Burst Initiation Points displacement upon Electrical Stimulation

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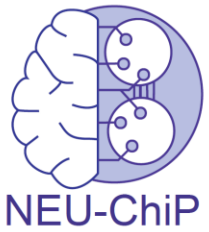
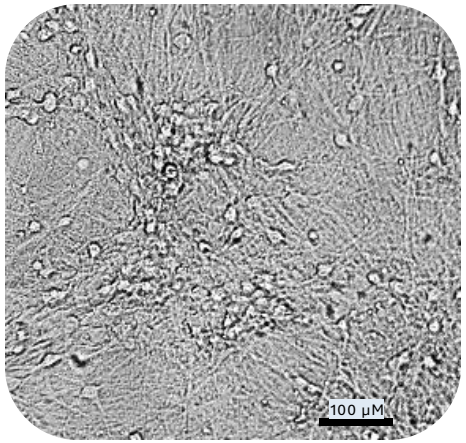
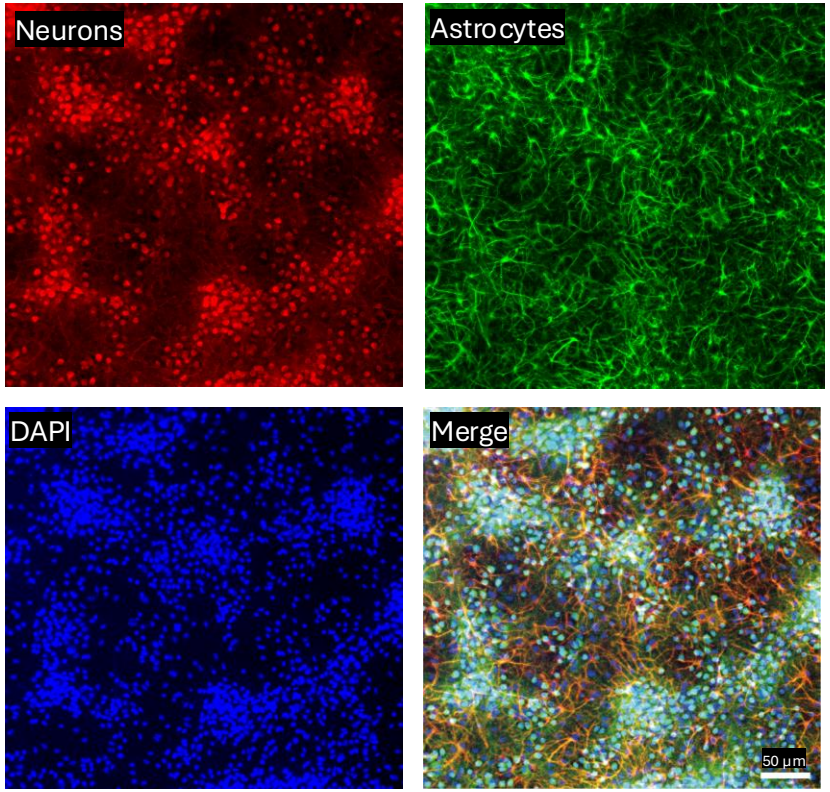
Cargèse, 25 October 2024

