Interictal Epileptiform Discharges Disrupt Neural Computations Underlying Cognitive Control and Value-based Decision Making

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Abstract

This research investigates how Interictal Epileptiform Discharges (IEDs) affect cognitive control and decision-making in epileptic patients. Using the Balloon Analog Risk Task (BART) to examine decisions made under risk, our study suggests that IEDs lengthen both response times and balloon inflation times and indicates that these discharges disrupt cognitive functions associated with the prefrontal cortex. The results emphasize the need for customized interventions to mitigate these effects and improve cognitive efficiency and decision-making quality in individuals with epilepsy.

Keywords: Interictal epileptiform discharge; Human prefrontal cortex; Decision making; Cognitive control; Response time.

Introduction

Epilepsy is a neurological disorder defined by recurrent seizures made up of repetitive, spatio-temporally evolving paroxysmal bursts of neural activity. Interictal Epileptiform Discharges (IEDs) are large amplitude pathological bursts of activity that occur between seizures (Engel, 1984; Reed et al., 2020). IEDs have a detrimental impact on memory and cognitive processes (Nair, Morse, Mott, Burroughs, & Holmes, 2014; Henin et al., 2021; Warsi et al., 2022), and significantly impact response time in decision-making tasks (Browne, Penry, Poter, & Dreifuss, 1974; Holmes, McKeever, & Adamson, 1987; Krestel et al., 2023). In this study we sought to understand how these endogenous neural disruptions affected behavior and brain activity during value-based decisions under risk. We show that IEDs affect neural computations in neural circuits associated with decision-making, leading to slower response times (RTs) and prolonged balloon inflation times (ITs) in Balloon Analog Risk Task (BART).

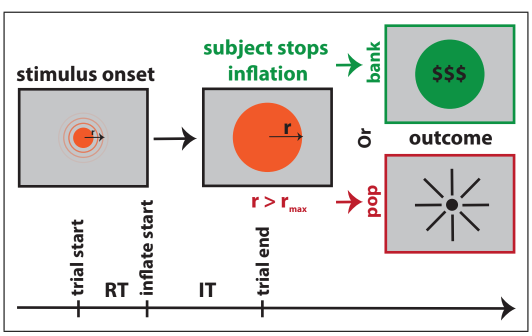

Figure 1: **BART trial timeline:** In each trial, a balloon is displayed on screen. Patients use a video game controller to inflate the balloon, pressing the same button to halt inflation and accumulate points based on the balloon's size. If the balloon pops before inflation is stopped, no points are awarded. RT represents response time; IT represents the inflation time; and r represents the radius of balloon during the inflation time while r_{max} is the maximum radius capacity of the balloon. The balloon will pop after when r gets larger than the maximum radius capacity (r_{max}) for that trial.

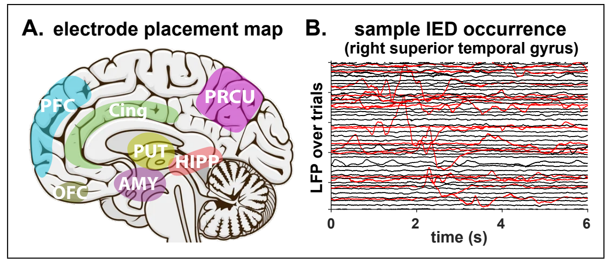

Figure 2: **A. A subset of brain regions where electrodes were implanted in patients:** A medial view of relevant brain areas. PRCU: precuneus, Cing: cingulate gyrus, PFC: prefrontal cortex, OFC: orbitofrontal cortex, AMY: amygdala, PUT: putamen, HIPP: hippocampus. **B. Example IEDs:** A patient's multi-trial neural activity is depicted for right Superior Temporal Gyrus (STG). The plot shows the amplitude of neural signals over time for different trials, with trials containing IEDs highlighted in red. The x-axis represents time (s), and the y-axis represents the LFP signal in different trials.

Methods

BART (Lejuez et al., 2002) is used to assess decision-making under risk by simulating the inflation of a balloon, which increases potential rewards but also the risk of popping and losing all gains (Figure 1). In this work, we investigated the influence of IEDs on RT and IT during BART. We examined a previously collected dataset of neural recordings from 43 participants (21 female, mean age = 36 $\pm$ 10 years) who completed an average of 233.2 $\pm$ 23.8 trials of BART while undergoing invasive neuromonitoring for drug-resistant epilepsy. Local field potentials (LFPs) were recorded from 3,259 stereo-electroencephalography (sEEG) and electrocorticography (ECoG) contacts (M= 72.42 $\pm$ 17.17 electrodes per participant). Numerous brain regions, such as anterior cingulate cortex (ACC), medial frontal cortex (MFC), orbitofrontal cortex (OFC), medial frontal lobe (MFL), basal ganglia, medial temporal lobe (MTL), occipital lobe, entorhinal cortex, and insula that are relevant to cognitive control were implanted. Figure 2A displays a subset of the relevant regions of the brain where electrodes were placed. Electrodes were recorded bilaterally.

