

sEEG-based device for concomitant neural recordings and drug delivery into the brain - feasibility bench and in vivo studies

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INTRODUCTION

Convection enhanced delivery (CED) of therapeutic compounds into the brain is used in clinical trials for various neurological conditions (e.g., epilepsy, Parkinson's). The existing CED devices consist of cannulas able to deliver infusate, but unable to record neural activity. This severely limits the ability to evaluate drug effects on neural activity.

Stereoencephalography (sEEG) electrodes are routinely used in the evaluation of patients with drug resistant epilepsy. The electrodes are FDA-cleared for stereotactic implantation and indicated for temporary (<30 days) monitoring, recording and stimulation of neural activity at the subsurface level of the brain.

OBJECTIVES

We have developed a sEEG-based device capable of drug delivery, DD-sEEG. Here we present feasibility bench and in vivo studies.

METHODS

1. Bench testing

- Test system: 0.6% agarose gel using 1% Methylene Blue dye
- Infusion parameters: flow rates from 0.5 to 15 μ l/min

2. In vivo testing

- Animal models; rodent, swine. All experiments were conducted under an approved IACUC protocol at the Mayo Clinic.
- Stereotactic sEEG implantation in the hippocampus and putamen
- Drugs: Penicillin (5000 u/ μ l) for modulating neural activity (induction of seizure-like activity)
- Diffusion volume assessment: MRI (swine), histology (rodent)

Model	Infusion area	Volume (μ l)	Rate (μ l/min)	Infusion duration (min)	Electrophysiological recordings	Vd assessment
Rodent	HC /thalamus	5	0.5	10	HC	Histology
Swine	Putamen	60	0.5-5	30	n/a	Post infusion MRI
	HC	60	0.5-5	30	HC	Post infusion MRI

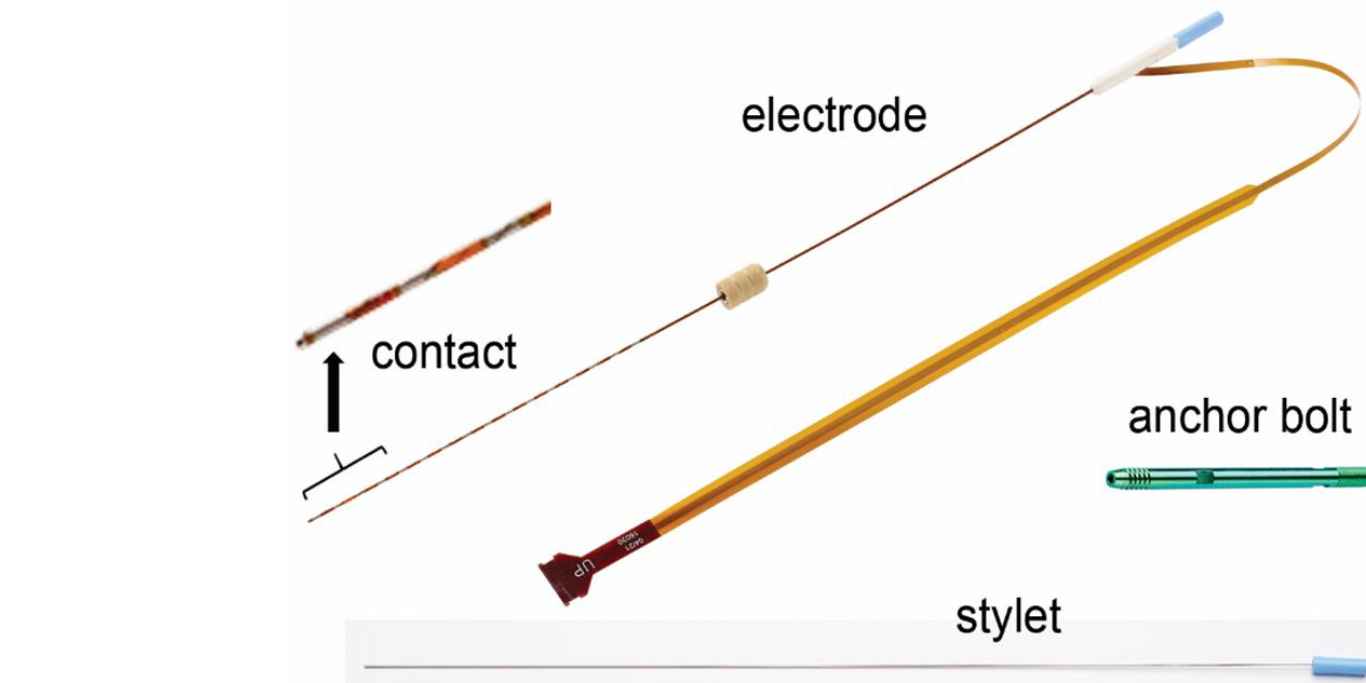
HC, Hippocampus

RESULTS

1. DEVICE DESCRIPTION

A. sEEG-based system

- Diameter: 0.8 mm
- Number of Contacts: 5 - 16
- Contact Spacing: 1.5 mm
- Contact Size: 2 mm