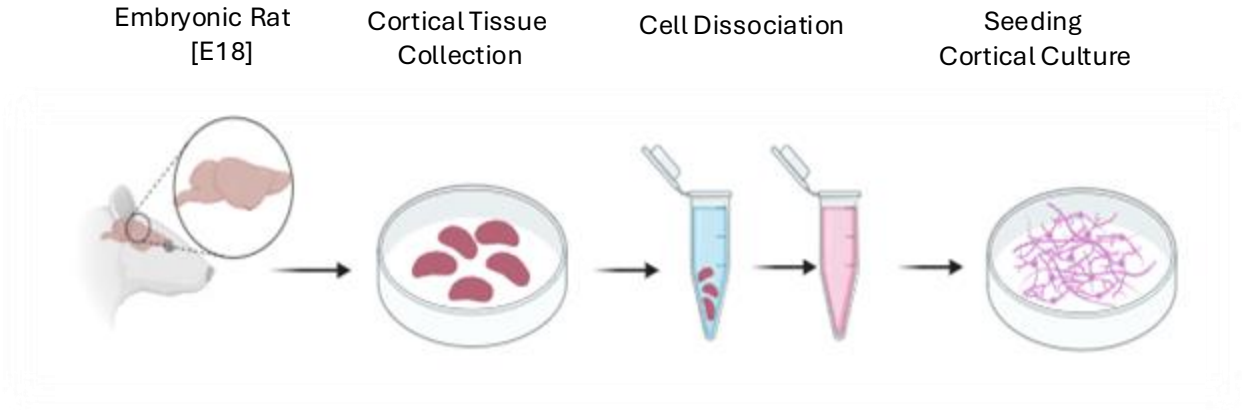


In-vitro cell culture

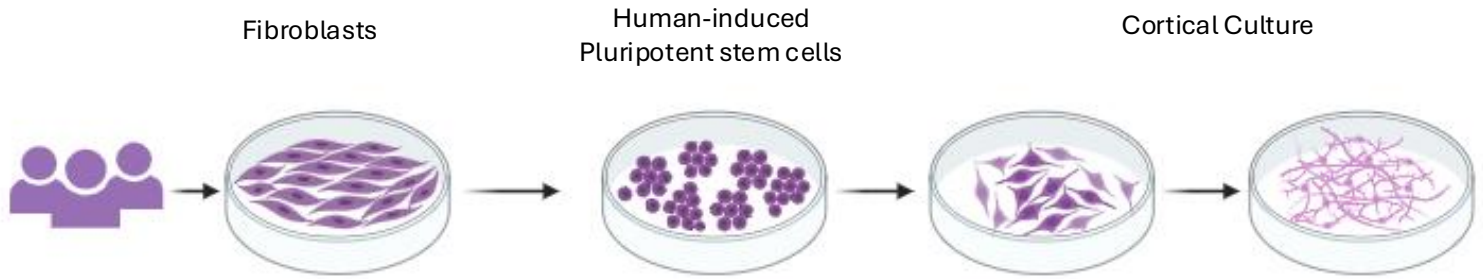




Primary neuronal culture

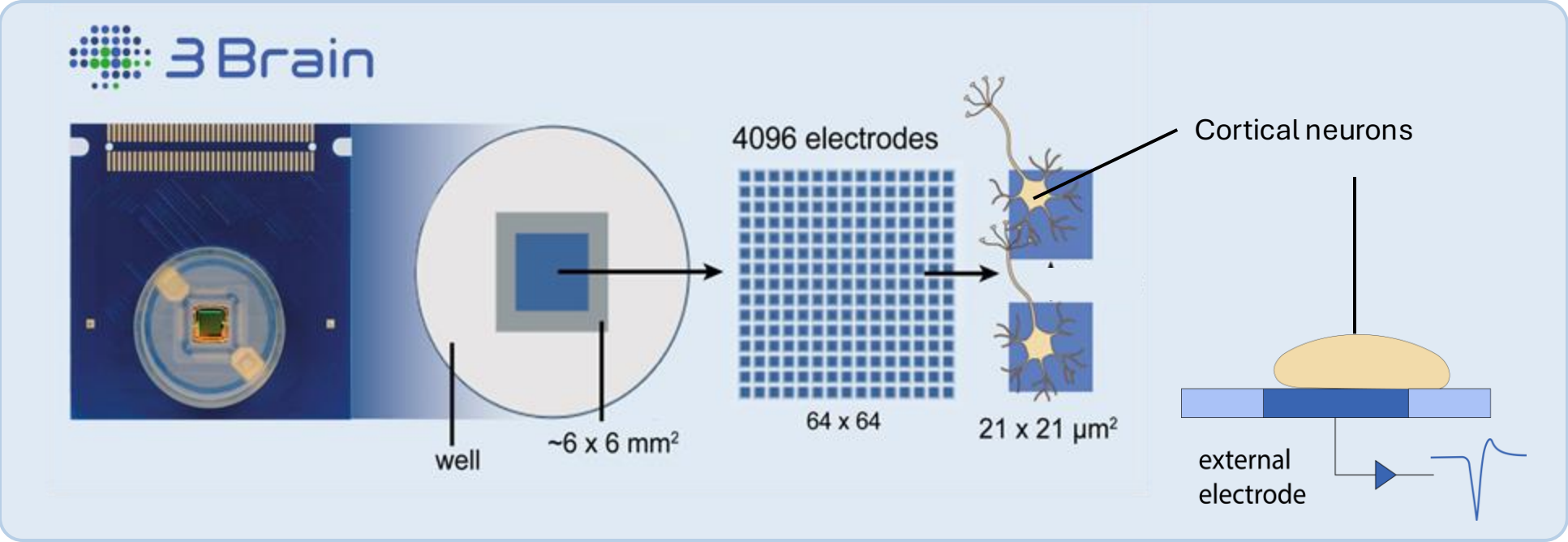


Human iPSC-derived neuronal networks



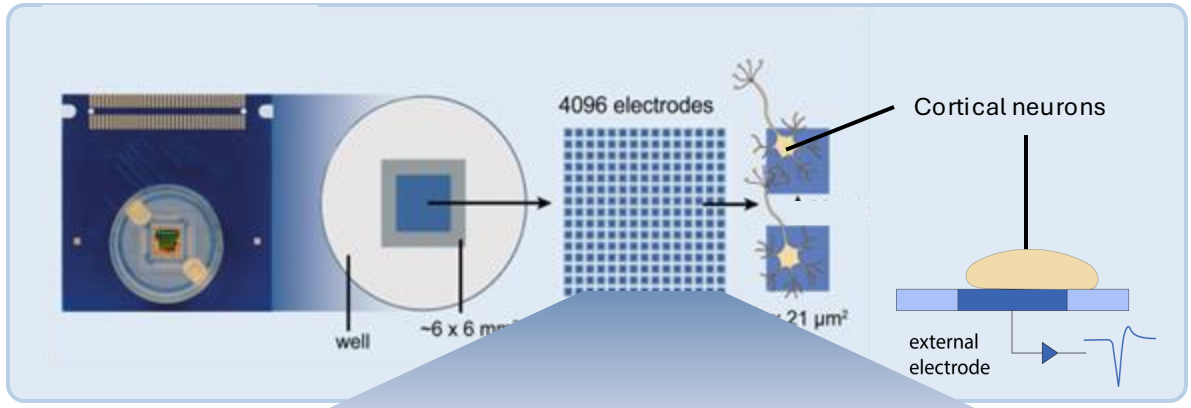
[1] S. Wang et. al 2023

Neuronal activity development on multielectrode arrays

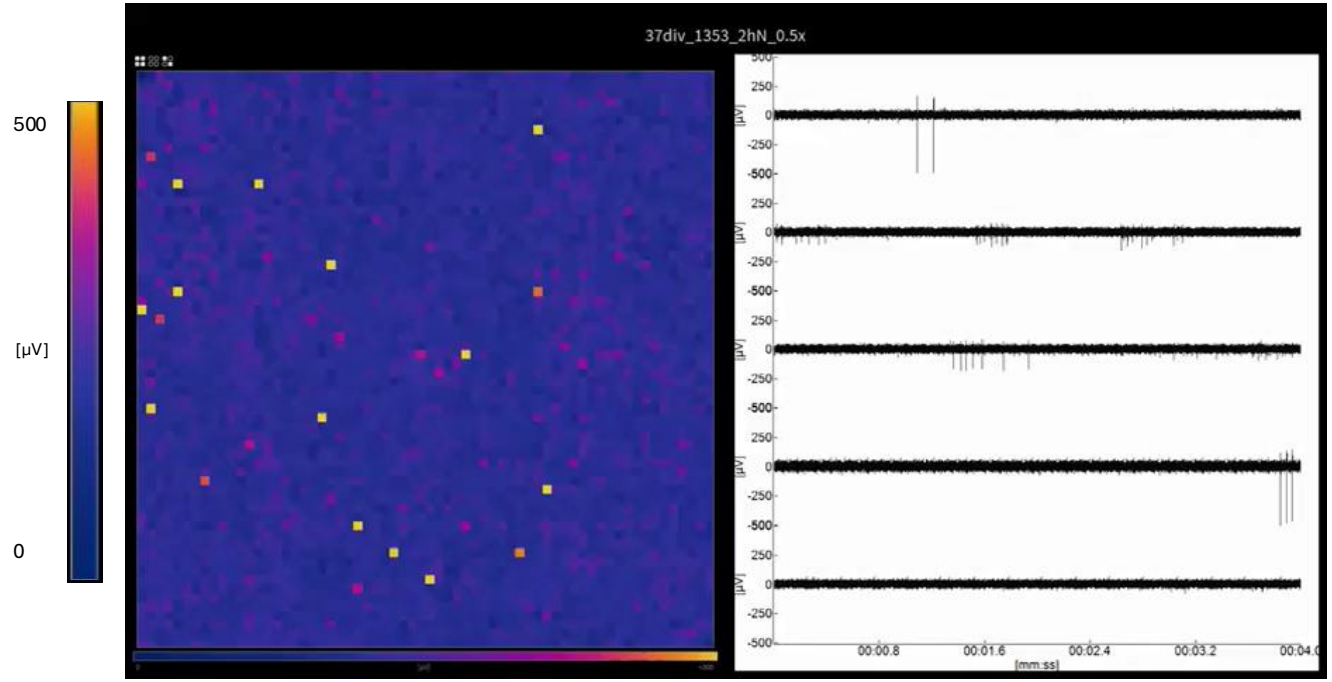


- High-resolution tracking of neuronal activity dynamics.
  - Valuable data for modelling neural networks and understanding neuroplasticity and therapeutic strategies.
- Monitor the same network over different time points.

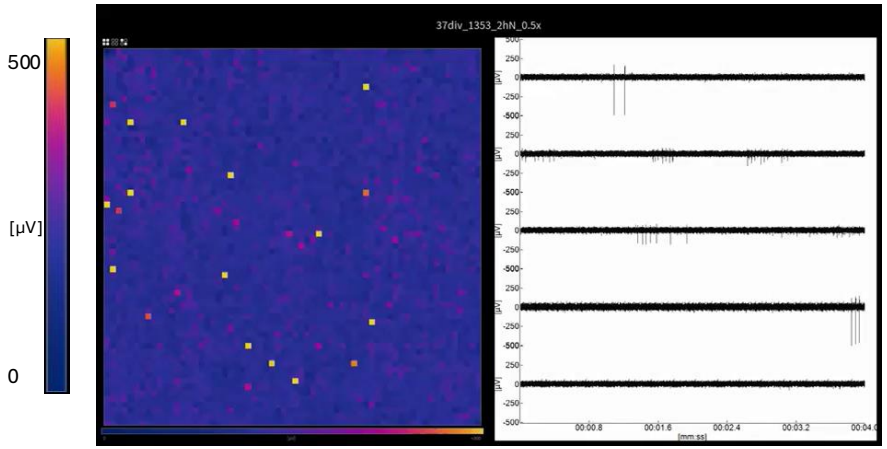
Neuronal activity development on multielectrode arrays



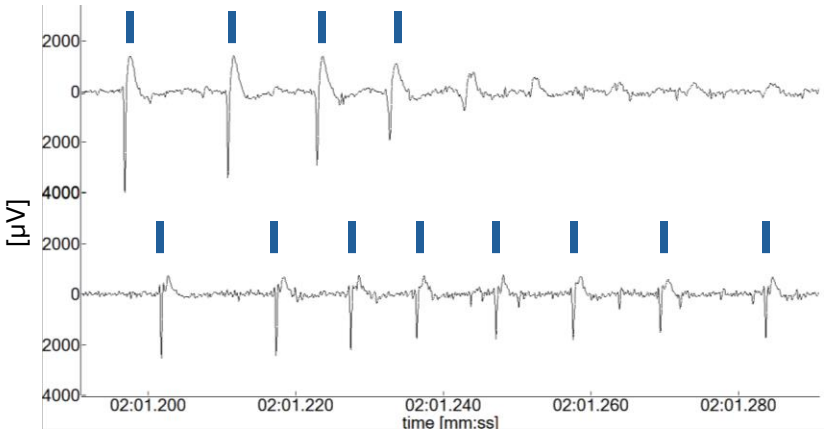
Raw activity map **Selected raw traces**



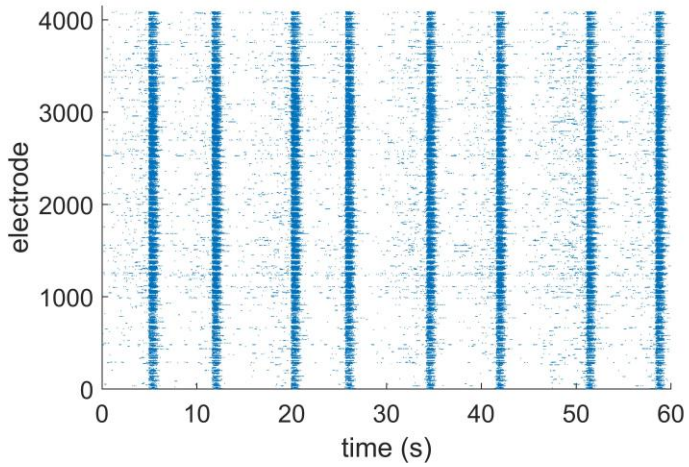
Neuronal activity development on multielectrode arrays



