientists and entrepreneurs assess the divide between neuroscience and computing.

TURING AT 100
A legacy that spans science:
nature.com/turing

DENNIS BRAY

Brain emulation requires cells

Department of Physiology, Development and Neuroscience, University of Cambridge

Take-home keywords

- Brain diseases
- Neurohybrid
- Complexity
- Dynamical Richness
- Intelligence

Take-home messages (and hopes)

- Talk more to people with different background: promote events like this!
- Exploit what is already there (do not re-invent the wheel)
- Find synergies

Brooks, R., Hassabis, D., Bray, D. & Shashua, A. ***Nature*** *482, 462-463, (2012).*