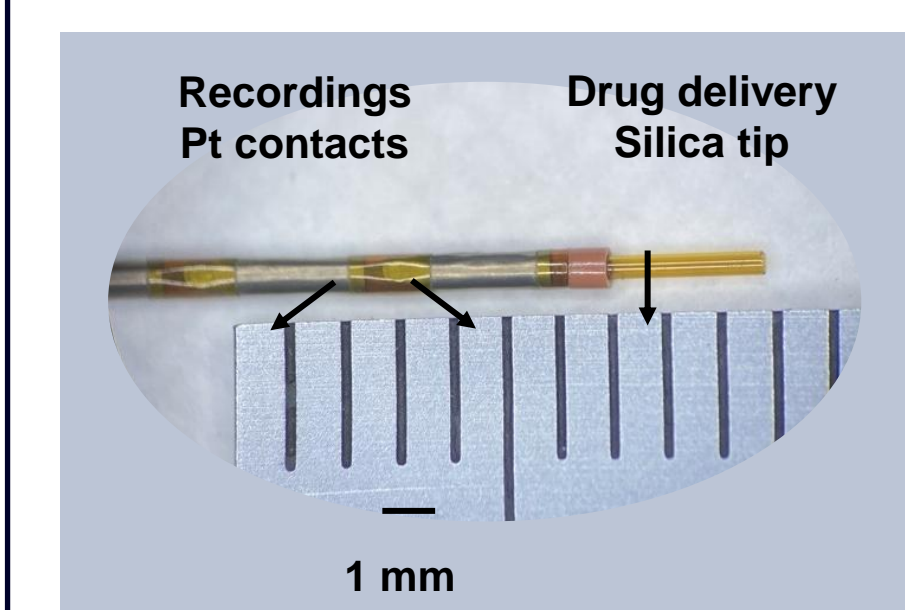
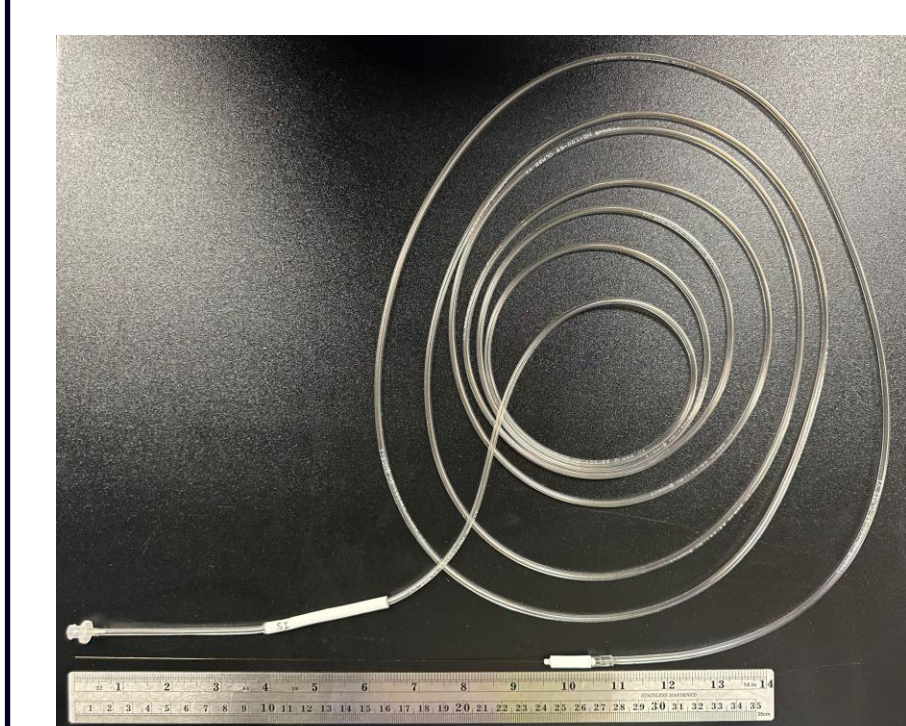


- Disposable cable for intracranial EEG recordings
- Standard DIN42802 touch-proof connectors compatible with standard headboxes.