Raw traces

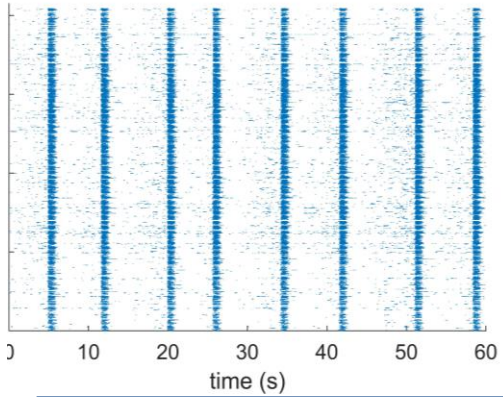


Raster plot

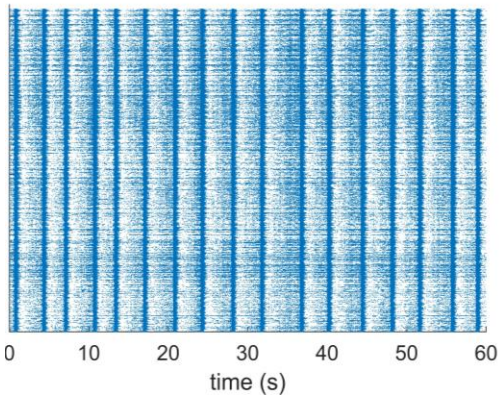


Dynamic changes in neuronal functional activity over time

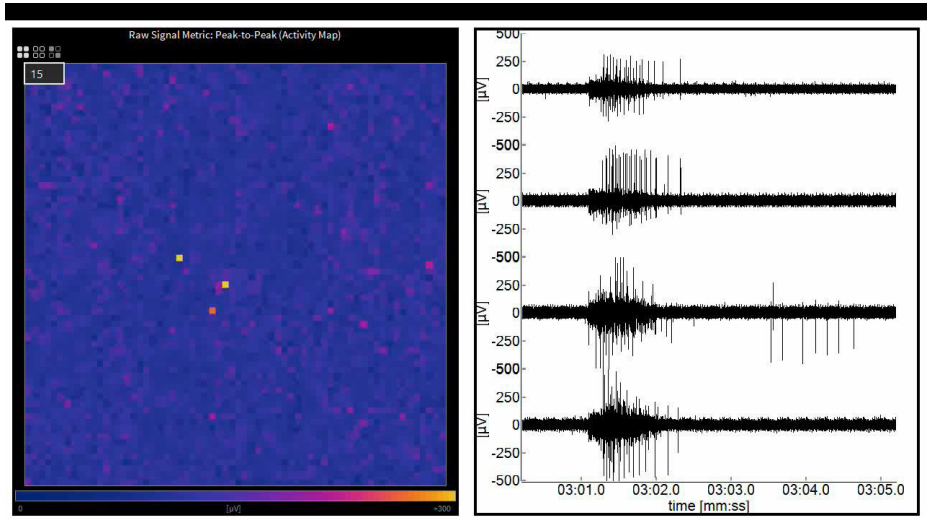
Early timepoint

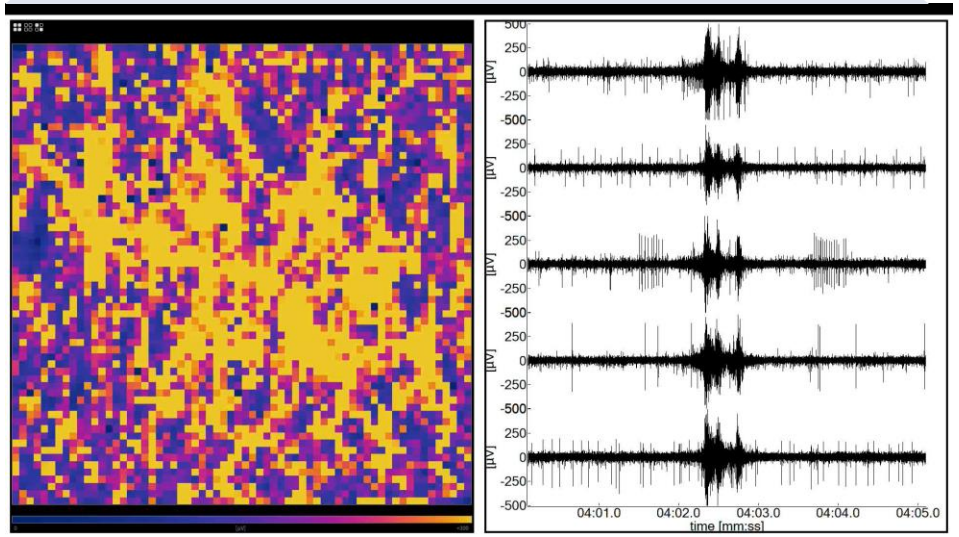


Late timepoint

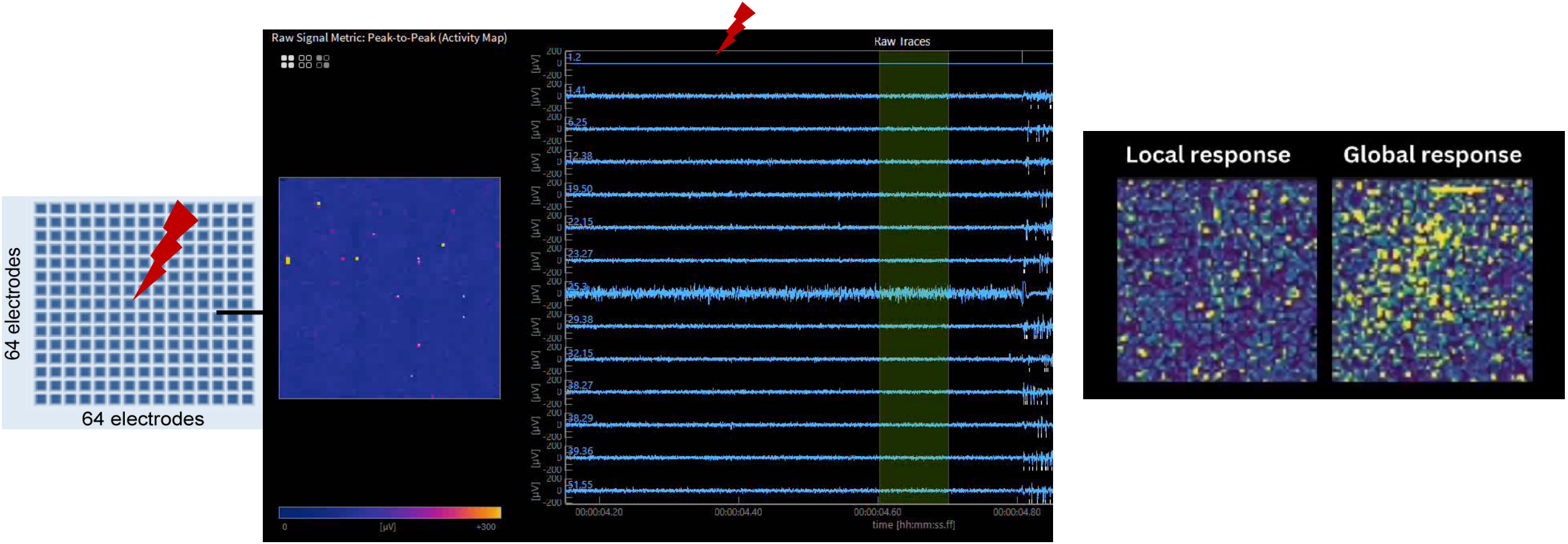


- Stronger network activity over time.
- Synchronicity levels are increased gradually.

