



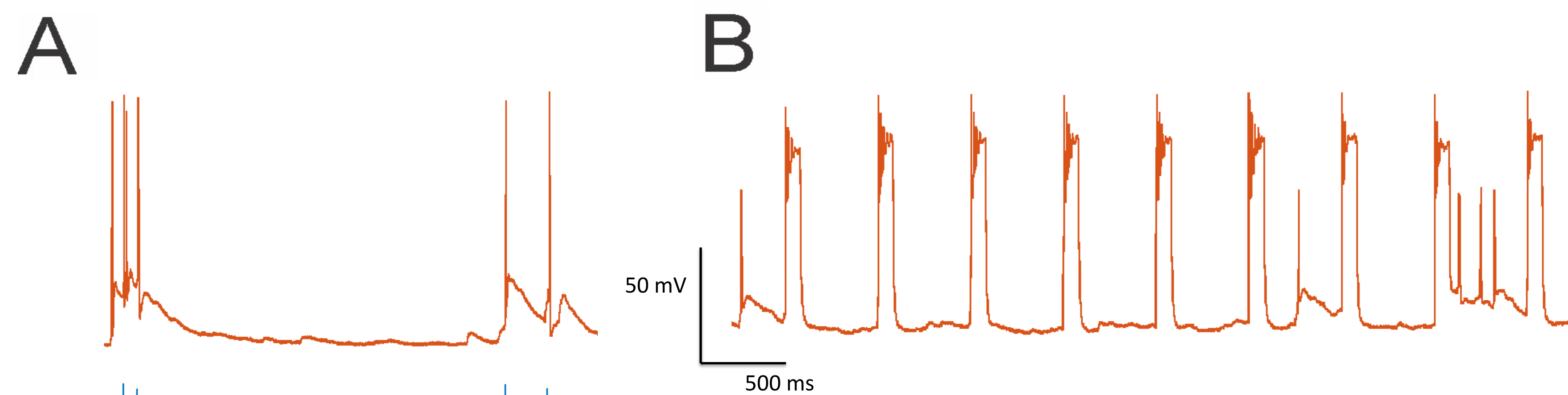
# Failure of Synaptic Transmission may Contribute to Seizure Propagation