Figure 1. Device

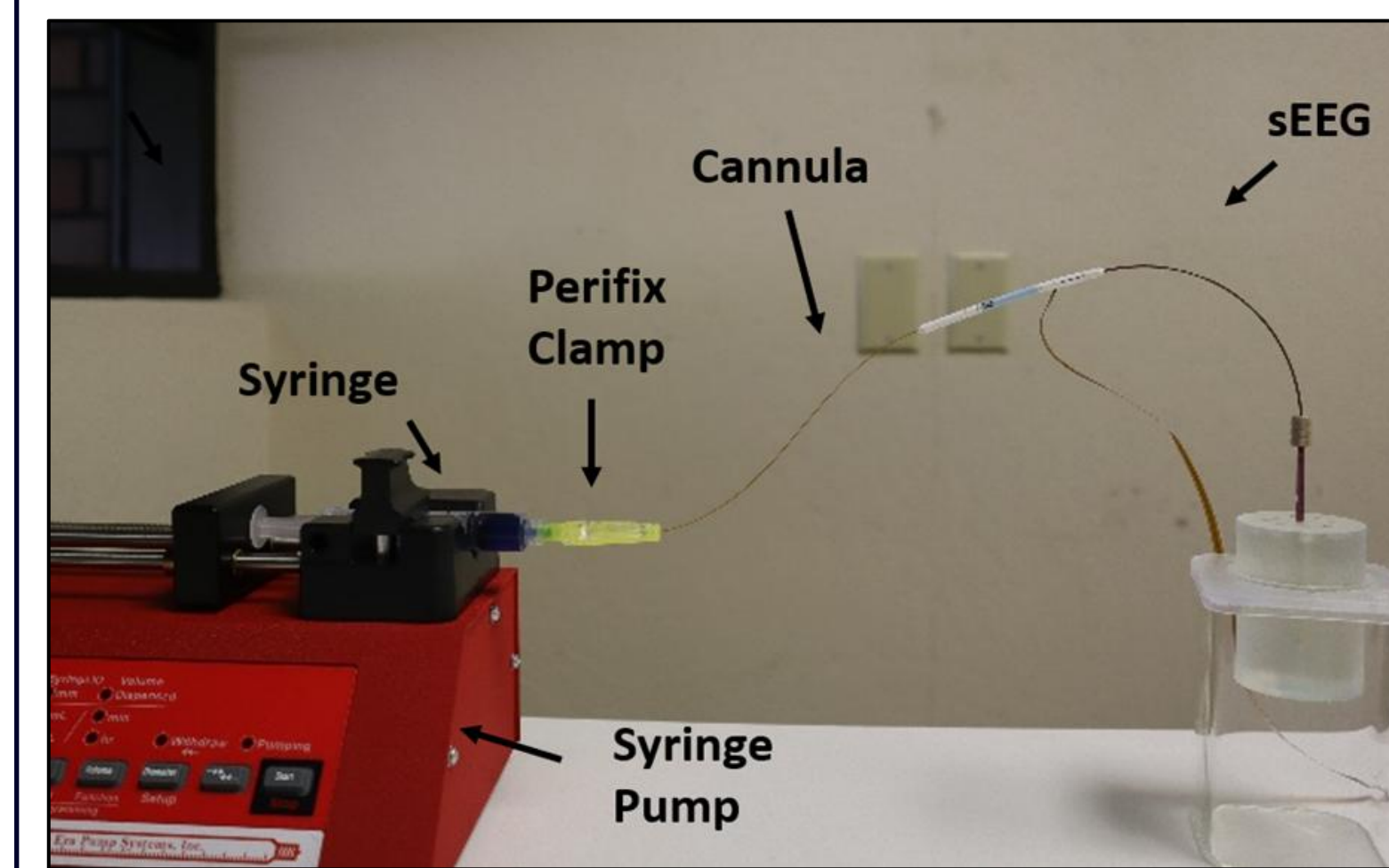
B. Cannula for drug delivery

- used when drug delivery is