



# Thalamic Stimulation to Stay Stimulated After a Seizure

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## Thalamic Stimulation Improves Postictal Cortical Arousal and Behavior

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The postictal state following seizures is characterized by impaired consciousness and has a major negative impact on individuals with epilepsy. Previous work in disorders of consciousness including the postictal state suggests that bilateral deep brain stimulation (DBS) of the thalamic intralaminar central lateral nucleus (CL) may improve level of arousal. We tested the effects of postictal thalamic CL DBS in a rat model of secondarily generalized seizures elicited by electrical hippocampal stimulation. Thalamic CL DBS was delivered at 100 Hz during the postictal period in 21 female rats while measuring cortical electrophysiology and behavior. The postictal period was characterized by frontal cortical slow waves, like other states of depressed consciousness. In addition, rats exhibited severely impaired responses on two different behavioral tasks in the postictal state. Thalamic CL stimulation prevented postictal cortical slow wave activity but produced only modest behavioral improvement on a spontaneous licking sucrose reward task. We therefore also tested responses using a lever-press shock escape/avoidance (E/A) task. Rats achieved high success rates responding to the sound warning on the E/A task even during natural slow wave sleep but were severely impaired in the postictal state. Unlike the spontaneous licking task, thalamic CL DBS during the E/A task produced a marked improvement in behavior, with significant increases in lever-press shock avoidance with DBS compared with sham controls. These findings support the idea that DBS of subcortical arousal structures may be a novel therapeutic strategy benefitting patients with medically and surgically refractory epilepsy.

## Commentary

Seizures often result in a postictal state associated with a range of cognitive, behavioral, and psychological impairments. This postictal state can last for hours to days and the reduction in arousal level can be significantly debilitating to patients, leading to development of comorbid neuropsychiatric disease and poor scholastic and work performance.<sup>1</sup> The postictal period is often also marked by generalized suppression of EEG activity.<sup>2</sup> The duration of this EEG suppression may confer increased risk of sudden unexpected death in epilepsy (SUDEP),<sup>3</sup> the leading cause of death in patients with refractory epilepsy.<sup>4</sup> Thus, understanding mechanisms by which seizures lead to this postictal state and devising ways to mitigate impaired arousal could reduce morbidity and mortality.

Neurostimulation techniques, including deep brain stimulation (DBS), have long been employed in the treatment of a range of neurological conditions,<sup>5</sup> including epilepsy.<sup>6</sup> Past work in disorders of consciousness demonstrates that DBS of the intralaminar central lateral (CL) nucleus of the thalamus improves arousal.<sup>7</sup> Although it has been shown that stimulation can qualitatively improve arousal in rats,<sup>8</sup> whether such

stimulation could quantitatively improve arousal was unknown. Xu et al, set out to test this in freely behaving female rats following focal limbic seizures with secondary generalization induced by hippocampal stimulation.<sup>9</sup>

Twenty-one female Sprague-Dawley rats were implanted with electrodes in right lateral orbital frontal cortex for local field potential (LFP) recording, bilateral hippocampus (HC) for seizure induction and LFP recording, and bilateral CL for DBS. To examine the effect of CL DBS on performance in a positive reinforcement task, one group of 12 animals was trained on the sucrose-licking reward task. The presence and quantity of licking provides a quantifiable measure of cognitive function. Animals were then implanted as above and underwent anesthetized stimulation titration. After surgery, animals repeated task training and underwent awake stimulus titration. During trials, rats received simultaneous HC (0.1-1.5 mA, 60 Hz, 2 ms square wave pulses, 2 s) and bilateral CL DBS (50-250  $\mu$ A, 100 Hz, 1 ms square wave pulses per side, 600 s) or sham (0.1  $\mu$ A per side) stimulation while performing the sucrose-licking task. Stimulation parameters were determined empirically for each animal. In both DBS and sham trials, poly-spike activity was





recorded in frontal cortical and HC LFP, evidencing generalized seizure. In the sham group, large amplitude delta slowing was observed in frontal LFP in the postictal period, but these were abolished in the CL DBS. In both trial groups, licking stopped during the seizure but resumed in the postictal period. There was a trend toward increased lick rate in the DBS group during the postictal period, but this was not statistically significant; however, there was a significant increase in lick rate in the poststimulus period.


