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Minimally-invasive electric stimulation techniques to target hippocampal theta in the urethane-anesthetized rat

Electrical brain stimulation shows significant potential for studying normal and treating abnormal brain function, owing to the electrical nature of the brain. Non-invasive techniques, while attractive due to their affordability, ease of use, and low-risk nature, have limited effectiveness and mechanisms that are not well understood. Moreover, their ability to target deep brain regions is restricted, often affecting only surface areas. A novel technique, Temporal Interference (TI), has emerged as a promising method for reaching deeper targets. In this study, we used a virtual rat head model to optimize the locations for skull-mounted electrodes to stimulate the hippocampus. The hippocampus is a deep brain region that spontaneously generates theta, which is the brain's largest amplitude rhythm, associated with learning, memory, and has possible antiepileptic effects. We employed a range of stimulation techniques and observed their effects on brain rhythms. We used a novel stimulus artifact removal technique, Independent Component Analysis (ICA), to increase the certainty of the results. Our results indicated that all stimulation methods, in a stimulus intensity-dependent manner, increased the likelihood of spontaneous theta, as well as the frequency and power of theta at the onset of the stimulus, which persisted after the stimulus. TI and amplitude-modulated (AM) stimulation generated phase-locked theta to the wave envelope of the stimulation. We also found the magnitude of the effect was dependent on the pre-stimulus power of theta, indicating a dependency on brain state. This study is significant in advancing our understanding of electrical stimulation techniques for deep brain modulation, potentially leading to safe, low-cost, non-invasive treatments or experimental tools that can target previously inaccessible brain structures.