needed - acute <24h



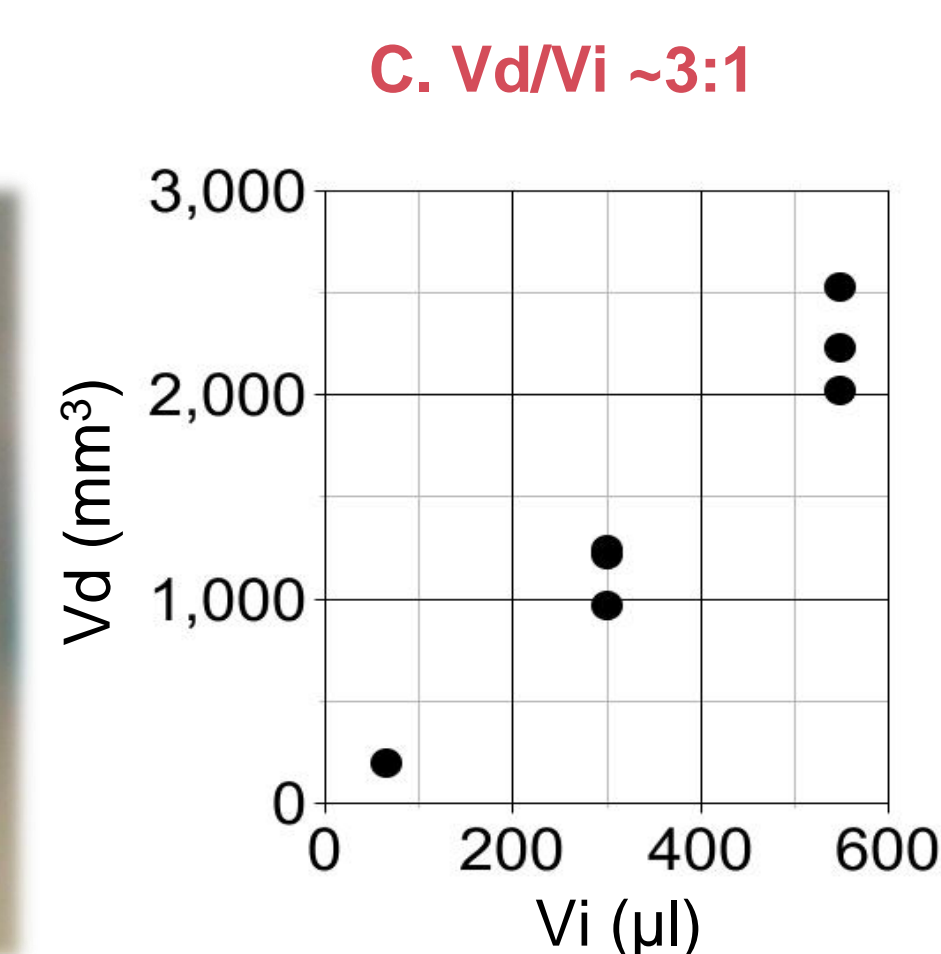
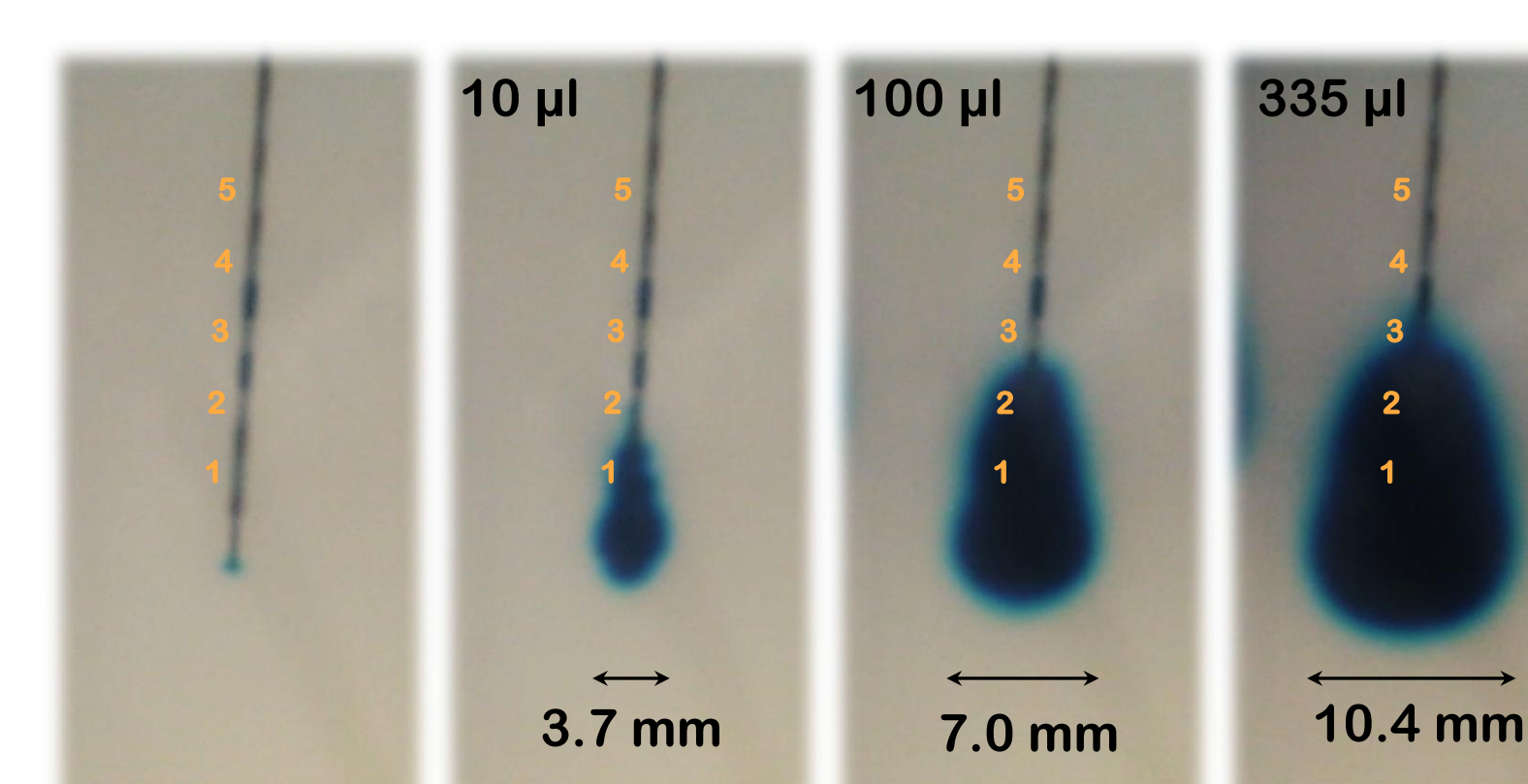
2. BENCH TESTING