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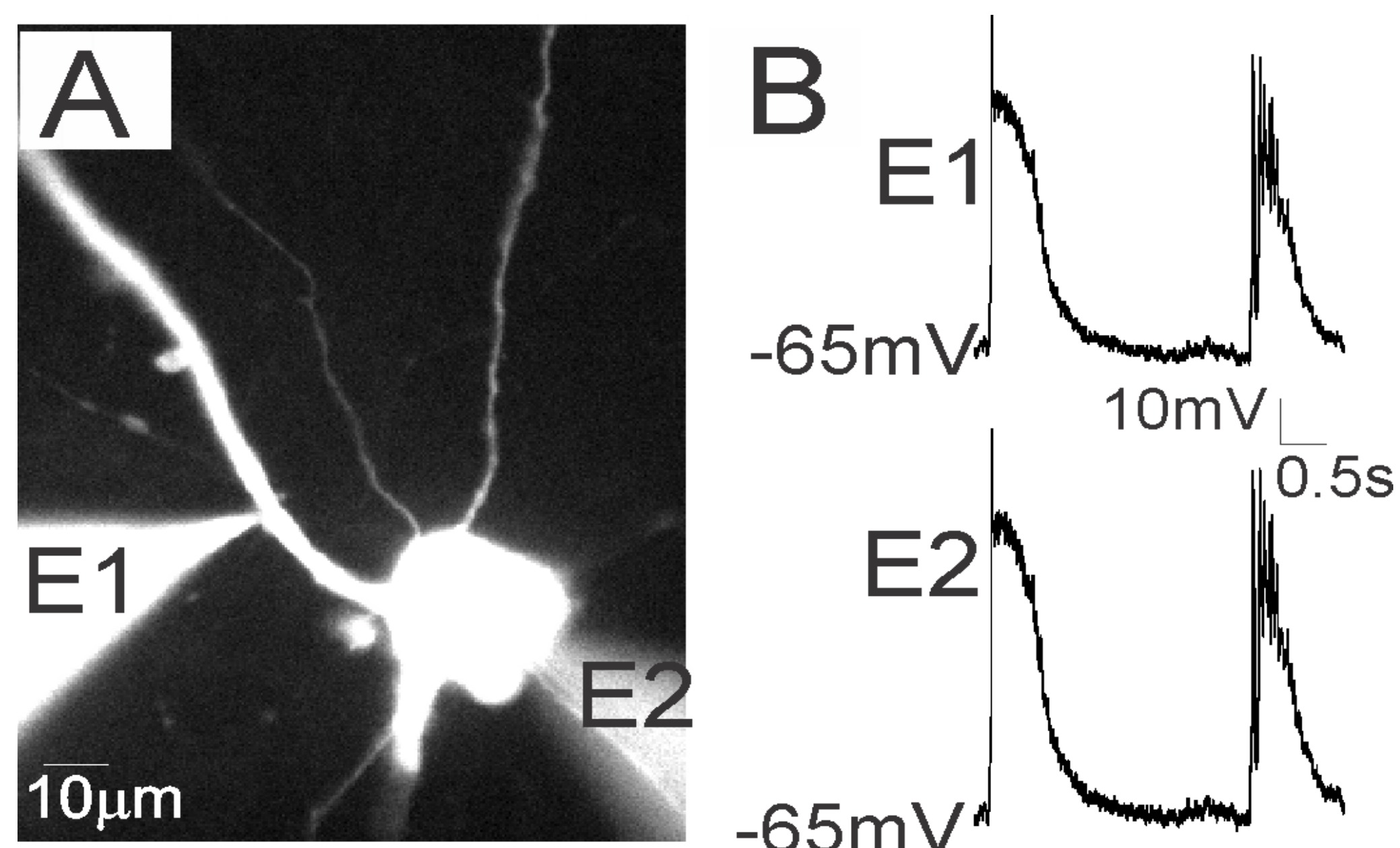
**INTRODUCTION:** Epilepsy is one of the most prevalent neurological diseases, but the mechanisms underlying seizure initiation, propagation and termination are not well understood. For neurons embedded in an active network, it is generally assumed that there are straightforward linear or sigmoidal relationships between net synaptic input and neuronal firing. However, due to the extreme conditions during a seizure, such a straightforward input-output relationship may vanish. A paroxysmal depolarization shift (PDS) can occur, in which a neuron undergoes high-amplitude suprathreshold synaptic depolarization while it fails to generate action potentials. The PDS burst, a cellular hallmark of epilepsy, represents a neuronal activity-driven depolarization block that affects transmission within the network and may contribute to counterintuitive emergent behavior during seizures (Meijer et al.).