To detect IEDs, we found trials with outlying voltage ranges using Inter-Percentile Range (IPR) method (Olver, 2010) (Figure 2B). We then found the approximate time of IED occurrence in each trial on each electrode. To do this, LFP signals were first band pass-filtered with a 4th-order, Butterworth filter with a bandwidth of 5–25 Hz. Then the Hilbert transform was applied to the filtered data to obtain the analytic signal, from which the magnitude of the analytic signal was extracted. Then, we found the the peak of the resulting signal, setting the minimum peak height at 50% of the signal maximum value to ensure only prominent peaks in each trial were considered. These peaks were further refined to ensure a minimum temporal separation of 100 ms, consistent with physiological limits on IED duration.

We tested for differences in RT and IT across three time windows relative to the stimulus onset (pre: 500 ms before balloon onset to balloon onset; peri: 250 ms before and 250 ms after balloon onset; post: 500 ms after balloon onset) using Wilcoxon rank sum test (also known as the Mann-Whitney U test). Using permutation test with 10,000 permutations, we then examined where in the human brain IEDs affected the decision-making computations that led to changed RTs and ITs. Some channels in some brain areas where IEDs were detected, demonstrates that their RTs and ITs significantly varied ($p<0.001$) from channels without IED detection.

Results

We first examined the effect of IEDs occurring in three time windows, coinciding with the appearance of the balloon, on behavioral measures during BART. We found both significantly longer aggregated RTs and ITs in trials in which IEDs occurred (*$p<0.001$; Figure 3). These results show that IEDs alter response behavior and risk assessment during BART. Our next analysis focused on understanding how endogenous disruptions of electrical brain activity in specific regions affected behavior. Figure 4 shows the brain regions where IEDs were detected that led to significantly altered RTs (Figure 4A) and ITs (Figure 4B). We found that IEDs in parietal, prefrontal, and thalamic regions had the largest effect on RT and IT during BART.

Discussion

Our findings indicate that IEDs in brain regions associated with cognitive functions are correlated with increased response times and prolonged balloon inflation times in BART. Variance in these behavioral measures increased markedly across patients suggesting the potential for idiosyncratic effects of IEDs on neural computation during decision making.

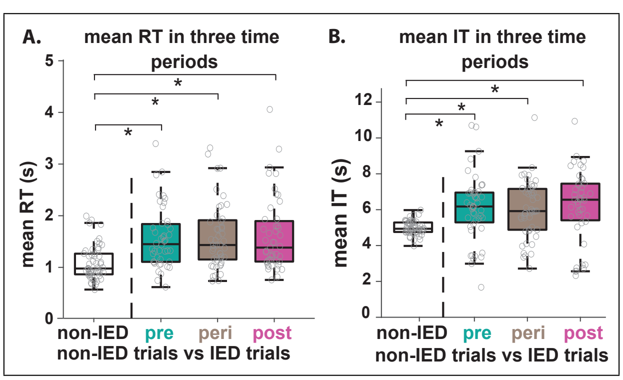

Figure 3: **Comparing A. RTs and B. ITs in IED and non-IED trials.** X-axes show different time periods relative to balloon onset. Y-axes show mean RT (A) and mean IT (B). Asterisks show statistical significance between IED and non-IED trials in terms of RT and IT. Each gray circle represents the mean RT or IT across channels with significant IEDs for each patient.