To examine the effect of CL DBS on a negative reinforcement task in which animals are more highly motivated to perform, a group of 9 rats was trained on a lever-press escape/avoidance (E/A) task, and underwent surgery, stimulus titration, and retesting as above. In this task, rats learn that a tone signifies an impending foot shock and press a lever to avoid the shock. In postictal testing without CL DBS or sham stimulation (120 s), presentation of the sound in the postictal period did not eliminate cortical slow waves (did not cause arousal), thus the animals did not press the lever in response to the tone, but did press the lever once a shock was delivered. During cortical slow waves produced by natural sleep, the tone abolished the cortical slow waves and the animal pressed the lever in response to the tone to avoid the shock. In trials with CL DBS or sham stimulation, CL DBS improved responses in the postictal period as evidenced by increased avoidance percentage and reduced reaction time compared to sham stimulation. Although neither of these was restored to preictal performance, levels that CL DBS reduced the impairment in arousal is remarkable.

The authors note that they did not notice an effect on ictal activity and thus do not believe the effect of CL DBS on arousal was due to a reduction in seizure severity; however, if CL DBS were to reduce seizure severity as well, this would not necessarily be bad. Given that cortical slowing is also seen in natural sleep, especially deeper stages of nonrapid eye movement sleep, E/A testing was performed during sleep in the absence of a seizure to differentiate behavioral responses during sleep from those in the postictal period. Auditory cues presented during sleep abolished cortical slow waves (caused arousal) and resulted in appropriate behavioral responses (lever press).


This study supports that DBS of subcortical arousal structures is a novel and feasible therapeutic strategy to improve postictal arousal in patients with treatment refractory epilepsy. Although it is exciting that they were able to improve performance on these tasks, that responsiveness was not restored back to baseline suggests that stimulation parameters could be optimized. As we think about translation to patients, a limitation of this study is that seizures had to be induced in order to time CL stimulation properly. Another limitation is that DBS is typically continuous open-loop stimulation on a set on-off schedule. Constant stimulation of arousal pathways would be presumed to disrupt normal sleep. Both limitations could be addressed in spontaneously seizing models with a closed-loop system with detectors in the seizure onset zone and stimulating leads in the CL. This would allow triggering of CL stimulation coincident with spontaneously occurring seizures.

In addition, there is more to be learned with respect to the molecular, cellular, and circuit level details underlying the beneficial effect of CL DBS on postictal arousal. Furthermore, it would be interesting and informative to delve deeper into how many of the varied phenotypes observed in the postictal period could be positively affected by the stimulation and whether parameters could be tuned to increase the benefit. Perhaps a similar stimulation paradigm could be employed to reduce seizure sequelae thought to increase risk for SUDEP, such as respiratory and autonomic dysregulation, in addition to impaired arousal.<sup>4,10</sup> That said, these details are not critical to begin testing whether similar stimulation can reduce postictal arousal impairment in patients. Indeed, this group has a clinical trial underway through the NIH Brain Initiative. As parameters and implementation procedures are optimized, it will be important to examine the role of preventing impaired awareness associated with focal impaired awareness seizures. This could go a long way toward allowing these patients to more fully participate in their lives again with less fear of whether they will have an awareness-impairing seizure.

In summary, Xu et al demonstrate 2 behavioral tasks that can be used to evaluate whether an intervention improves task performance after a seizure. They also establish that CL DBS improves arousal by reducing cortical slow activity in frontal cortex. And they establish that CL DBS improves task performance after a seizure. This is an exciting development for patients who experience prolonged impairment of arousal after seizures, and it has real potential to reduce seizure-related morbidity and mortality.

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