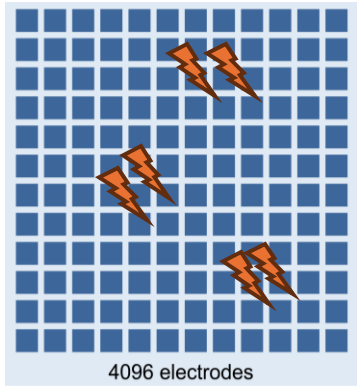


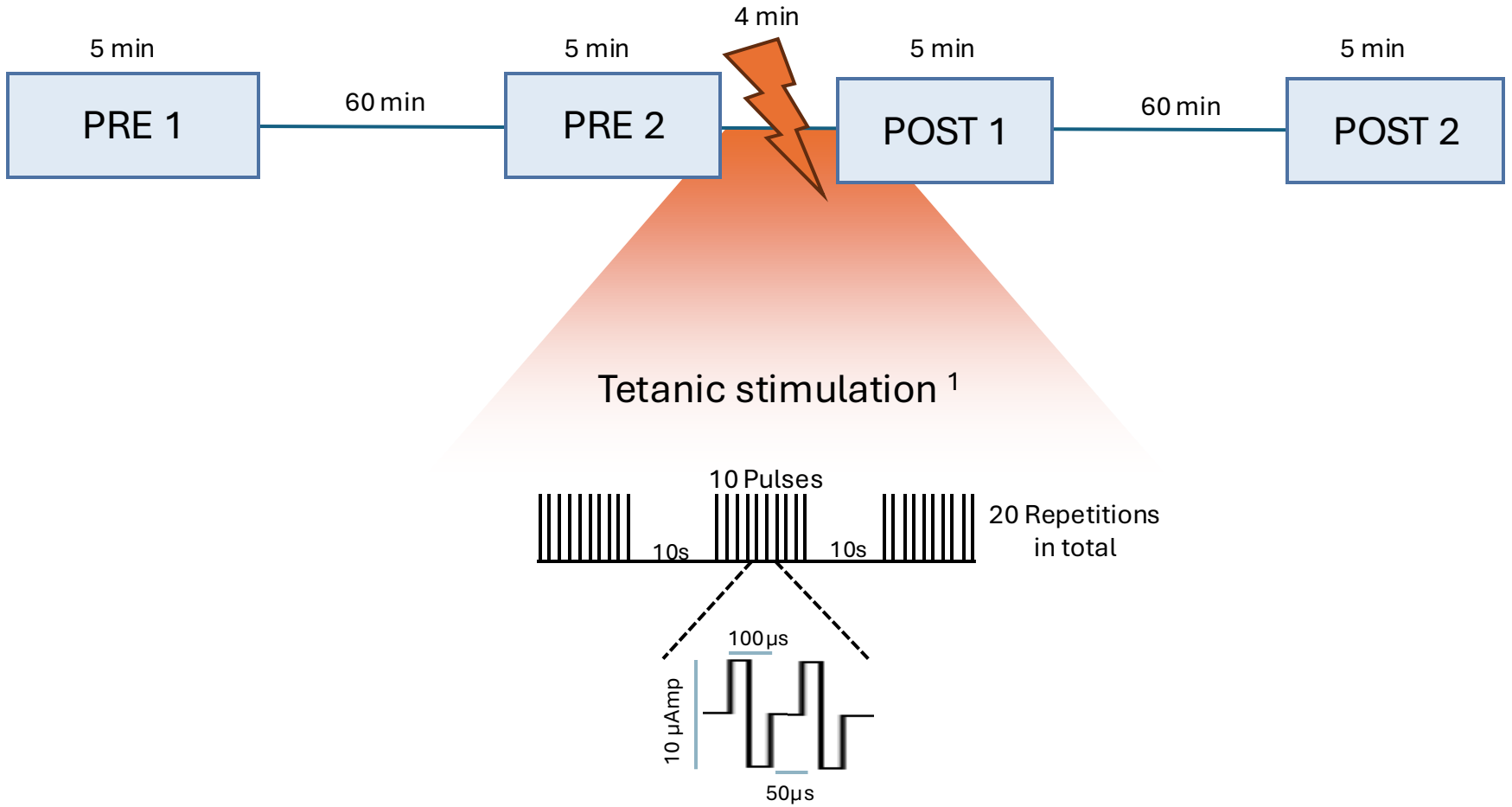


Electrical stimulations to investigate neuronal plasticity



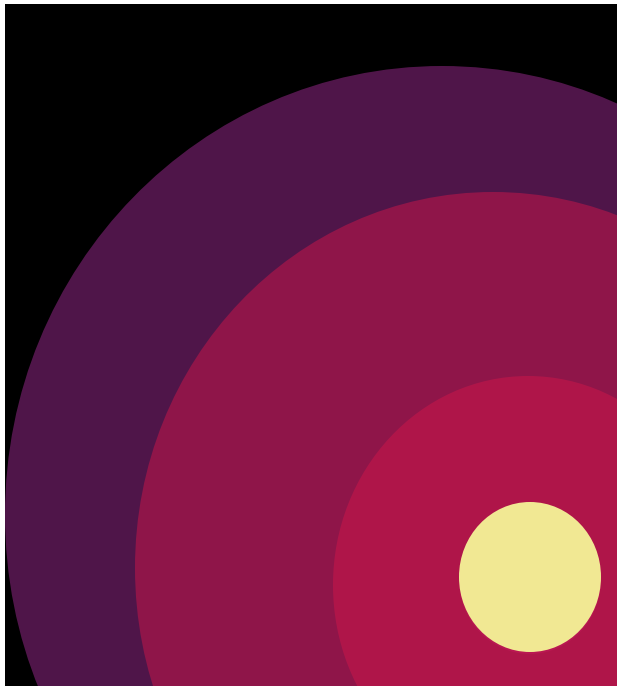
Experimental setup



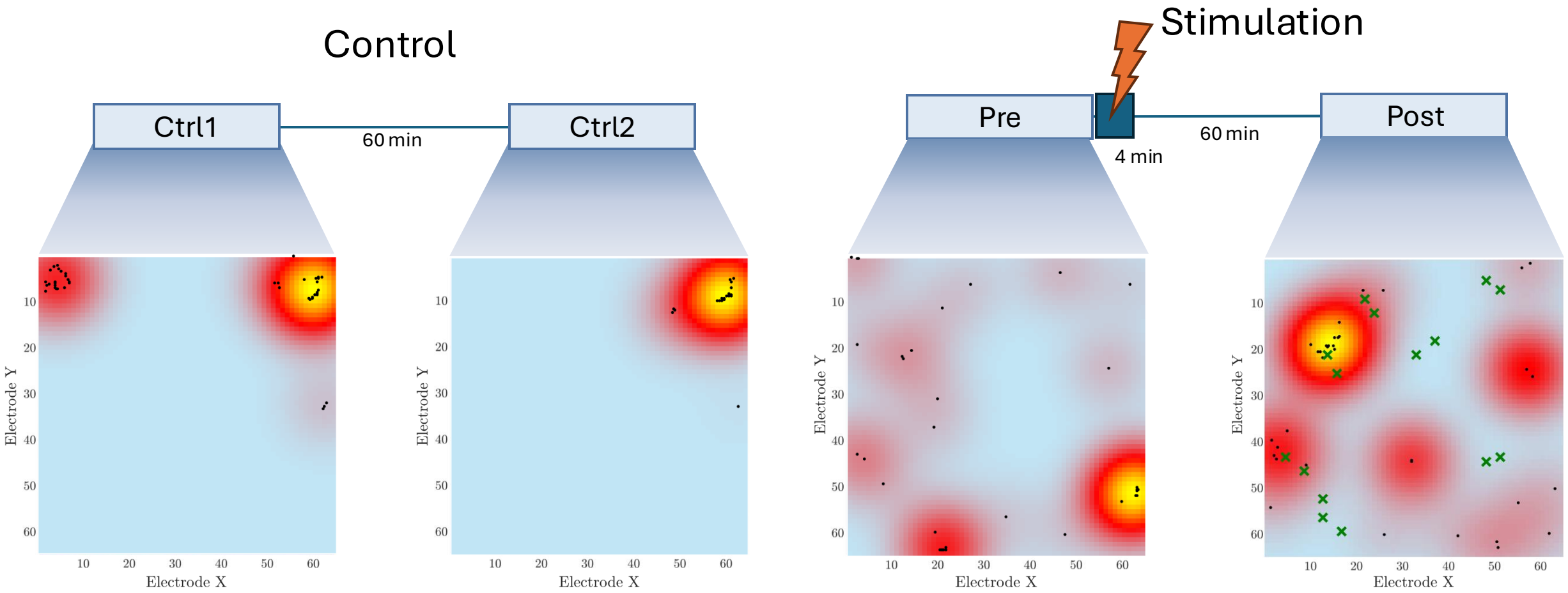


[1] M. Chiappalone et. al 2008

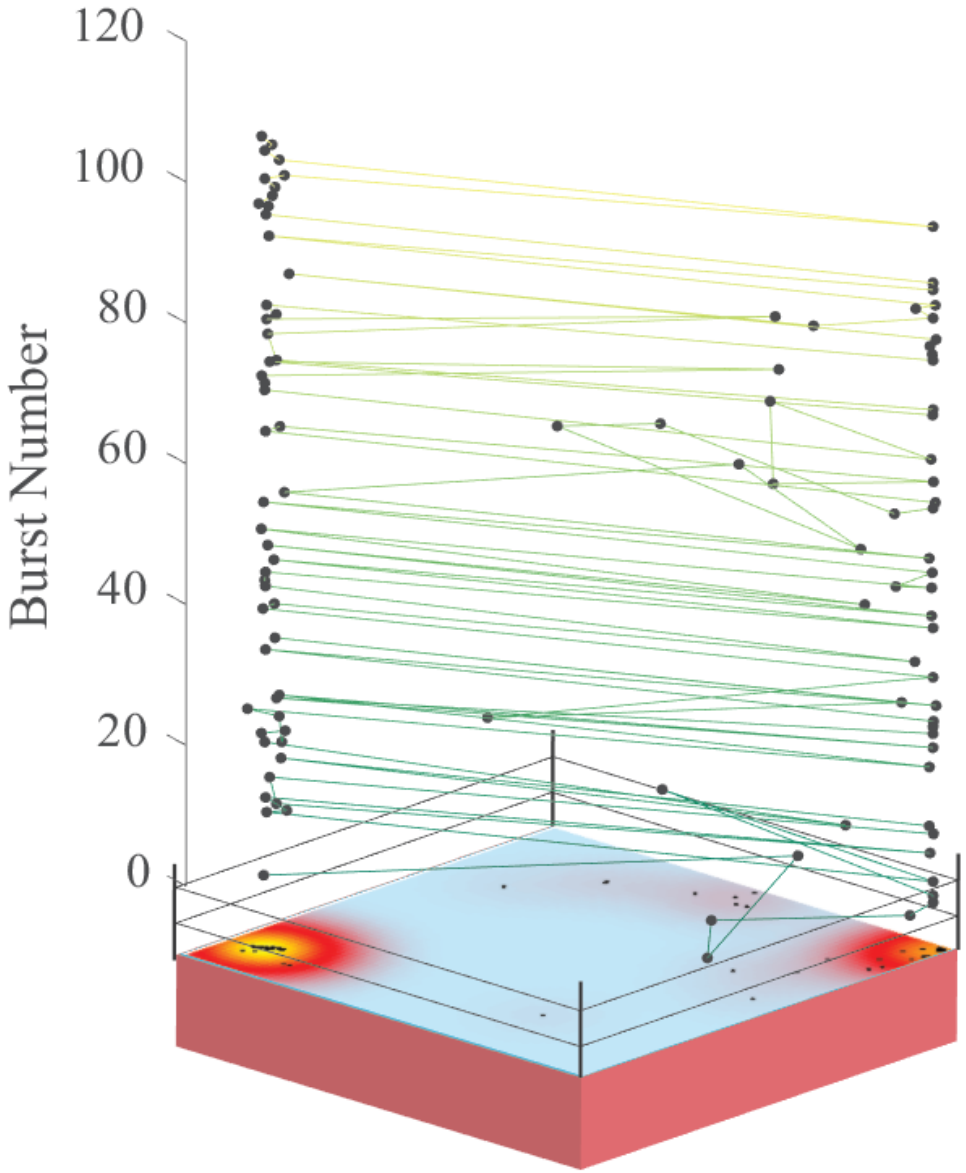
Explanation: Initiation point



Electrical stimulation induces changes in initiation points



Boxing model



- Initiation regions compete to trigger the collective bursts, leading to alternating origins.
- The existence of different zones can be hampered by the domination of a region with a higher natural frequency.
- Stimulation can modify this coupling, changing the leading initiation zone.

O. Feinerman, et al.,
J. Neurophysiol. (2007)

Connectivity analysis

O. Stetter, et al.,
PloS Comput. Biol. (2012)

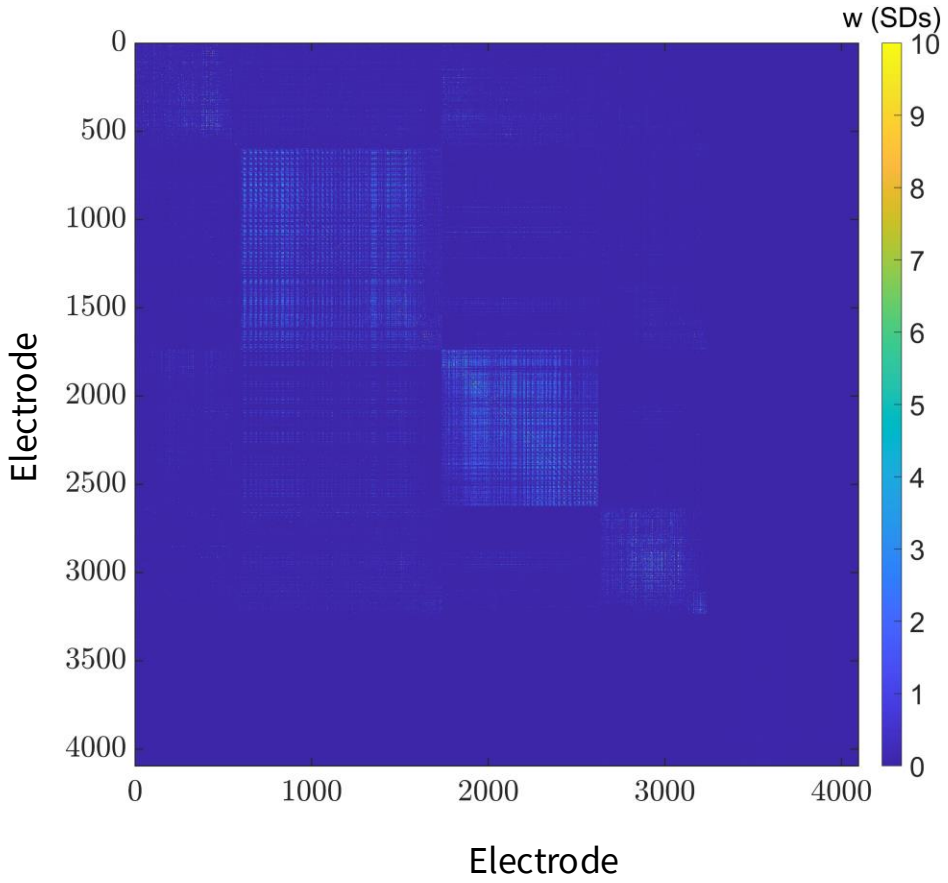
The connectivity matrix is obtained using the conditioned transfer entropy (TE)

$$TE^*_{Y\to X}(\tilde{g}) = \sum p(x_{n+1}, x_n^{(k)}, y_n^{(k)} | g_{n+1} < \tilde{g}) \log \frac{p(x_{n+1}|x_n^{(k)}, y_n^{(k)}, g_{n+1} < \tilde{g})}{p(x_{n+1}|x_n^{(k)}, g_{n+1} < \tilde{g})}$$

where $g_t = \frac{1}{N}\sum_{i=1}^{N} x_i(t)$ and $\tilde{g} = 0.1$

To account for firing rate effects, this value is normalised by the entropy of each time serie

$$TE^*_{Norm\ Y\to X} = \frac{TE^*_{\ Y\to X}}{-\sum p(x_n)\log p(x_n)}$$



Adjacency matrix (sorted by communities)

