Evaluation of Electrical Stimulation Parameters on Brain Activity in a Rodent Model of Migraine

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Background

Chronic pain affects millions of people and is difficult to treat because it involves complex brain activity and often resists traditional therapies. To improve treatment, we need to better understand how the brain responds to pain—and how it recovers after interventions.

One promising approach is electrical stimulation of the brain, which may help reset abnormal activity. However, we still don't know which stimulation settings work best.

In this study, we use a rodent model to test how different combinations of stimulation frequency and intensity influence brain activity. By comparing post-stimulation patterns to normal (pain-free) baseline recordings, we aim to find the most effective conditions for supporting recovery in pain-related brain regions.

Experimental Design

- **This study analyzes brain stimulation data collected from a rodent model of pain.**
  The experiment, conducted by collaborators, involved applying electrical stimulation at different frequencies and voltages following chemically induced pain. My analysis focuses on comparing post-stimulation brain activity to a pain-free baseline to determine which stimulation conditions best support neural recovery.

Baseline Recording:
The experiment began with baseline brain activity recordings from four brain regions: the anterior cingulate cortex (ACC), bilateral amygdala (RAMG and LAMG), and ventral tegmental area (VTA), while the rat was under light anesthesia.

Pain Induction:
A formalin injection (3%, 50 µL) was administered to the rat's left hind paw to simulate pain. Brain activity was monitored for 20 minutes post-injection to observe pain-induced changes.

Electrical Stimulation (ES):
The rat then received electrical stimulation for 11 seconds at various voltages and frequencies.

Post-Stimulation Rest Phases:
A 3-minute rest period followed to monitor neural recovery. These 12 rest phases were later compared to the baseline to assess which stimulation condition best restored normal brain activity.

Study Objective and Analysis Overview

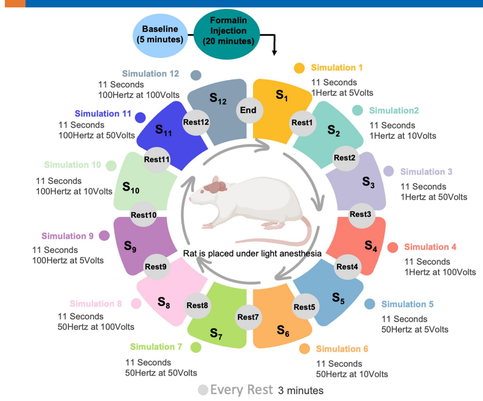

Figure 1. Experimental timeline showing baseline recording, pain induction via formalin injection, and 12 rounds of stimulation (S1–S12) followed by rest (R1–R12). Each stimulation varied in frequency and voltage.

Motivation
Understanding how the brain recovers from pain is critical for developing effective treatments. Electrical stimulation is a promising method for restoring normal brain activity, but it remains unclear which combinations of stimulation frequency and voltage are most effective.
To address this, we evaluate how different stimulation conditions impact brain recovery by comparing post-stimulation activity to a pain-free baseline. Our goal is to rank each condition from most similar to least similar to baseline activity.

Challenges
Brain data are high-dimensional and time-varying, making direct comparison computationally intensive. Measuring similarity across entire datasets becomes infeasible as matrix size increases.

Solution strategy
We propose a scalable, subset-based method:

1. Sampling: From the full baseline matrix $X \in R^{m \times p}$, we randomly sample n columns to obtain a reduced reference $X_n \in R^{m \times n}$.
2. Segmentation: Each rest matrix $Y^i \in R^{m \times q}$ is divided into non-overlapping windows $Y^{i,w} \in R^{m \times n}$, where $i = 1, \ldots 12$ and $w = 1, \ldots W$.
3. Compute pairwise distances:

   Intra-matrix similarity $d(X_n, X_n)$, $d(Y^{i,w}, Y^{i,w})$
   Inter-matrix similarity $d(X_n, Y^{i,w})$

4. Aggregate window-level p-values using Fisher's method:

$$\chi^2 = -2 \sum_{w=1}^{W} \ln(p_w)$$

Section 01 – Intra-Matrix Similarity: Internal Structure Comparison

Concept
If the internal distance distribution of a rest matrix Y^i is statistically similar to the baseline matrix X , it suggests that Y^i has an internal structure comparable to X .