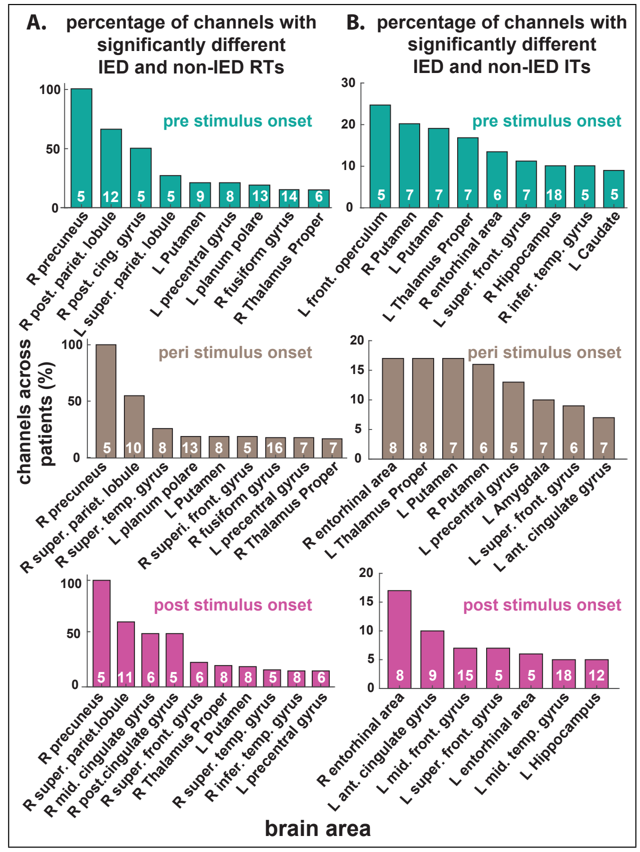

Figure 4: **Percentage of channels by brain region showing differences in IED vs. non-IED A. RTs and B. ITs.** X-axes highlight brain regions, sorted by decreasing percentage. Y-axes show the percentage of electrodes, aggregated across patients, whose ITs and RTs differed significantly in the presence of IEDs. This percentage of channels is calculated by dividing the number of significant channels in a specific brain area by the number of all channels in that brain area. The number inside each bar shows number of significant channels in a brain region across all patients. Each row shows the result of analysis in different time periods relative to stimulus onset. These panels are color coded as in Figure 3. L: left hemisphere, R: right hemisphere.

While all of the patients exhibited significantly increased RTs, some patients interestingly exhibited decreased mean ITs, suggesting that IEDs in some brain areas may increase patients propensity to stop balloon inflation earlier, thereby receiving a smaller reward. The specific brain regions highlighted here are important for decision-making and surprisingly overlap with brain areas that encode reward prediction and prediction error during BART (Cowan et al., 2024). Future research will explore the impact of IEDs on specific features of brain activity such as spectral representations and neural firing rates associated with BART performance.

Acknowledgments

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References

Browne, T. R., Penry, J. K., Poter, R. J., & Dreifuss, F. E. (1974). Responsiveness before, during, and after spike-wave paroxysms. *Neurology*, *24*(7), 659–659.

Cowan, R. L., Davis, T., Kundu, B., Rahimpour, S., Rolston, J. D., & Smith, E. H. (2024). More widespread and rigid neuronal representation of reward expectation underlies impulsive choices. *bioRxiv*, 2024–04.

Engel, J. (1984). A practical guide for routine eeg studies in epilepsy. *Journal of Clinical Neurophysiology*, *1*(2), 109–142.

Henin, S., Shankar, A., Borges, H., Flinker, A., Doyle, W., Friedman, D., ... Liu, A. (2021). Spatiotemporal dynamics between interictal epileptiform discharges and ripples during associative memory processing. *Brain*, *144*(5), 1590–1602.

Holmes, G. L., McKeever, M., & Adamson, M. (1987). Absence seizures in children: clinical and electroencephalographic features. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *21*(3), 268–273.

Krestel, H., Schreier, D. R., Sakiri, E., von Allmen, A., Abukhadra, Y., Nirkko, A., ... others (2023). Predictive power of interictal epileptiform discharges in fitness-to-drive evaluation. *Neurology*, *101*(9), e866–e878.

Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., ... Brown, R. A. (2002). Evaluation of a behavioral measure of risk taking: the balloon analogue risk task (bart). *Journal of Experimental Psychology: Applied*, *8*(2), 75.

Nair, S., Morse, R. P., Mott, S. H., Burroughs, S. A., & Holmes, G. L. (2014). Transitory effect of spike and spike-and-wave discharges on eeg power in children. *Brain and Development*, *36*(6), 505–509.

Olver, F. W. (2010). *Nist handbook of mathematical functions hardback and cd-rom*. Cambridge university press.

Reed, C. M., Mosher, C. P., Chandravadia, N., Chung, J. M., Mamelak, A. N., & Rutishauser, U. (2020). Extent of single-neuron activity modulation by hippocampal interictal discharges predicts declarative memory disruption in humans. *Journal of Neuroscience*, *40*(3), 682–693.

Warsi, N. M., Wong, S. M., Suresh, H., Arski, O. N., Yan, H., Ebden, M., ... others (2022). Interictal discharges delay target-directed eye movements and impair attentional set-shifting in children with epilepsy. *Epilepsia*, *63*(10), 2571–2582.