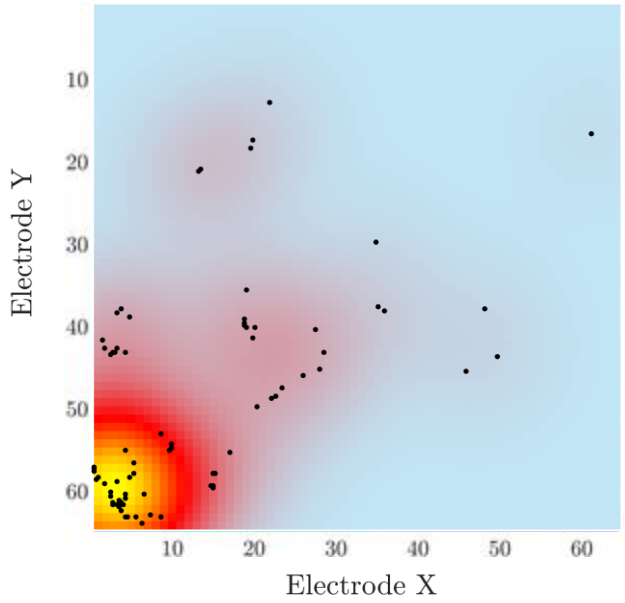
N. Timme, et al.,
PloS One. (2014)

Probability distributions

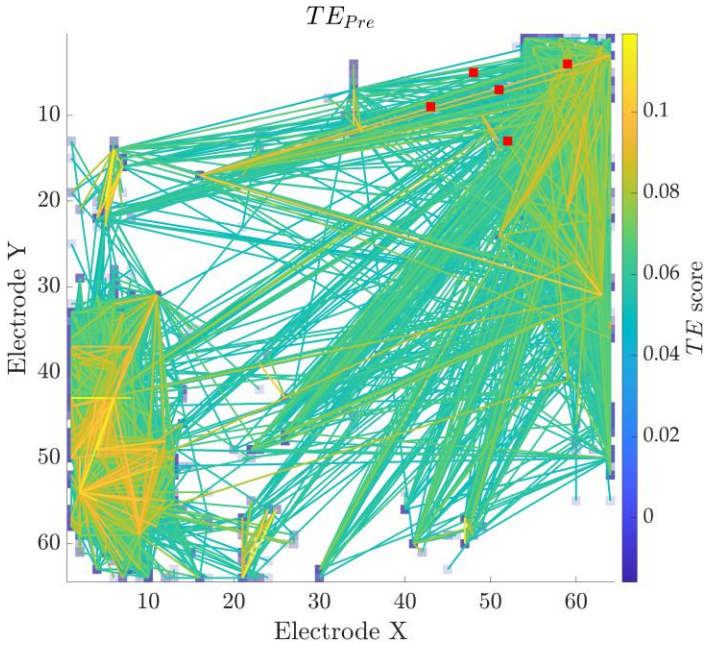
$$P_{ini}(x,y) = \sum_{r_x, r_i} \frac{1}{2\pi N \sigma^2} \cdot e^{-\frac{(x-r_x)^2+(y-r_y)^2}{2\sigma^2}}$$

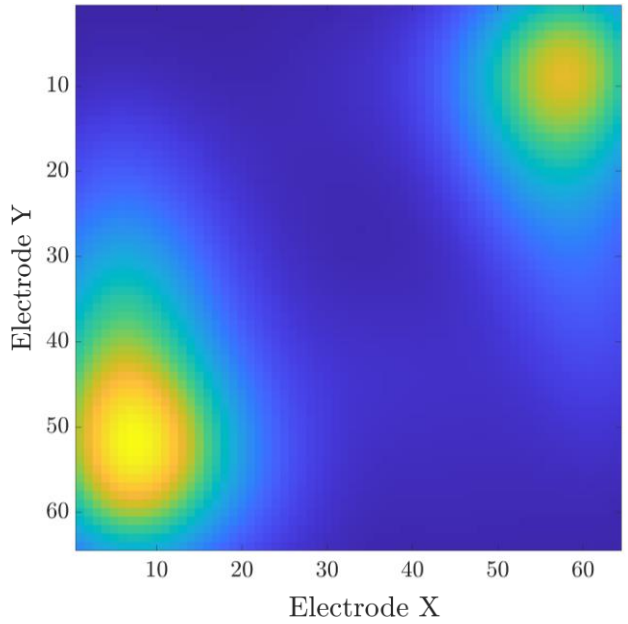
$$P_{dist}(a_i, b_i) = TE_{a_i,b_i} \cdot e^{-\frac{d^2_{a_i,b_i}}{2\sigma^2}}$$

$$P_{TE}(x,y) = \sum_{a_i,b_i} \frac{P_{dist}(a_i,b_i)}{(2\pi N\sigma^2)^2} \cdot e^{-\frac{(x-a_{i,x})^2+(y-a_{i,y})^2}{2\sigma^2}} \cdot e^{-\frac{(x-b_{i,x})^2+(y-b_{i,y})^2}{2\sigma^2}}$$



Initiation points (IPs) distribution





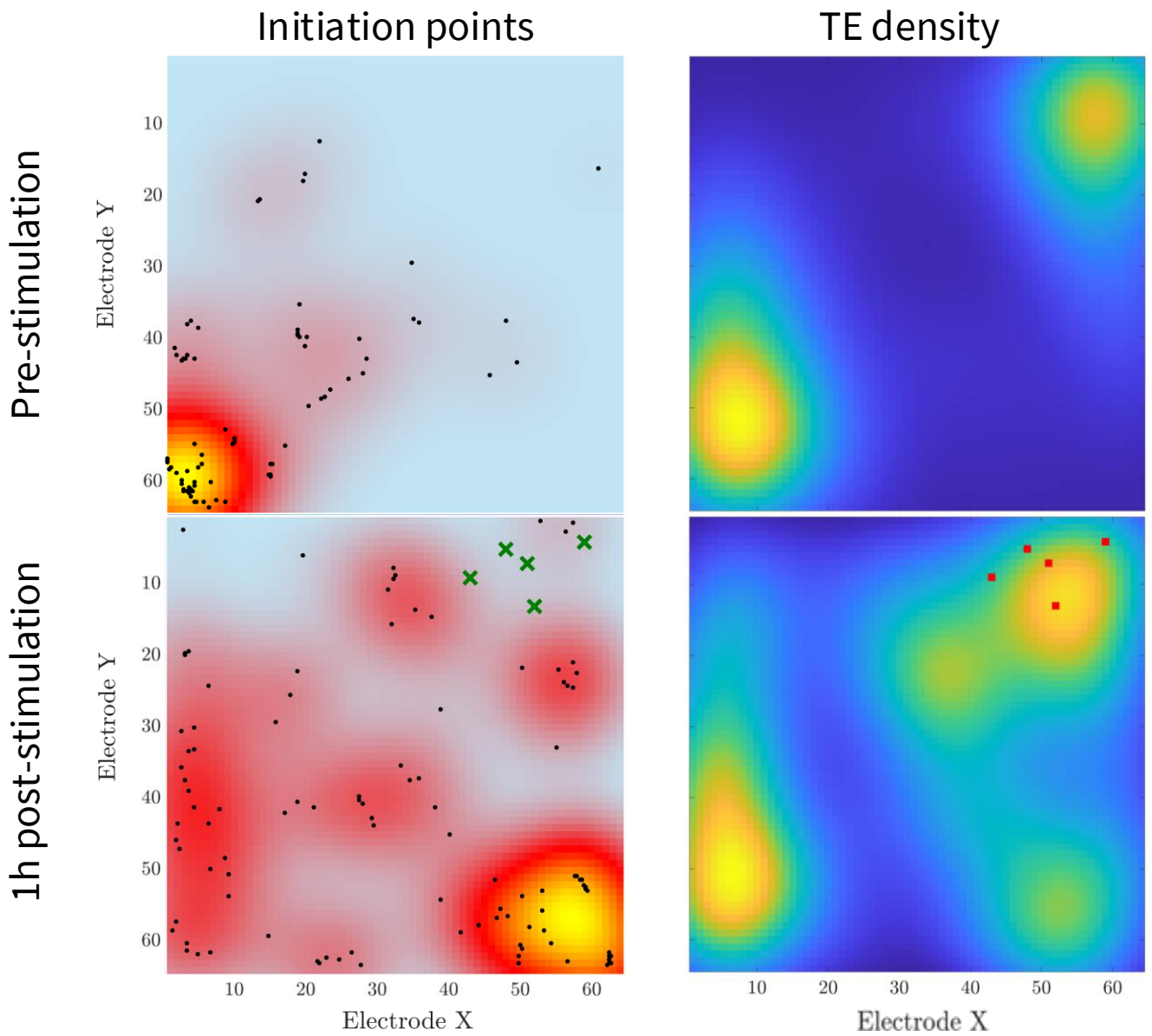
TE Weights distribution

J. Orlandi, et al.
Nat. Phys. (2013)

Stimulated rat primary culture

DIV24

- 1 hour after electrical stimulation, the main burst initiation zone has displaced to a new region.
- Since the mechanism underlying this phenomenon is not governed by local interactions, there is not a correspondence between the stimulated zone and the new leading burst initiation zone.

