

Submission ID #: 70618

Scriptwriter Name: Pallavi Sharma

Project Page Link: https://review.jove.com/files_upload.php?src=21538538

Title: A Protocol for Uncovering Neural Mechanisms of Neurotherapeutic Effects on Electroencephalography Using the Human Neocortical Neurosolver

Authors and Affiliations:

Nicholas Tolley, David W. Zhou, Austin E. Soplata, Dylan S. Daniels, Katharina Duecker, Carolina Fernandez Pujol, Joyce Gao, Stephanie R. Jones

Department of Neuroscience, Brown University

Corresponding Authors:

Nicholas Tolley (nicholas_tolley@brown.edu)

Email Addresses for All Authors:

Nicholas Tolley	(nicholas_tolley@brown.edu)
David W. Zhou	(david_zhou@brown.edu)
Austin E. Soplata	(austin_soplata@brown.edu)
Dylan S. Daniels	(dylan_s_daniels@brown.edu)
Katharina Duecker	(katharina_duecker@brown.edu)
Carolina Fernandez Pujol	(carolina_fernandez@brown.edu)
Joyce Gao	(joyce_gao@brown.edu)
Stephanie R. Jones	(stephanie_jones@brown.edu)

Author Questionnaire

1. Microscopy: Does your protocol require the use of a dissecting or stereomicroscope for performing a complex dissection, microinjection technique, or something similar?

2. Software: Does the part of your protocol being filmed include step-by-step descriptions of software usage?

Yes, all done

3. Filming location: Will the filming need to take place in multiple locations? **Enter Yes or No.**
No.

4. Testimonials (optional): Would you be open to filming two short testimonial statements **live during your JoVE shoot**? These will **not appear in your JoVE video** but may be used in JoVE's promotional materials.

No

Current Protocol Length

Number of Steps: 19

Number of Shots: 33

Interviews

Videographer: Obtain headshots for all authors available at the filming location.

INTRODUCTION:

~~REQUIRED: Summarize your research focus and the main questions it aims to answer.~~

- 1.1. **Stephanie Jones:** We develop models of brain circuitry that simulate the neural generators of EEG and apply them to discover how neurotherapeutics impact brain dynamics.
 - 1.1.1. INTERVIEW: Named Talent says the statement above in an interview-style shot, looking slightly off-camera.

~~Describe the research gap or limitation in existing methods and how this protocol addresses them.~~

- 1.2. **Nicholas Tolley:** Current methods cannot fully explain how neurotherapeutics alter brain circuits. This protocol combines EEG with circuit simulations to reveal underlying mechanisms.
 - 1.2.1. INTERVIEW: Named Talent says the statement above in an interview-style shot, looking slightly off-camera.

CONCLUSION:

~~What does this protocol allow researchers to study or measure?~~

- 1.3. **Austin Soplata:** Our simulations enable multiscale interpretation of EEG generation and can be used to build evidence about the mechanisms of neurotherapeutics on brain circuits.
 - 1.3.1. INTERVIEW: Named Talent says the statement above in an interview-style shot, looking slightly off-camera.

~~Describe the most important consideration or challenge when performing this protocol.~~

- 1.4. **Joyce Gao:** The simulation experiments require well-grounded hypotheses on potential mechanisms of neurotherapeutics, as they provide targets for model fitting and examination.

- 1.4.1. INTERVIEW: Named Talent says the statement above in an interview-style shot, looking slightly off-camera.

~~How can future studies build on this work? Describe the questions or research directions that can be investigated next.~~

- 1.5. **David Zhou:** Future studies using invasive electrophysiology or alternative types of imaging can inform modeling, supporting an iterative simulation and validation process.

- 1.5.1. INTERVIEW: Named Talent says the statement above in an interview-style shot, looking slightly off-camera.

Videographer: Obtain headshots for all authors available at the filming location.

Protocol

***Videographer:** Please always record an audio slate while filming each shot mentioned in the shotlist.*

2. Establish Pre-treatment Model Fit with Manual Tuning

Demonstrator: Nicholas Tolley

2.1. To begin, identify the treatment-induced electroencephalography-event-related potential or EEG-ERP (*E-E-G-E-R-P*) biomarker [1] and initialize the default Human Neocortical Neurosolver or HNN (*H-N-N*) model [2].

2.1.1. WIDE: Talent in front of the computer with the selected EEG-ERP markers displayed on the screen. ***Videographer:** Please obtain CU shot as well for this shot.*

2.1.2. SCREEN: 70618_2.1.2.mp4: 00:11-00:15

2.2. Then, start with the canonical HNN event-related potential simulation and its default parameters [1]. Manually tune the scaling factor and exogenous drive parameters to fit the pre-treatment event-related potential [2].