## Spontaneous and Evoked Synaptic Activity



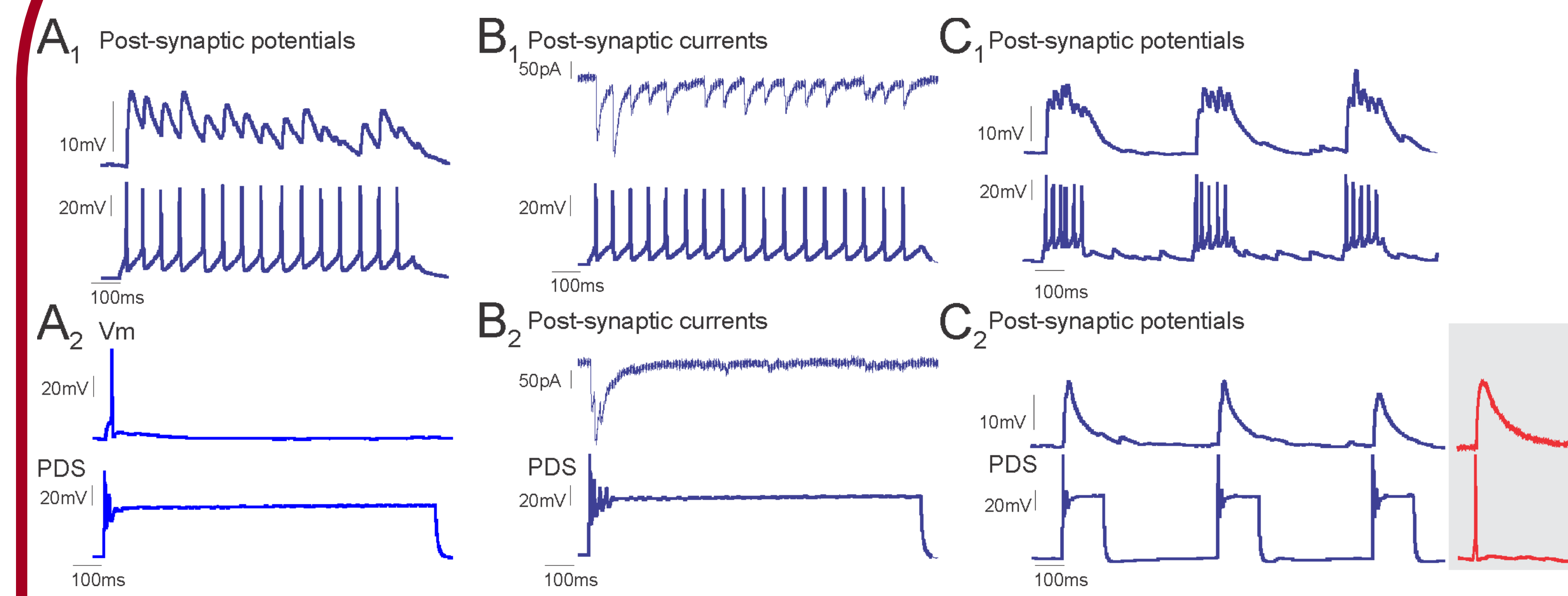
A) Spontaneous activity between two synaptically coupled neurons demonstrates intuitive behavior, i.e. action potentials (APs) and bursts in the target (red) cell generate proportional responses in the coupled (blue) cell.  
B) Depolarizing current injection that generates PDS depolarization block in the target cell leads to sub-threshold EPSPs in the coupled cell, which is evidence of synaptic transmission failure. Note that non-PDS activity leads to transmission.

## Identifying the Source of Synaptic Transmission Failure During PDS Bursts



A) Two electrodes are used to patch-clamp multiple neuronal compartments (E1 = dendrite, E2 = soma) and B) examine the propagation of spontaneous PDS bursts or bursts of action potentials within the same neuron.