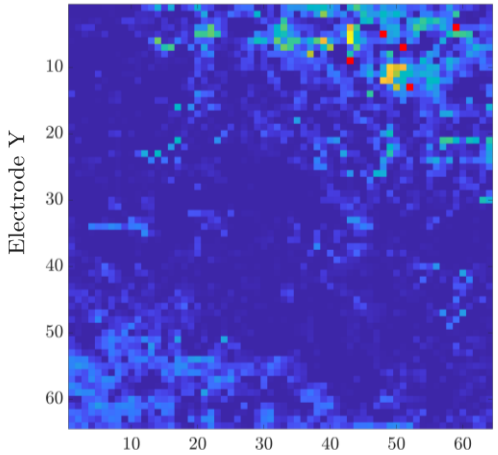


Stimulated rat primary culture

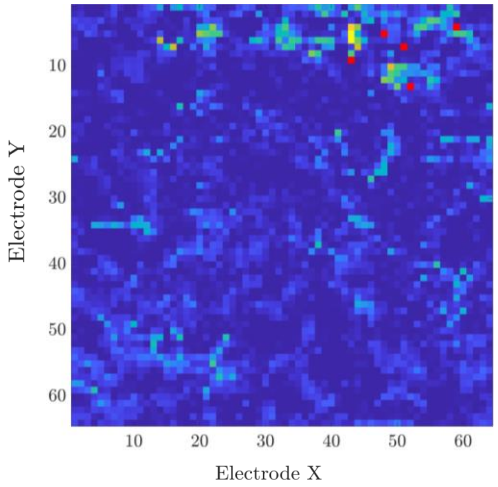
DIV24

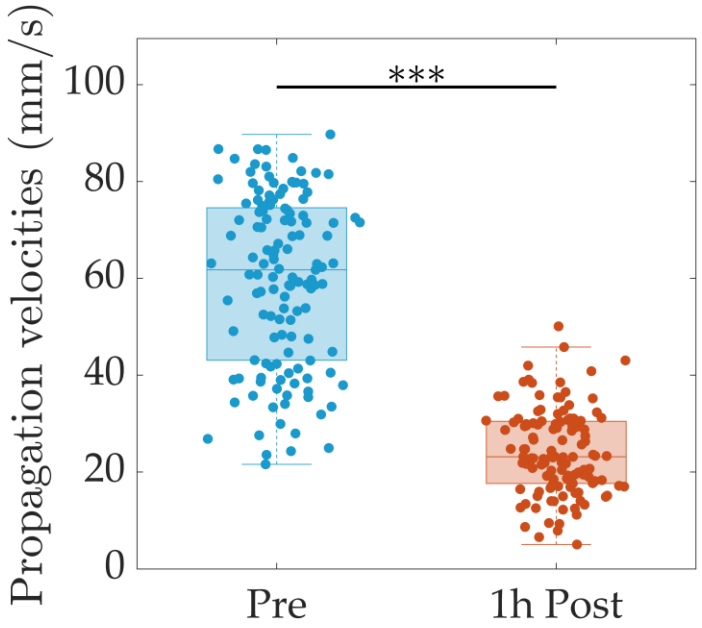
Eigenvalue centrality

Pre-stimulation



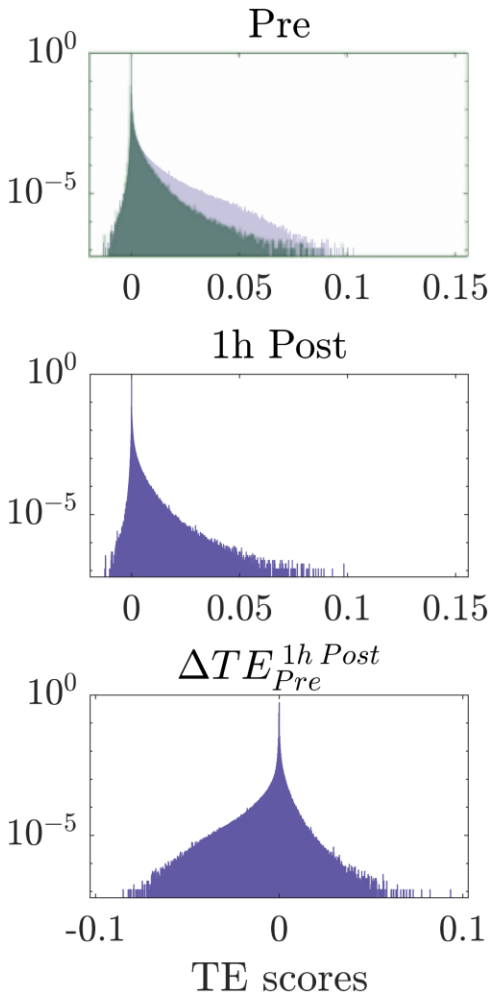
1h post-stimulation





- No changes are observed in centrality, as claimed by *X. Jia et al. Front. Neurosci. 2022.*
- The propagation dynamics are modified, as is reflected in the velocities.
- There is a reduction in the post-stimulation average weights.

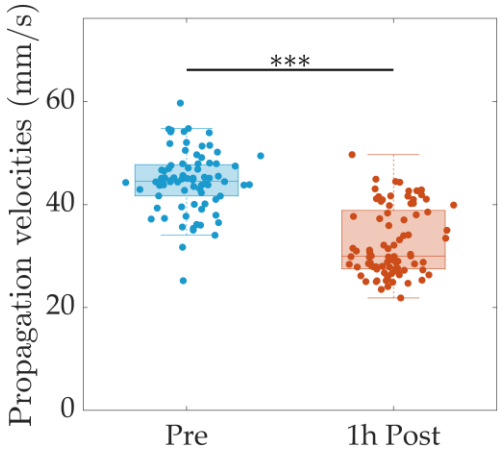
TE Probability Density Function

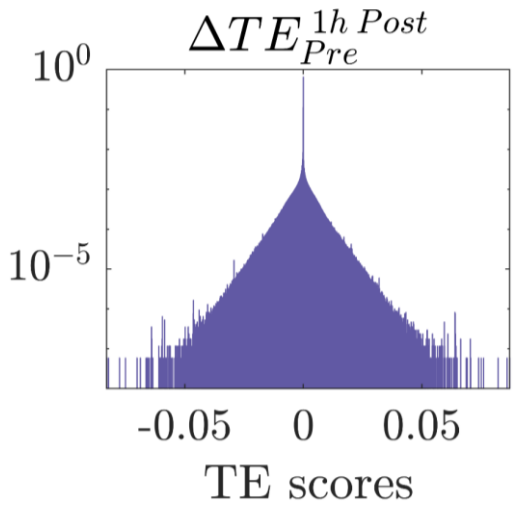


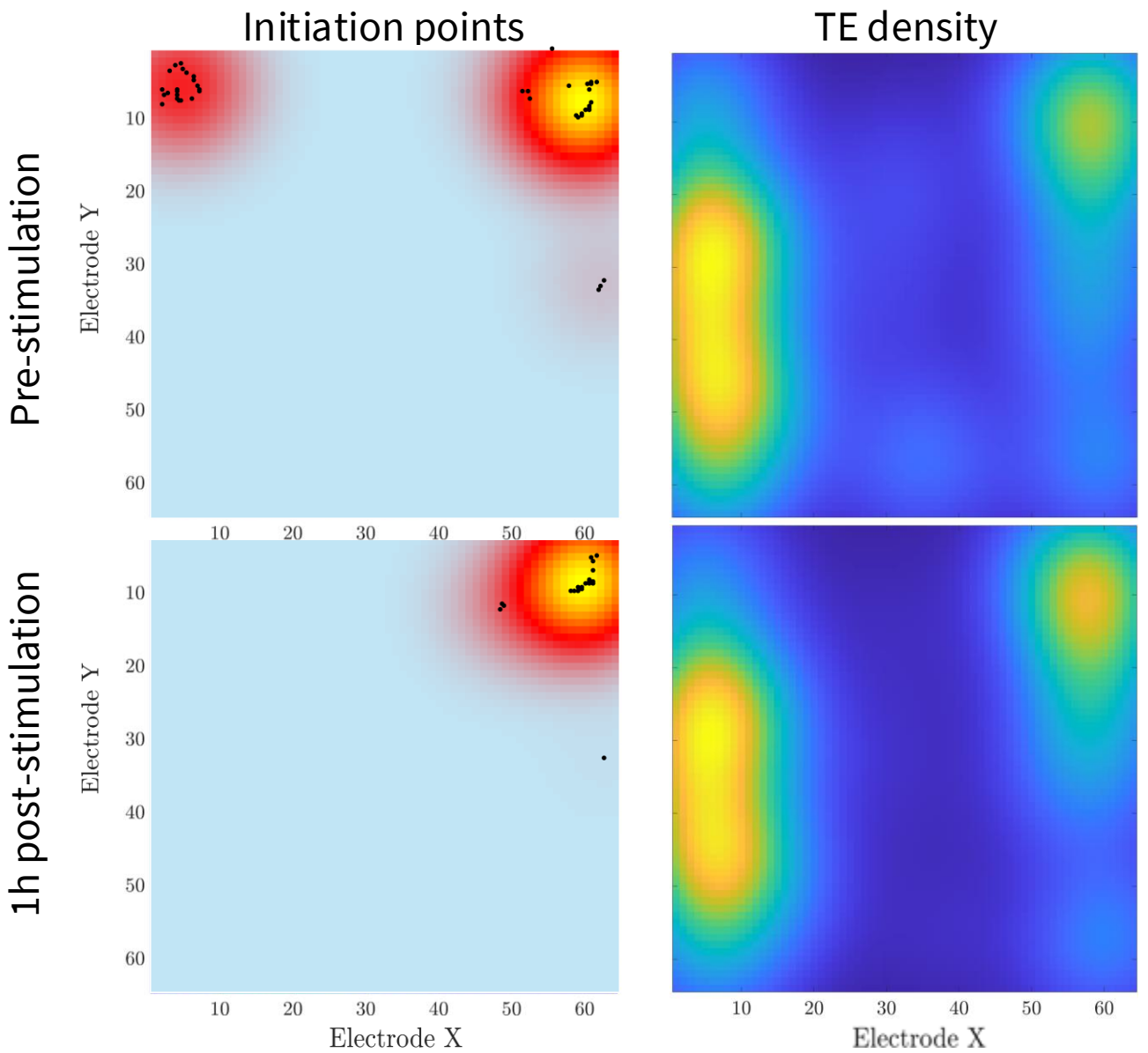
Control rat primary culture

DIV17

- The main burst initiation zone does not change, as well as the TE density.
- However, the velocity decreases.
- The TE distribution is not drastically altered.