2.2.1. SCREEN: 70618_2.2.1-2.2.2.mp4: 00:08-00:17

2.2.2. SCREEN: 70618_2.2.1-2.2.2.mp4: 00:18-00:26

2.3. Click the **Load data** button on the menu bar located on the lower left portion of the graphical user interface window [1].

2.3.1. SCREEN: 70618_2.3.1.mp4: 00:04-00:12

2.4. In the file browser window, select a CSV file or text file containing the event-related potential waveform to be modeled as the target waveform [1]. Ensure the file is comma-delimited with two columns: time and source-localized empirical dipole waveform [2].

2.4.1. SCREEN: 70618_2.4.1-2.4.2.mp4: 00:04-00:09

2.4.2. SCREEN: 70618_2.4.1-2.4.2.mp4: 00:09-00:20

2.5. In the **Simulation Parameters** panel, set the desired values of **tstop** (*T-Stop*) to control the simulation length, **dt** (*D-T*) for the integration time step, and **Trials** for the number

of repeated simulations with identical model parameters [1]. Select **Backend** as either **Joblib** for serial simulations over trials or **MPI (M-P-I)** for parallel simulations and specify the number of computer **Cores** [3].

2.5.1. SCREEN: 70618_2.5.1.mp4.

2.5.2. SCREEN: 70618_2.5.2.mp4 00:03-00:12

- 2.6. Click the **Run** button to start the default simulation of a canonical event-related potential [1].

2.6.1. SCREEN: 70618_2.6.1_start.mp4: 00:04-00:10; 70618_2.6.1_end: 00:04-00:07

- 2.7. Click the **Visualization** tab on the top left of the graphical user interface window [1]. Then, click the dropdown menu labeled **Data to compare** and select the loaded target waveform from the previous step [2]. Click **Clear axis** to reset the plot [3].

2.7.1. SCREEN: 70618_2.7.1-2.8.2.mp4: 00:03-00:05

2.7.2. SCREEN: 70618_2.7.1-2.8.2.mp4: 00:09-00:13.

2.7.3. SCREEN: 70618_2.7.1-2.8.2.mp4: 00:13-00:17

- 2.8. Click **Add plot** to generate a new plot with the simulated initial ERP waveform and the target waveform overlaid together [1]. Display the automatically calculated correlation coefficient and root mean squared error between the 2 waveforms [2].

2.8.1. SCREEN: 70618_2.7.1-2.8.2.mp4: 00:18-00:21

2.8.2. SCREEN: 70618_2.7.1-2.8.2.mp4: 00:23-00:25

- 2.9. Next, modify the scaling factor by manual hand tuning to approximately match the magnitudes of the simulated and empirical dipole waveforms [1]. Set the default **Dipole scaling** parameter in the **Simulation** tab to 3000 [2].

2.9.1. SCREEN: . 70618_2.9.2_updated.mp4: 00:02-00:17

2.9.2. SCREEN: 70618_2.9.2_updated.mp4: 00:17-00:27

- 2.10. Identify the simulated ERP peaks that are misaligned in time with the empirical ERP waveform [1].

2.10.1. SCREEN: 70618_2.11.1.mp4: 00:03-00:13

- 2.11. Click the **External drives** tab on the top left of the graphical user interface window [1].

Click the dropdown menu of the exogenous drive whose **Mean time** is closest to the misaligned peak [2].

2.11.1. SCREEN: 70618_2.12.1-2.13.2.mp4: 00:01-00:04

2.11.2. SCREEN: 70618_2.12.1-2.13.2.mp4: 00:04-00:08

- 2.12. Modify the values in the **Mean time** and **Std dev time** (*Standard deviation time*) text boxes to better match the timing and width of peaks in the target waveform [1].

2.12.1. SCREEN: 70618_2.12.1-2.13.2.mp4: 00:10-00:14

- 2.13. Set the **Mean time** of the **evprox1** (*E-V-Prox-One*) external drive to 60 milliseconds, **evdist1** (*E-V-Dist-One*) to 100 milliseconds, and **evprox2** (*E-V-Prox-Two*) to 150 milliseconds [1].

2.13.1. SCREEN: 70618_2.14.1.mp4: 00:05-00:20

- 2.14. Next, manually tune the synaptic weights of exogenous drives to obtain a closer fit to the magnitudes of empirically recorded ERP peaks [1]. Identify the simulated ERP peaks that are misaligned in magnitude with the empirical ERP waveform [2].