A. Set-up for bench studies



CED in agarose

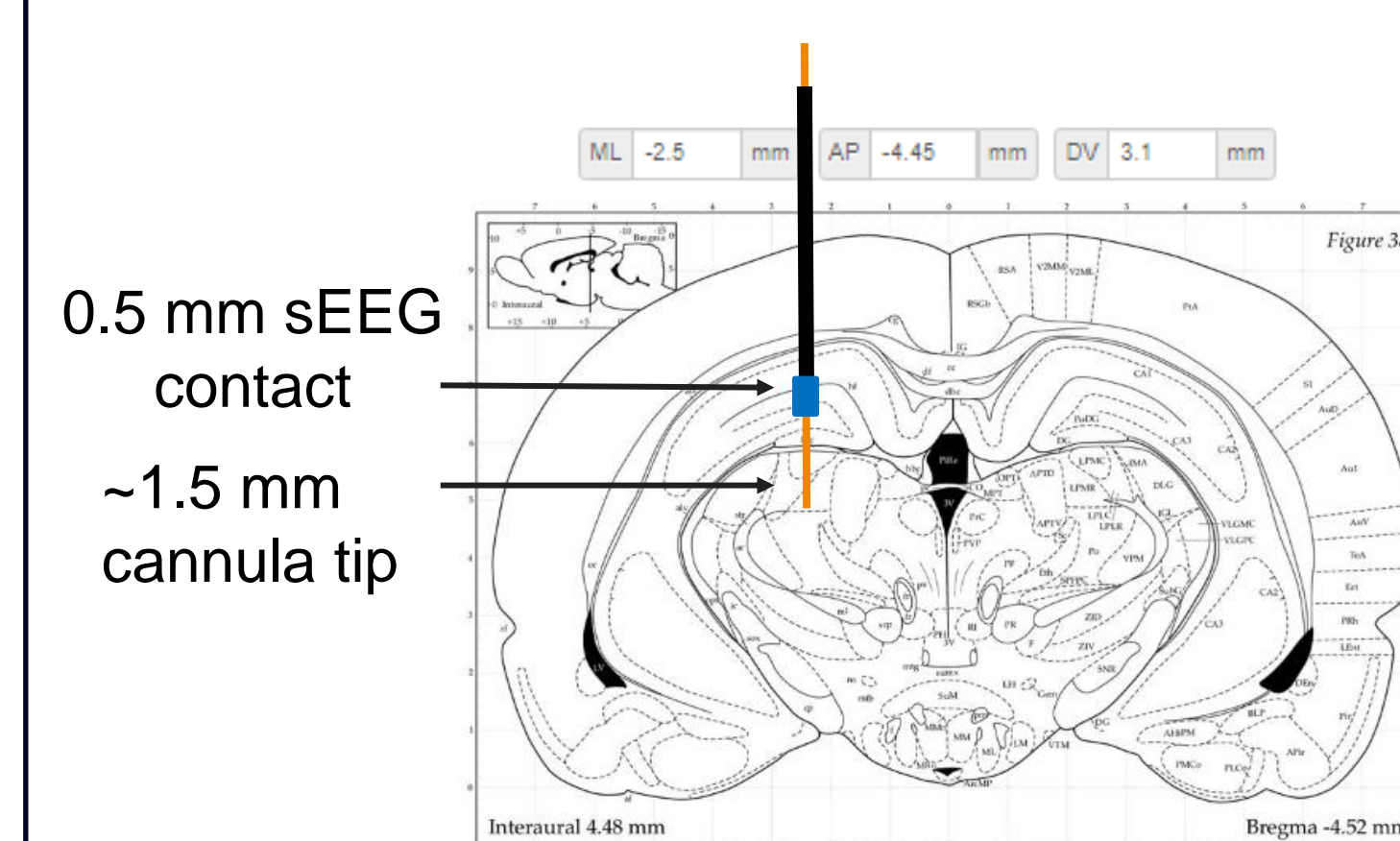
B. Number of contacts covered by diffusion (Vd) volume is proportional to the infusion volume (Vi)