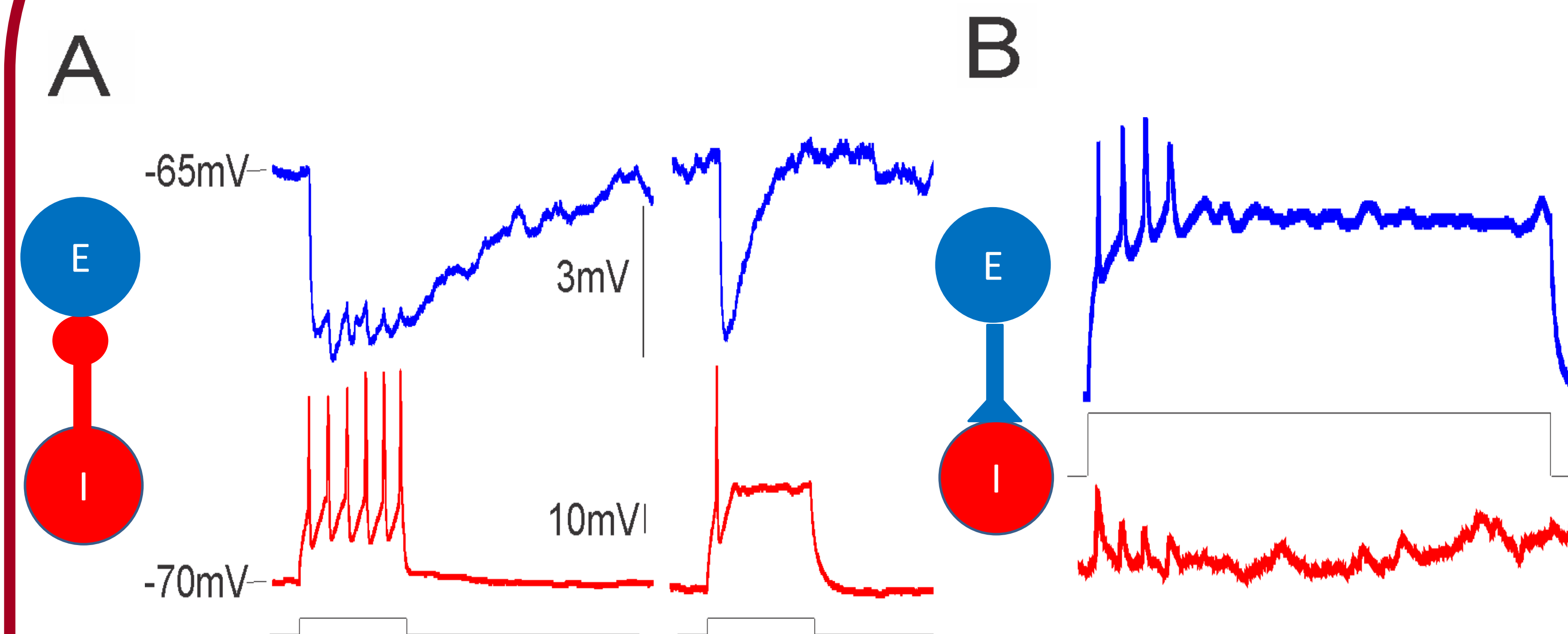
## Synaptic Transmission Fails During PDS Bursts



A1, B1, C1: Top traces demonstrate that depolarizing current injection generating APs in the target cell cause EPSPs (A1) and EPSCs (B1) in synaptically coupled cells. Similarly, inducing bursts in the target cell causes temporal summation in the coupled cell (C1).

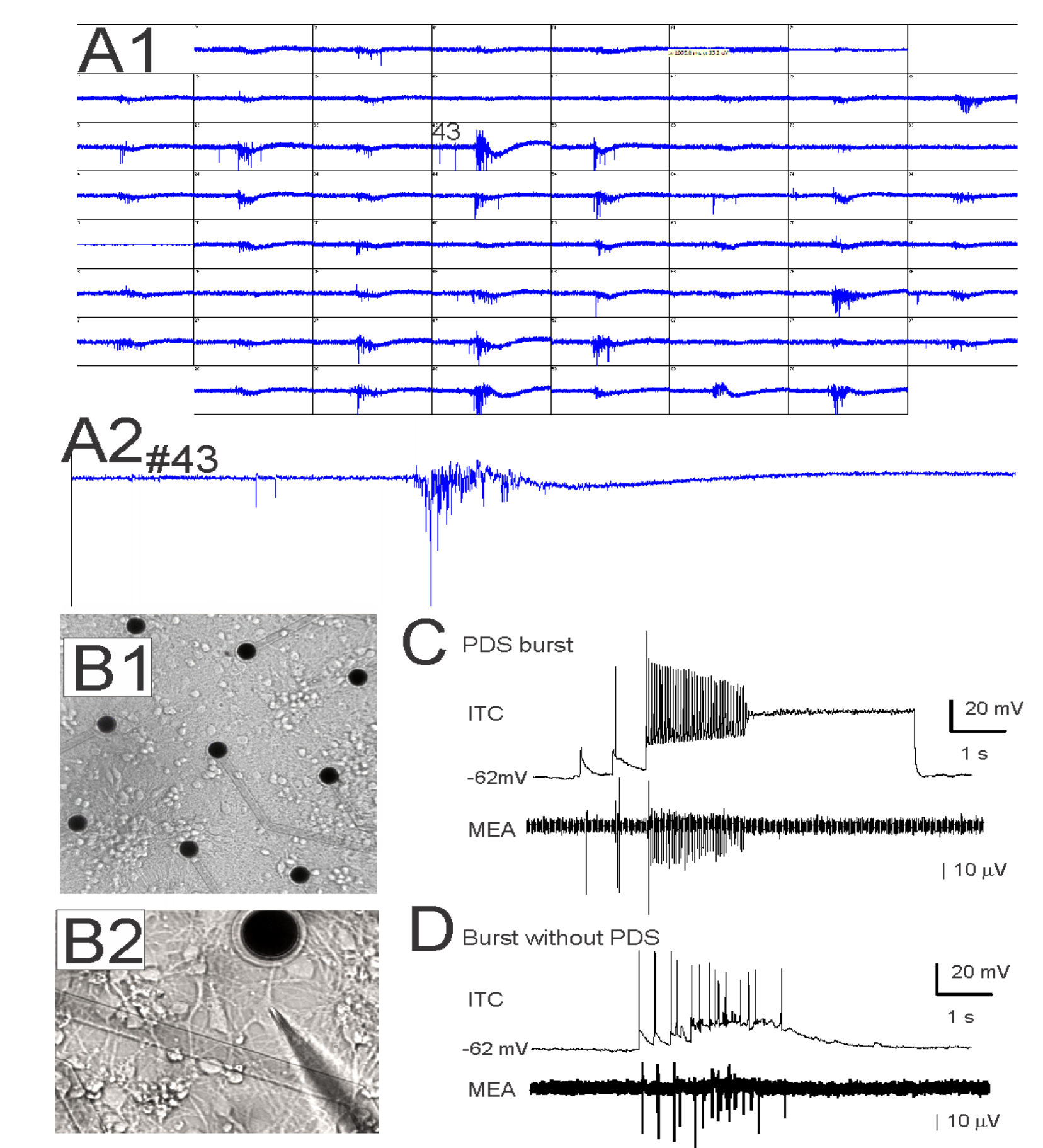
A2, B2, C2: Larger depolarizing current injection into the target cell (bottom trace) evokes initial AP activity followed by a PDS-like depolarization block, during which the coupled cell does not demonstrate EPSPs (A2) or EPSCs (B2). High amplitude injections inducing PDS-like bursts generate the same post-synaptic activity as a single presynaptic AP (C2). (n=6 pairs)