2.14.1. Talent tuning the synaptic weights of exogenous drives.

2.14.2. SCREEN: 70618_2.15.1-2.17.2.mp4: 00:03-00:09

- 2.15. Click the **External drives** tab on the top left of the graphical user interface window. Click the dropdown menu of the exogenous drive whose **Mean time** is closest to the misaligned peak [1].

2.15.1. SCREEN: 70618_2.15.1-2.17.2.mp4: 00:13-00:22

- 2.16. Set the **AMPA weights** of the **evdist1** drive to 0.014243 for L5_pyramidal and 0.0000007 for L2_pyramidal [1]. Assign the **NMDA weights** of the **evdist1** drive as 0.0080074 for L5_pyramidal and 0.0004317 for L2_pyramidal [2].

2.16.1. SCREEN: 70618_2.18.1-2.19.2.mp4: 00:07-00:16.

2.16.2. SCREEN: 70618_2.18.1-2.19.2.mp4: 00:18-00:24

- 2.17. For the **evprox2** drive, configure the **AMPA weights** to 0.0684013 for L5_pyramidal and 0.143884 for L2_pyramidal [1].

2.17.1. SCREEN: 70618_2.18.1-2.19.2.mp4: 00:35-00:54.

2.18. After completing the modifications in the previous steps, click the **Simulation** tab and enter “pre-treatment_handtuned” in the **Name** text box [1].

2.18.1. SCREEN: 70618_2.20.1.mp4: 00:04-00:15

2.19. Click the **Run** button to simulate the modified parameter set [1]. Inspect the generated plot in the figure panel [2]. Access previous plots using the corresponding figure tabs and save the model outputs [3]. Select the Data to compare dropdown menu and regenerate the plot to compare the new simulation to the loaded data [4].

2.19.1. SCREEN: 70618_2.21.2-2.21.3.mp4: 00:04-00:08.

2.19.2. SCREEN: 70618_2.21.2-2.21.3.mp4: 00:23-00:25

2.19.3. SCREEN: 70618_2.21.2-2.21.3.mp4: 00:26-00:30

2.19.4. SCREEN: 70618_2.21.2-2.21.3.mp4: 00:12-00:20.

Video editor: Insert title card to show the given information

- Establish post-treatment model fit
- Uncertainty quantification with SBI and separability assessment
- Perform examination, validation, and further model constraint

Results

3. Results

- 3.1. The parameter distributions for pre-treatment and post-treatment ERPs were visualized using a pairplot [1].
 - 3.1.1. LAB MEDIA: Figure 10A.
- 3.2. Thalamocortical synchrony exhibited the greatest pre- to post-treatment separability with the lowest overlap value of 0.07 [1], which increased following treatment [2].
 - 3.2.1. LAB MEDIA: Figure 10A(i). *Video editor: Highlight the overlap value labelled "OVL: 0.07" above the thalamocortical synchrony distribution*
 - 3.2.2. LAB MEDIA: Figure 10A(iii). *Video editor: Highlight the red post-treatment distribution shifted to the right of the blue pre-treatment distribution*
- 3.3. Pre-treatment waveforms closely matched simulations generated from posterior samples, with a correlation coefficient of 0.99 [1]. Post-treatment waveforms closely matched simulations generated from posterior samples, with a correlation coefficient of 0.96 [2].
 - 3.3.1. LAB MEDIA: Figure 10B. *Video editor: Highlight the blue pre-treatment waveform closely overlapping the black posterior sample waveforms and zoom in on the text "Corr: 0.99"*
 - 3.3.2. LAB MEDIA: Figure 10C. *Video editor: Highlight the red post-treatment waveform closely overlapping the black posterior sample waveforms and zoom in on the text "Corr: 0.96"*
- 3.4. Simulated ERPs sampled from pre-treatment and post-treatment parameter distributions were shown alongside corresponding cell-specific spiking activity [1].
 - 3.4.1. LAB MEDIA: Figure 11A and Figure 11B.
- 3.5. Reduced spiking activity in layer 5 pyramidal neurons was observed following treatment [1].
 - 3.5.1. LAB MEDIA: Figure 11C and Figure 11D. *Video editor: Highlight the red spike activity dots in the lower panels*