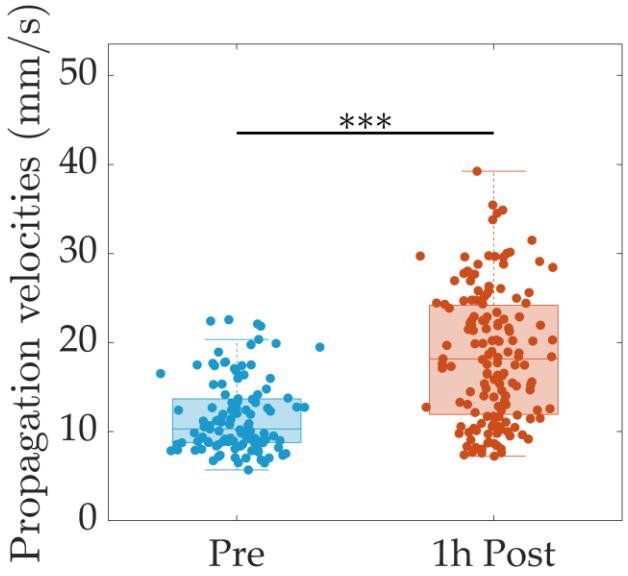


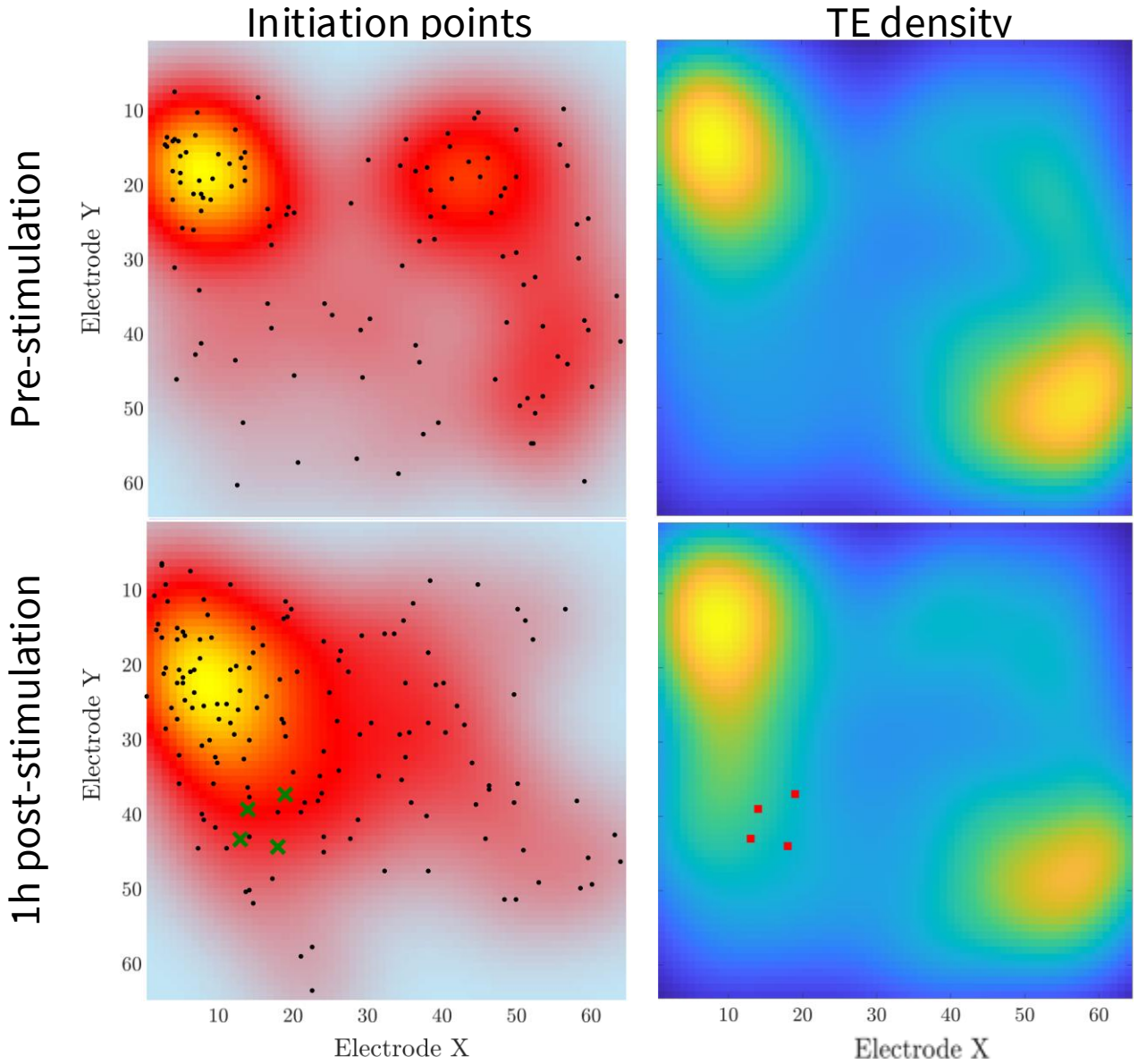


Stimulated Human iPSC (excitatory only)

DIV73

- While in rat primary cultures the strongest connections are grouped in clusters, here they distribute more homogeneously.
- The firing rate raises, as well as the propagation velocities.

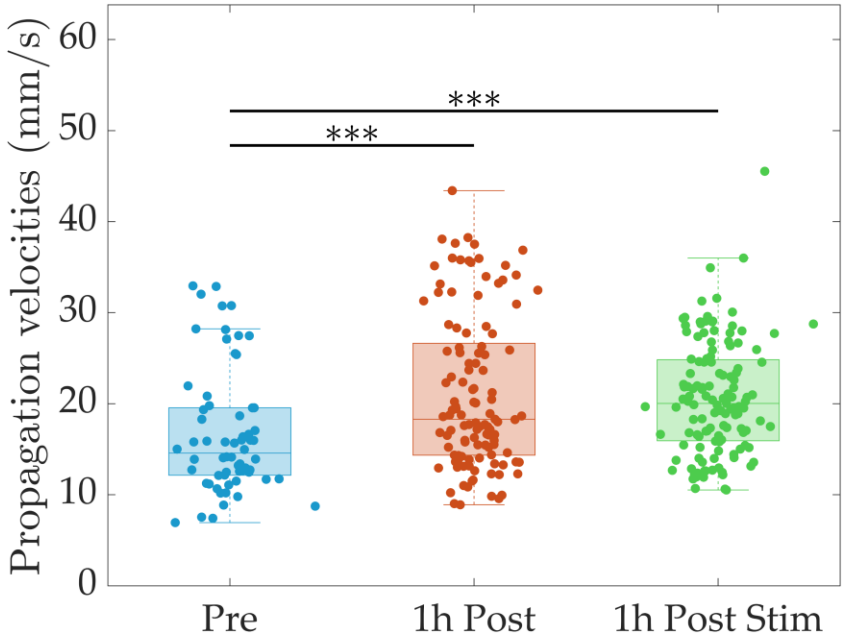


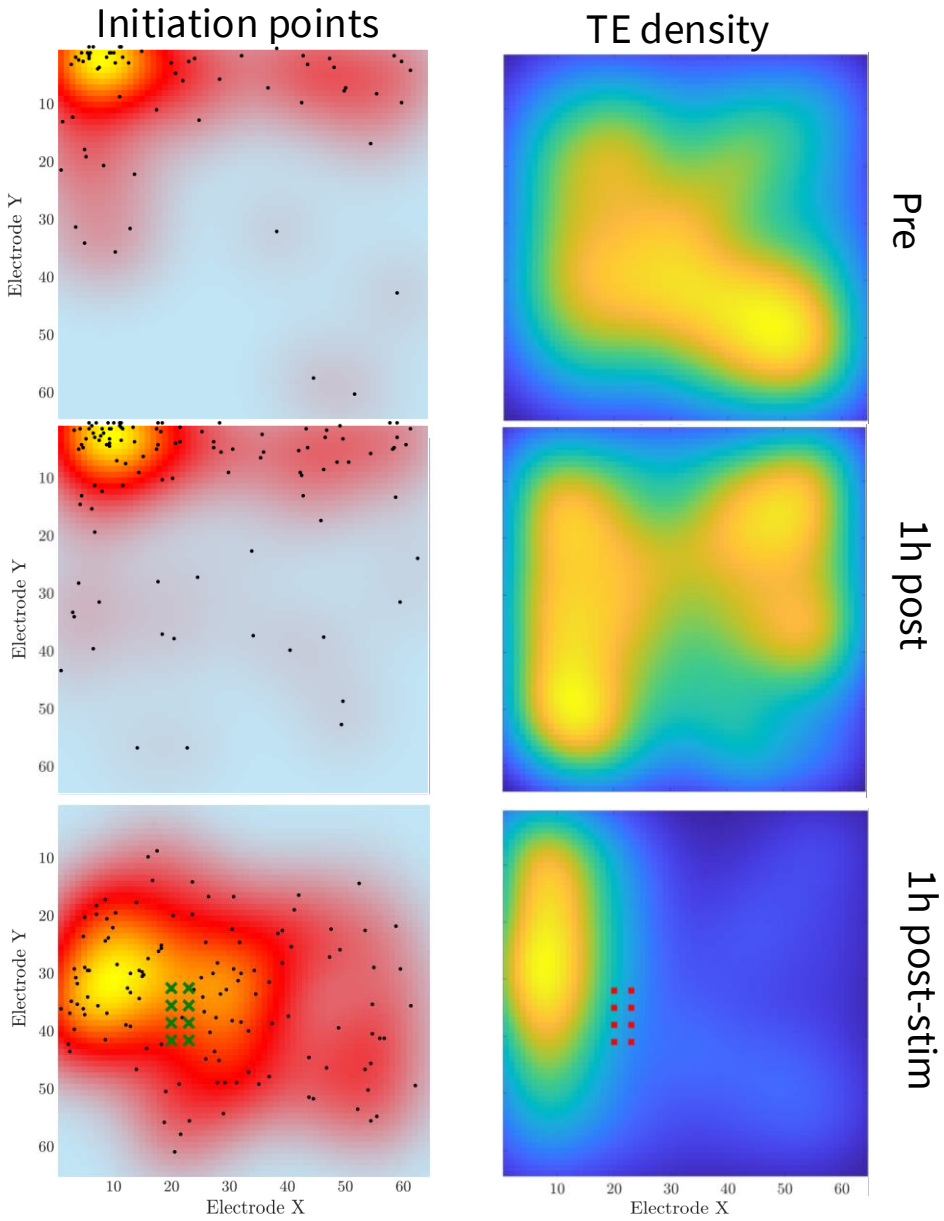


Control Human iPSC (excitatory only)

DIV85

- While in rat primary cultures the strongest connections are grouped in clusters, here they distribute more homogeneously and cover longer distances.
- The TE density map does not necessarily match with the initiation points distribution.