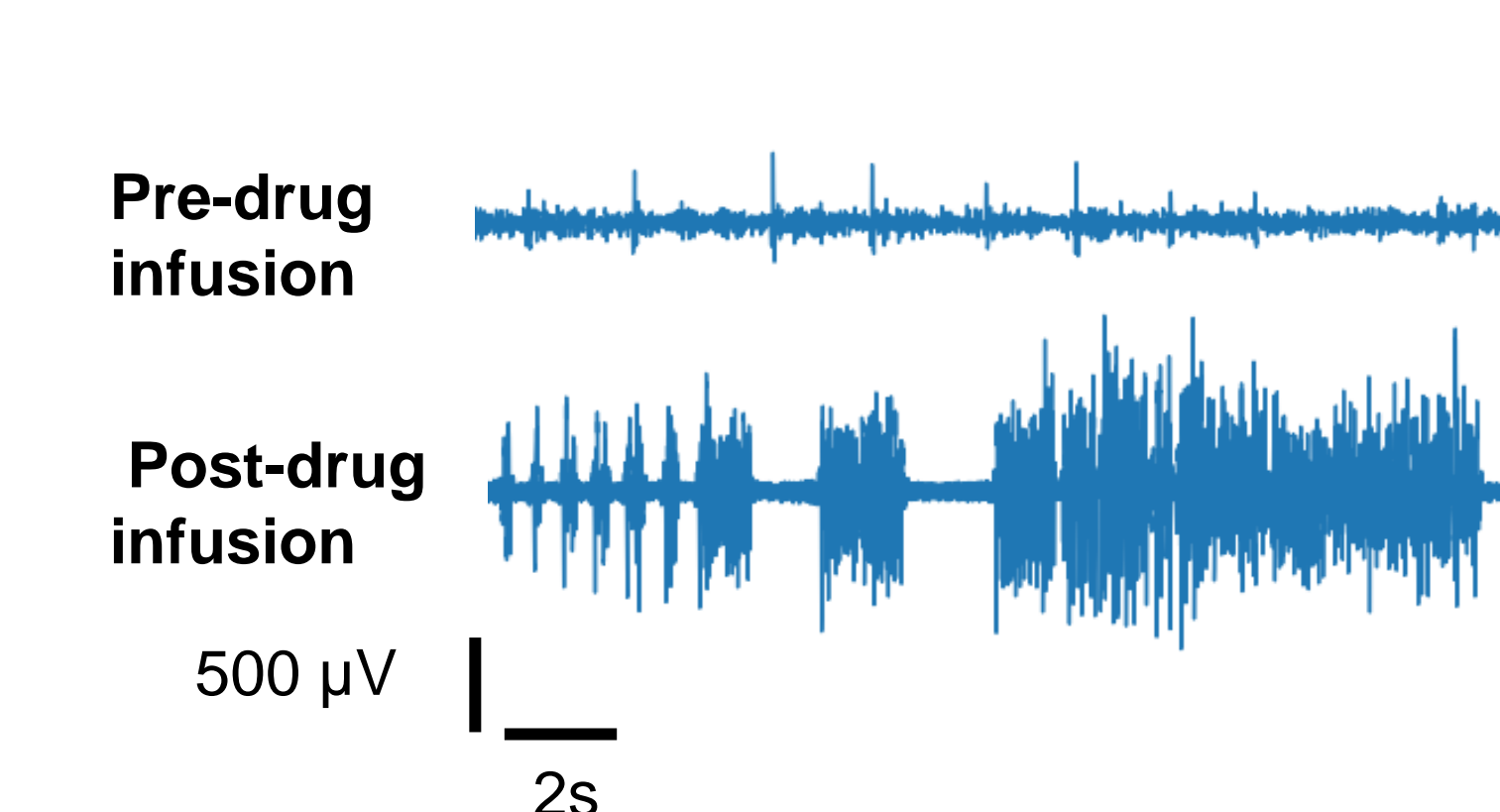
3. IN VIVO TESTING

1. Rodent model

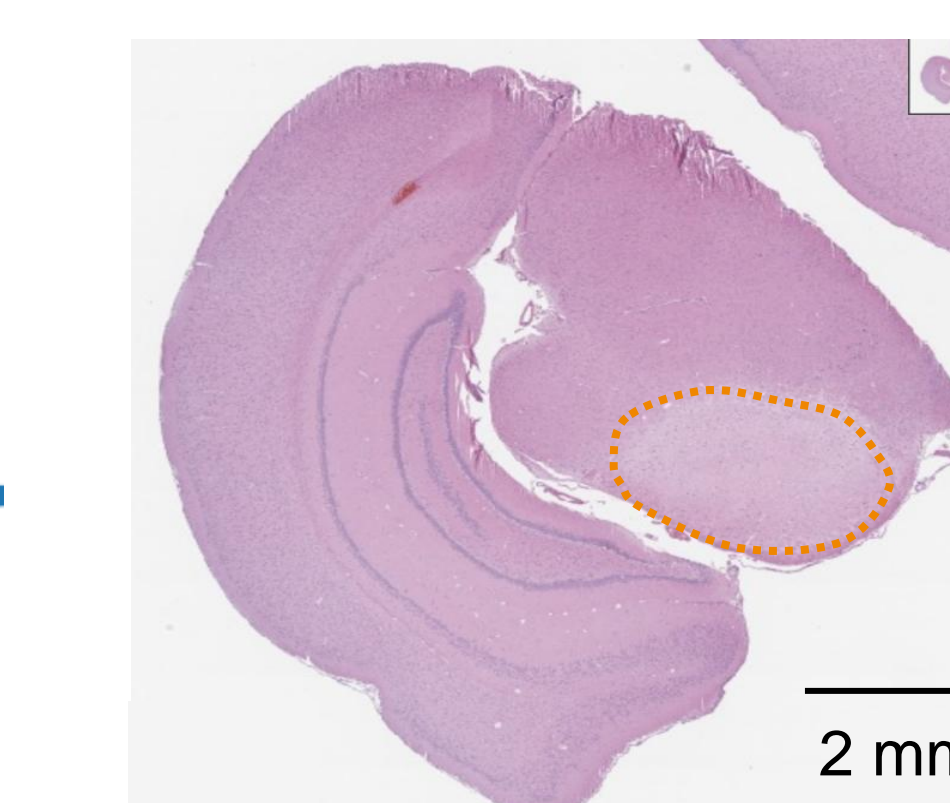
A. Stereotactic implantation



B. Real-time recordings of brain activity: pre and post drug delivery



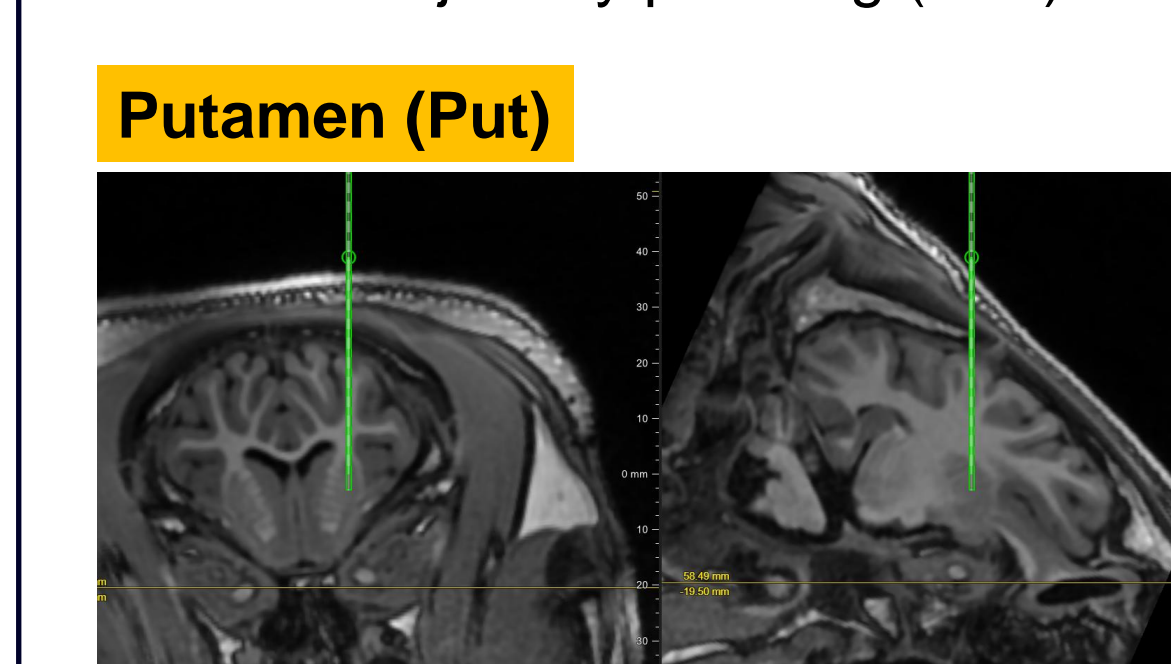
C. Localized infusion H&E sections illustrating Vd