## Inhibition Fails Before Excitation During PDS-like Bursts



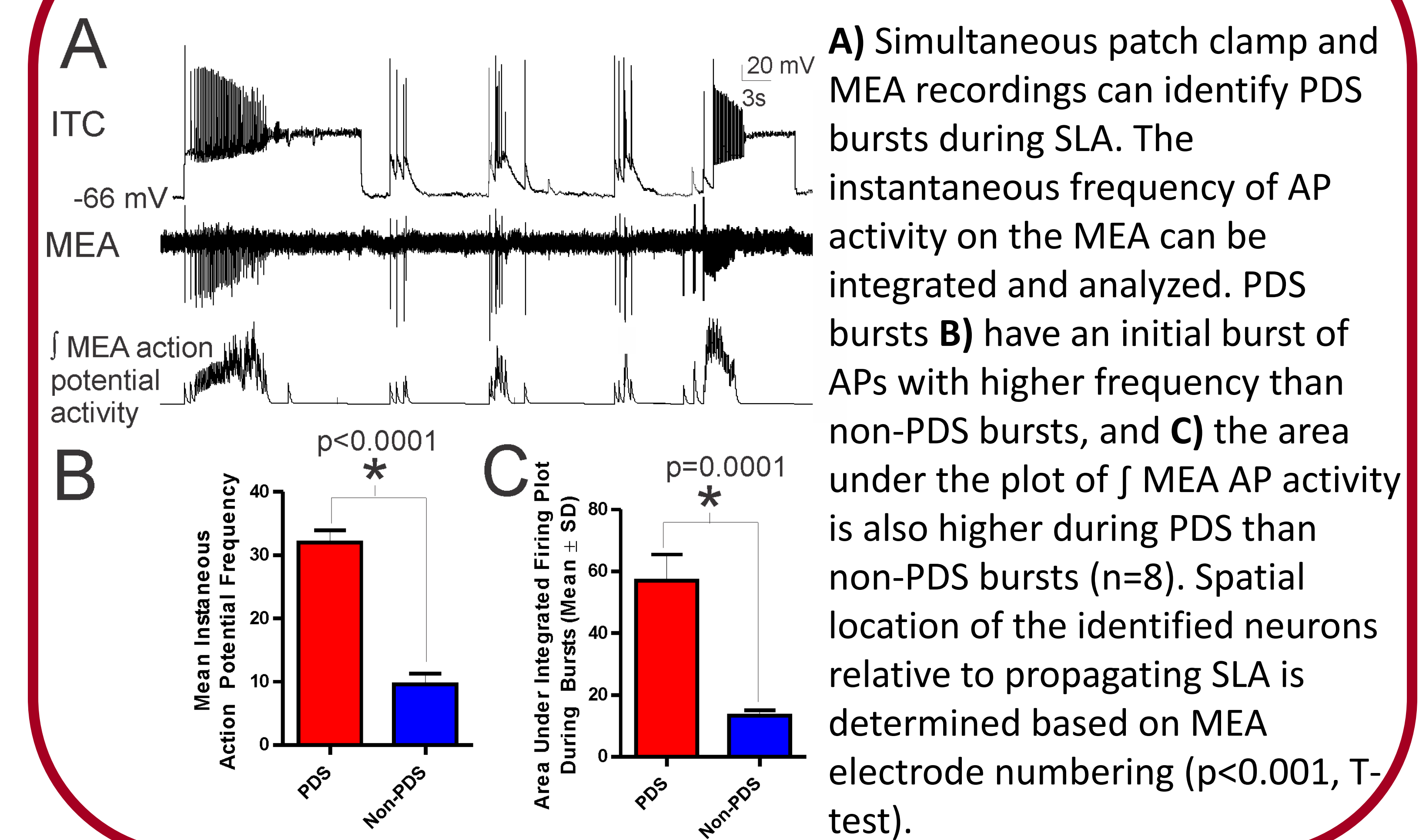
A) Depolarizing current injection triggers APs in the inhibitory neuron (red) that evoke inhibitory post-synaptic potentials (IPSPs) in a synaptically coupled excitatory neuron (blue). Current injections were increased to determine the minimum amount of depolarizing current required to trigger a PDS-like depolarization block, resulting in reduced inhibition of the excitatory cell.  
B) Depolarizing current injection into an excitatory neuron (blue) generated a PDS-like depolarization block that resulted in reduction of synaptic transmission to a coupled inhibitory neuron (red). The minimal amount of current injection required to evoke a PDS-like depolarization block was significantly greater (>50%) in excitatory versus inhibitory neurons (n=2 inhibitory/excitatory pairs).

## Monitoring Network Activity During PDS-like Bursts



A1) Multi-array electrode (MEA) recordings of dissociated neuron cultures reveal spontaneous seizure like activity (SLA) propagating across 60-channels, and A2) an expansion of a SLA population burst in channel #43. B1-B2) Patch-clamping of neurons simultaneously recorded on adjacent MEA electrodes is used to determine whether neurons in the network are generating C) PDS bursts or D) spontaneous bursts without PDS depolarization block.

## Detecting PDS Bursts During SLA in MEA Recordings



A) Simultaneous patch clamp and MEA recordings can identify PDS bursts during SLA. The instantaneous frequency of AP activity on the MEA can be integrated and analyzed. PDS bursts B) have an initial burst of APs with higher frequency than non-PDS bursts, and C) the area under the plot of MEA AP activity is also higher during PDS than non-PDS bursts (n=8). Spatial location of the identified neurons relative to propagating SLA is determined based on MEA electrode numbering (p<0.001, T-test).

## Conclusions

- Increased excitatory input resulting in PDS-bursts can result in **decreased** synaptic transmission.
- PDS bursts reduce inhibitory synaptic transmission before excitatory transmission is affected.
- These small-scale neuronal behaviors may explain the collapse of inhibitory signaling responsible for seizure propagation across macroscopic networks.

## References

Meijer et al. Modeling focal epileptic activity in the Wilson-Cowan model with depolarization block. *Journal of Mathematical Neuroscience* 2015 Mar 27; 5:7.

## Acknowledgements

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