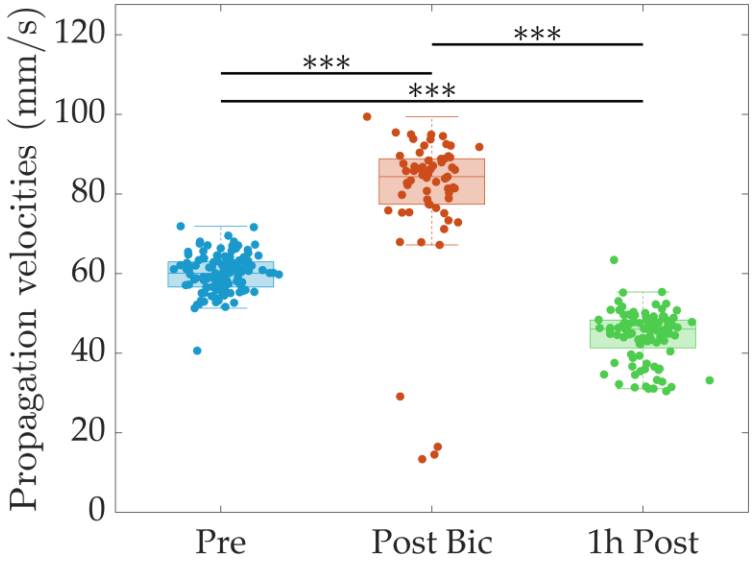


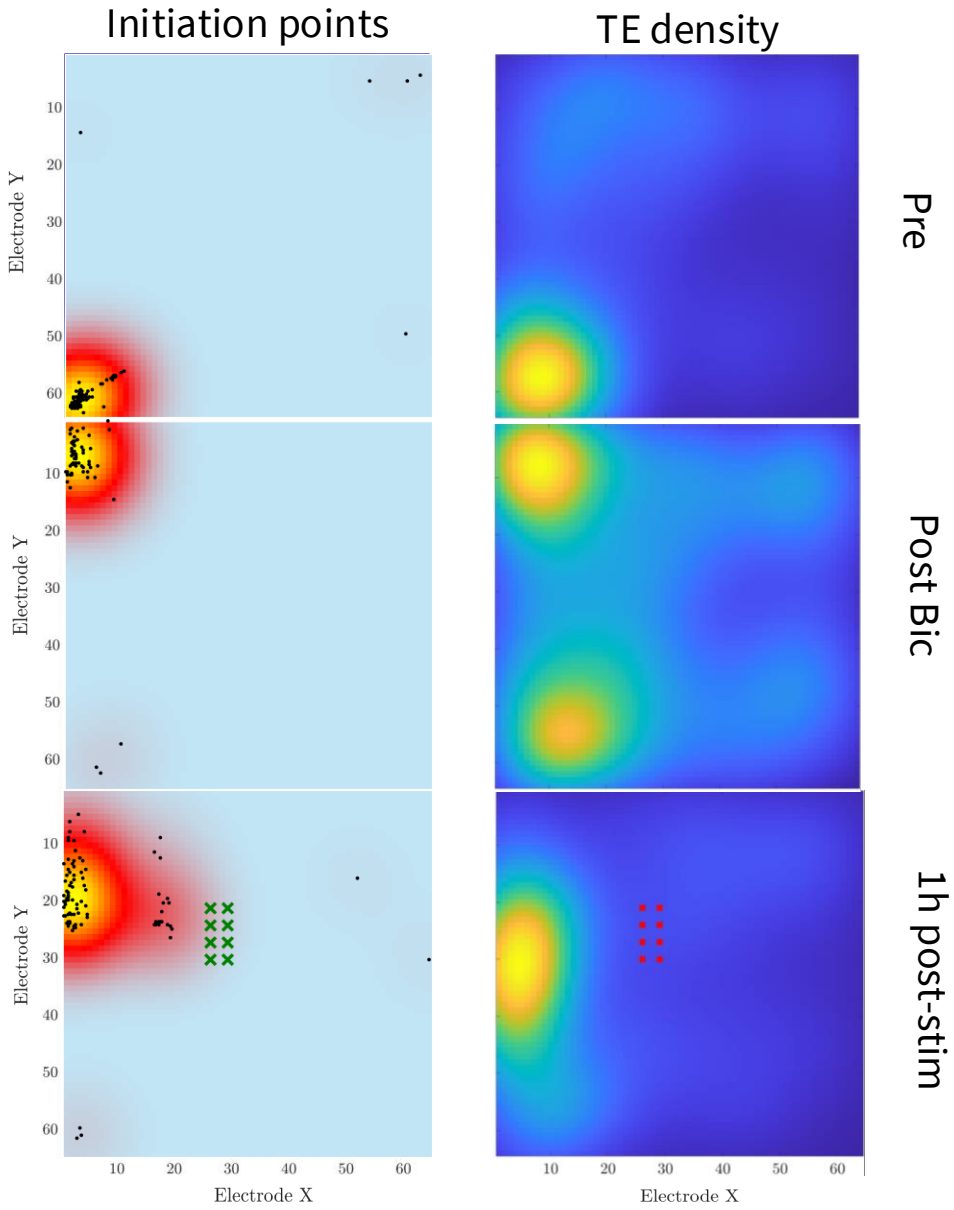


Rat primary culture blocking inhibition

DIV21

- Blocking inhibitory synapses using bicuculline induces a reshaping of functional connectivity.
- The firing rate raises, as well as the propagation velocities.
- The cultures do not behave as in the excitatory-only hiPSC case.





Conclusions

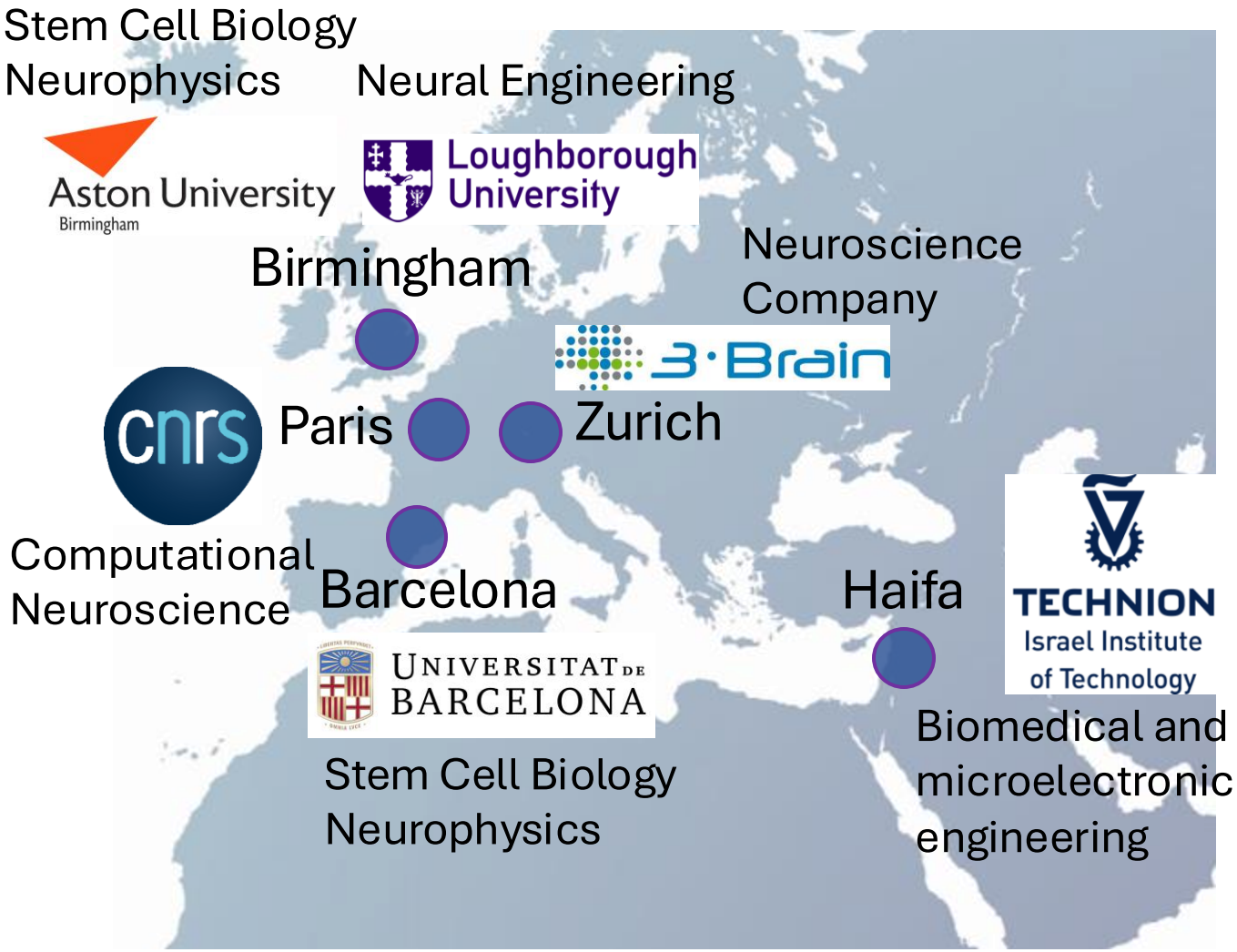
- Electrical stimulation through MEAs can modify spontaneous neuronal activity by displacing the initiation zones of the bursts.

- A functional connectivity analysis reveals the strengthening of connection grouped in clusters, correlated with the initiation regions, for the primary cultures.

- A higher correlation does not translate into a burst initiation domination, since there is a complex and non-linear interplay between the activity, the stimulation, and the collective events ignition.

- The absence of inhibition changes dramatically the activity, as well as the response to stimulation, showing different behaviors for excitatory-only networks and for primary cultures where inhibition is blocked.

NEU-CHiP consortium



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