1. Electroencephalography
Pronunciation link: <https://www.merriam-webster.com/dictionary/electroencephalography>
IPA: /ɪˌlek.troʊ.ɛn.sɛf.əˈlɑː.grə.fi/
Phonetic Spelling: ih·lek·troh·en·sef·uh·laa·gruh·fee
2. Biomarker
Pronunciation link: <https://www.merriam-webster.com/dictionary/biomarker>
IPA: /ˈbaɪoʊ.mɑːrkər/
Phonetic Spelling: by·oh·mar·kur
3. Neocortical
Pronunciation link: <https://www.howtopronounce.com/neocortical>
IPA: /ˌniːoʊˈkɔːrtɪkəl/
Phonetic Spelling: nee·oh·kor·tih·kuhl
4. Neurosolver
Pronunciation link: No confirmed link found
IPA: /ˈnɜroʊ.səːlvər/
Phonetic Spelling: nyur·oh·sol·vur
5. Canonical
Pronunciation link: <https://www.merriam-webster.com/dictionary/canonical>
IPA: /kəˈnɑːnɪkəl/
Phonetic Spelling: kuh·non·ih·kuhl
6. Exogenous
Pronunciation link: <https://www.merriam-webster.com/dictionary/exogenous>
IPA: /ekˈsɑːdʒənəs/
Phonetic Spelling: ek·saj·uh·nuhs
7. Graphical
Pronunciation link: <https://www.merriam-webster.com/dictionary/graphical>
IPA: /ˈgræfɪkəl/
Phonetic Spelling: graf·ih·kuhl
8. Interface
Pronunciation link: <https://www.merriam-webster.com/dictionary/interface>
IPA: /ˈɪntərˌfeɪs/
Phonetic Spelling: in·tur·fays
9. Comma-delimited
Pronunciation link: <https://www.howtopronounce.com/delimited>
IPA: /dɪˈlɪmɪtɪd/
Phonetic Spelling: dih·lim·ih·tid
10. Empirical
Pronunciation link: <https://www.merriam-webster.com/dictionary/empirical>
IPA: /ɪmˈpɪrɪkəl/
Phonetic Spelling: em·peer·ih·kuhl
11. Dipole
Pronunciation link: <https://www.merriam-webster.com/dictionary/dipole>
IPA: /ˈdaɪ.pəl/
Phonetic Spelling: dye·pohl

12. Integration

Pronunciation link: <https://www.merriam-webster.com/dictionary/integration>

IPA: /,ɪntəˈɡreɪʃən/

Phonetic Spelling: in·tuh·gray·shuhn

13. Parallel

Pronunciation link: <https://www.merriam-webster.com/dictionary/parallel>

IPA: /ˈperəˌleɪ/

Phonetic Spelling: pair·uh·leɪ

14. Visualization

Pronunciation link: <https://www.merriam-webster.com/dictionary/visualization>

IPA: /ˌvɪʒuələˈzeɪʃən/

Phonetic Spelling: vɪzh·oo·uhl·uh·zay·shuhn

15. Correlation

Pronunciation link: <https://www.merriam-webster.com/dictionary/correlation>

IPA: /ˌkɔːrəˈleɪʃən/

Phonetic Spelling: kor·uh·lay·shuhn

16. Misaligned

Pronunciation link: <https://www.howtopronounce.com/misaligned>

IPA: /ˌmɪsəˈlaɪnd/

Phonetic Spelling: मिस·uh·lynd

17. Synaptic

Pronunciation link: <https://www.merriam-webster.com/dictionary/synaptic>

IPA: /sɪˈnæptɪk/

Phonetic Spelling: suh·nap·tik

18. AMPA

Pronunciation link: No confirmed link found

IPA: /ˈæmpə/

Phonetic Spelling: am·puh

19. NMDA

Pronunciation link: No confirmed link found

IPA: /ˌɛn ɛm diː ˈeɪ/

Phonetic Spelling: en·em·dee·ay

20. Pyramidal

Pronunciation link: <https://www.merriam-webster.com/dictionary/pyramidal>

IPA: /pəˈræmɪdəl/

Phonetic Spelling: puh·ram·ih·duhl

21. Pairplot

Pronunciation link: No confirmed link found

IPA: /ˈperˌplɑːt/

Phonetic Spelling: pair·plot

22. Thalamocortical

Pronunciation link: <https://www.howtopronounce.com/thalamocortical>

IPA: /ˌθæləməˈkɔːrtɪkəl/

Phonetic Spelling: thal·uh·muh·kor·tih·kuhl

23. Separability

Pronunciation link: <https://www.howtopronounce.com/separability>

IPA: /,sepərəˈbɪləti/

Phonetic Spelling: sep·uh·ruh·bil·uh·tee

24. Posterior

Pronunciation link: <https://www.merriam-webster.com/dictionary/posterior>

IPA: /pɑːˈstɪriər/

Phonetic Spelling: pos·teer·ee·ur

25. Neurons

Pronunciation link: <https://www.merriam-webster.com/dictionary/neuron>

IPA: /ˈnɒr,ɑːn/, /ˈnjʊr,ɑːn/

Phonetic Spelling: nyur·on; nyoo·ron