Goal
Identify which rest phases Y^i resemble the baseline in terms of internal structure (how similar the vectors in Y^i are to each other).

Hypothesis Test:

$$H_0 : \mu_{d(X_n, X_n)} = \mu_{d(Y^{i,w}, Y^{i,w})}$$
$$H_1 : \mu_{d(X_n, X_n)} \neq \mu_{d(Y^{i,w}, Y^{i,w})}$$

Result:
Rest11
Rest2
Rest12
Rest4

Rest Phase	Intra p-value
Rest11	0.07969
Rest2	0.06672
Rest12	0.06298
Rest4	0.05862
Rest5	0.04530
Rest10	0.02615
Rest7	0.02568
Rest8	0.03807
Rest3	0.03215
Rest6	0.01305
Rest9	0.02047
Rest1	0.00161

Table1. Shows how similar each rest phase is to the baseline based on internal structure. Higher p-values = more similar.

Section 02 – Inter-Matrix Similarity: External Structure Comparison

Concept
If the distance between vectors in Y^i and vectors in baseline X is statistically similar to the internal distances within X, it implies that Y^i "blends in" with X's structure.

Goal
Identify which rest phases Y^i resemble the baseline in terms of internal structure (how similar the vectors in Y^i are to each other).

Hypothesis Test:

$$H_0 : \mu_{d(X_n, X_n)} = \mu_{d(X_n, Y^{i,w})}$$
$$H_1 : \mu_{d(X_n, X_n)} \neq \mu_{d(X_n, Y^{i,w})}$$

Result:
Rest6
Rest9
Rest1
Rest10

Rest Phase	Inter p-value
Rest6	0.13015
Rest9	0.06915
Rest1	0.05406
Rest10	0.04457
Rest12	0.03398
Rest7	0.02319
Rest8	0.01755
Rest5	0.01728
Rest3	0.01342
Rest11	0.01167
Rest4	0.00982
Rest2	0.00230

Table2. Shows how well each rest phase blends with the baseline structure. Higher p-values = more similar.

Rank	Rest Phase	Fisher Combined p-value	Similarity (%)
1	Rest12	0.015294	100.0
2	Rest6	0.012533	91.7
3	Rest9	0.010700	83.3
4	Rest10	0.009037	75.0
5	Rest11	0.007423	66.7
6	Rest5	0.006111	58.3
7	Rest7	0.004950	50.0
8	Rest8	0.003911	41.7
9	Rest3	0.003017	33.3
10	Rest4	0.002157	25.0
11	Rest2	0.001500	16.7
12	Rest1	0.000900	8.3

Table3. Final ranking of rest phases based on combined intra and inter p-values.
Rank 1 = most similar to baseline.

Conclusion

Our findings suggest that higher-frequency and higher-voltage electrical stimulation (specifically, 100 Hz at 100V) results in post-stimulation brain activity that most closely resembles the pain-free baseline.

Two statistical tests were used to evaluate:

•Internal structure similarity (intra-matrix): How similar the rest phases were to themselves compared to baseline.

•External structure similarity (inter-matrix):How well rest phases "blended in" with baseline activity.

Both measures consistently ranked Rest12 (100 Hz, 100V) as the most similar to baseline. This suggests that neural recovery improves progressively across sessions and is optimized under intense, high-frequency stimulation.
These results support the potential for using high-frequency stimulation protocols to **accelerate recovery** of healthy brain dynamics following pain induction.

Significance & Future Work

This work introduces a non-parametric, distance-based statistical framework to evaluate neural recovery by comparing brain signal similarity to baseline activity.

Significance:

•Provides a scalable and interpretable approach to identify which electrical stimulation parameters most effectively restore normal brain dynamics.

Future Directions:

•Incorporate advanced statistical techniques such as permutation testing, kernel methods, or manifold learning to capture more nuanced structural differences.

References

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