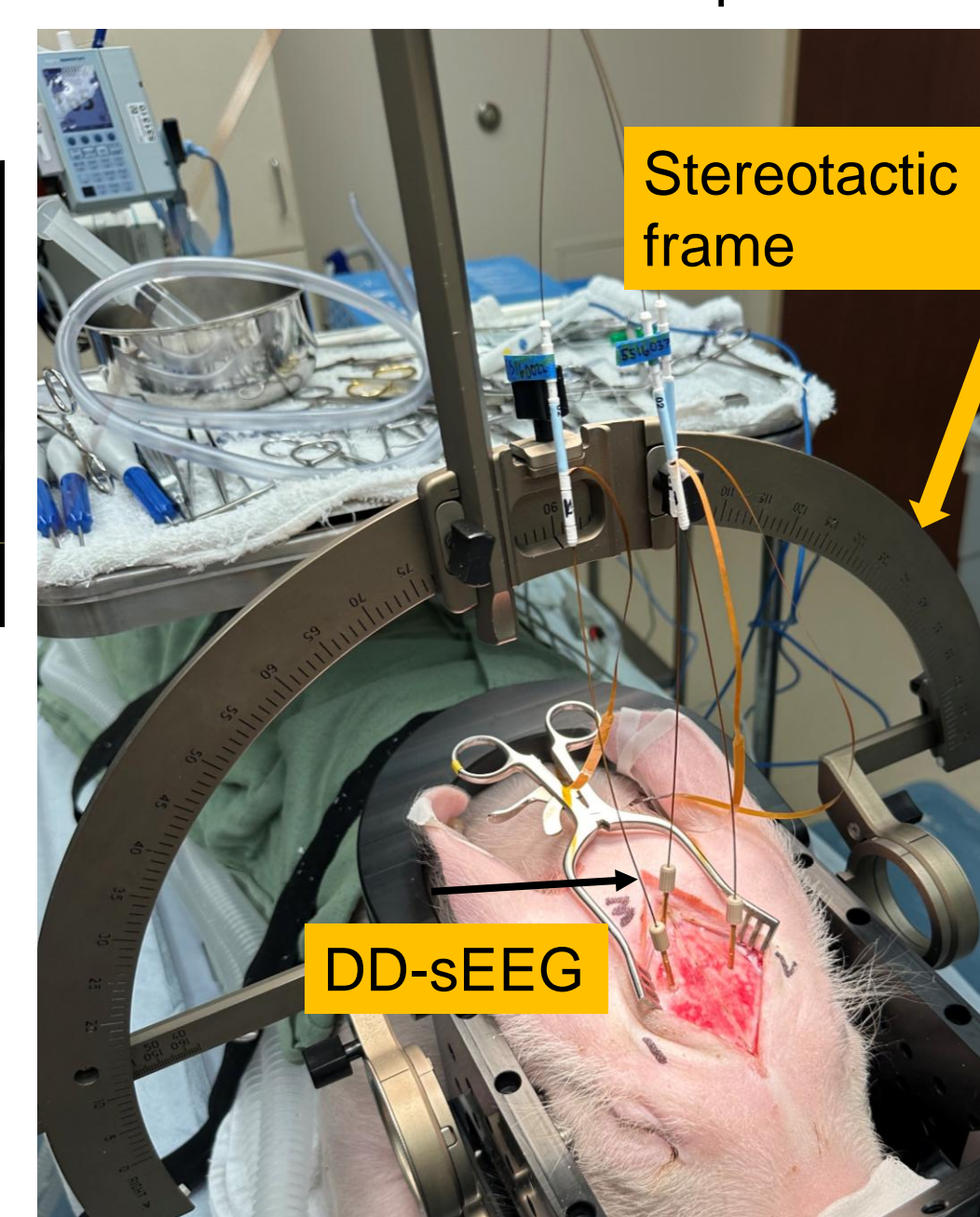
2. Swine model

1. Integration/use within the sEEG workflow

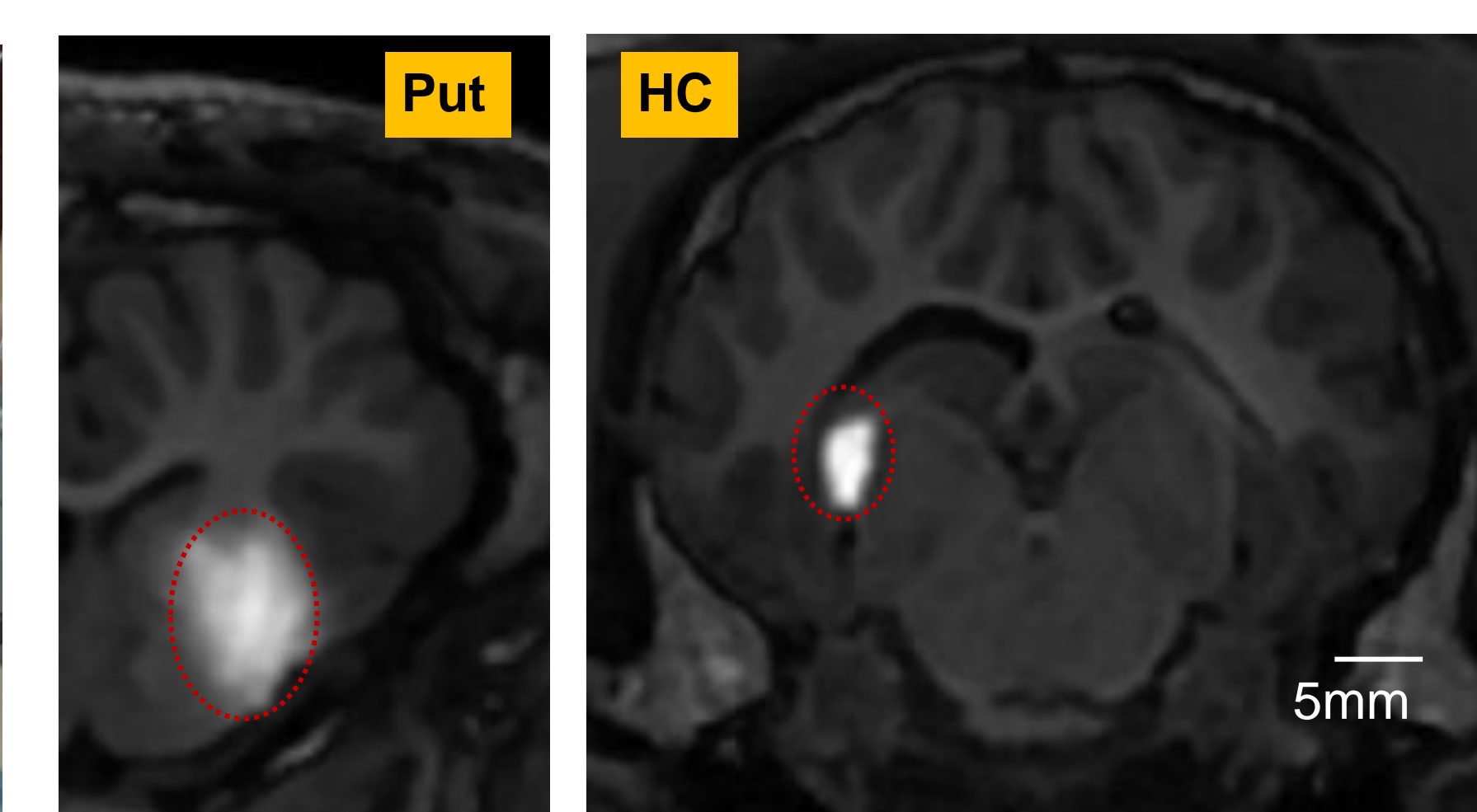
A. sEEG trajectory planning (MRI)



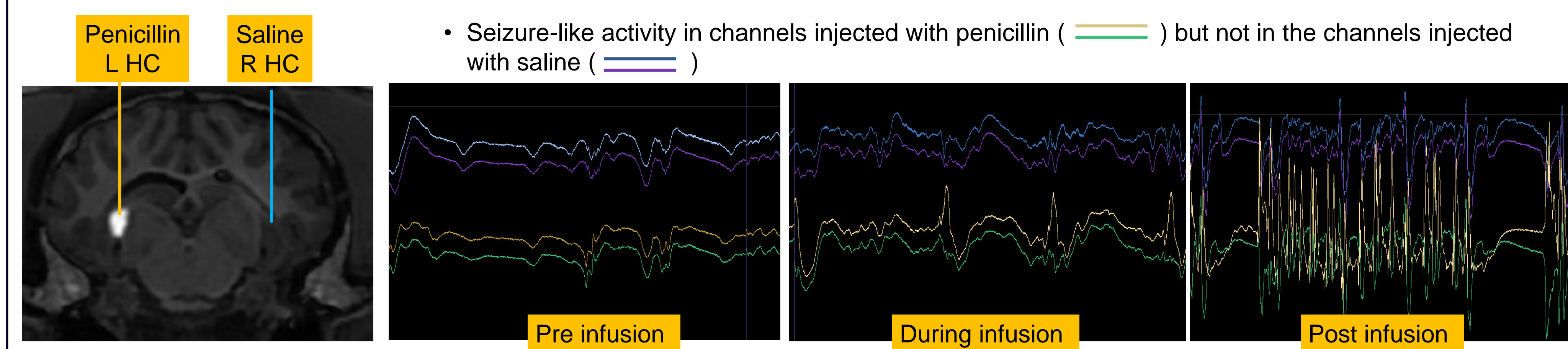
B. sEEG stereotactic implantation



2. CED in in vivo: localized infusions in specific brain areas



3. Real-time recordings of brain activity: pre-, during and post- drug delivery



SUMMARY AND CONCLUSIONS

- A prototype device consisting of a modified sEEG with a drug delivery cannula attachment was built and tested for CED in bench and in vivo models.
- The prototype device was able to perform the desired functions, monitor neural activity and deliver therapeutic compounds.

Implications:

- The availability of drug delivery capability in an sEEG makes possible real-time monitoring of neural activity before, during and after drug delivery.
- This can potentially have significant impact on identifying the target location (particularly in epilepsy), screening of new compounds, safety of treatments, evaluating the onset, mechanism of action and efficacy of therapeutic compounds, especially for therapies intended to alter neural activity (e.g. for epilepsy).

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