Flicker stimulation shines in clinical trial for epilepsy

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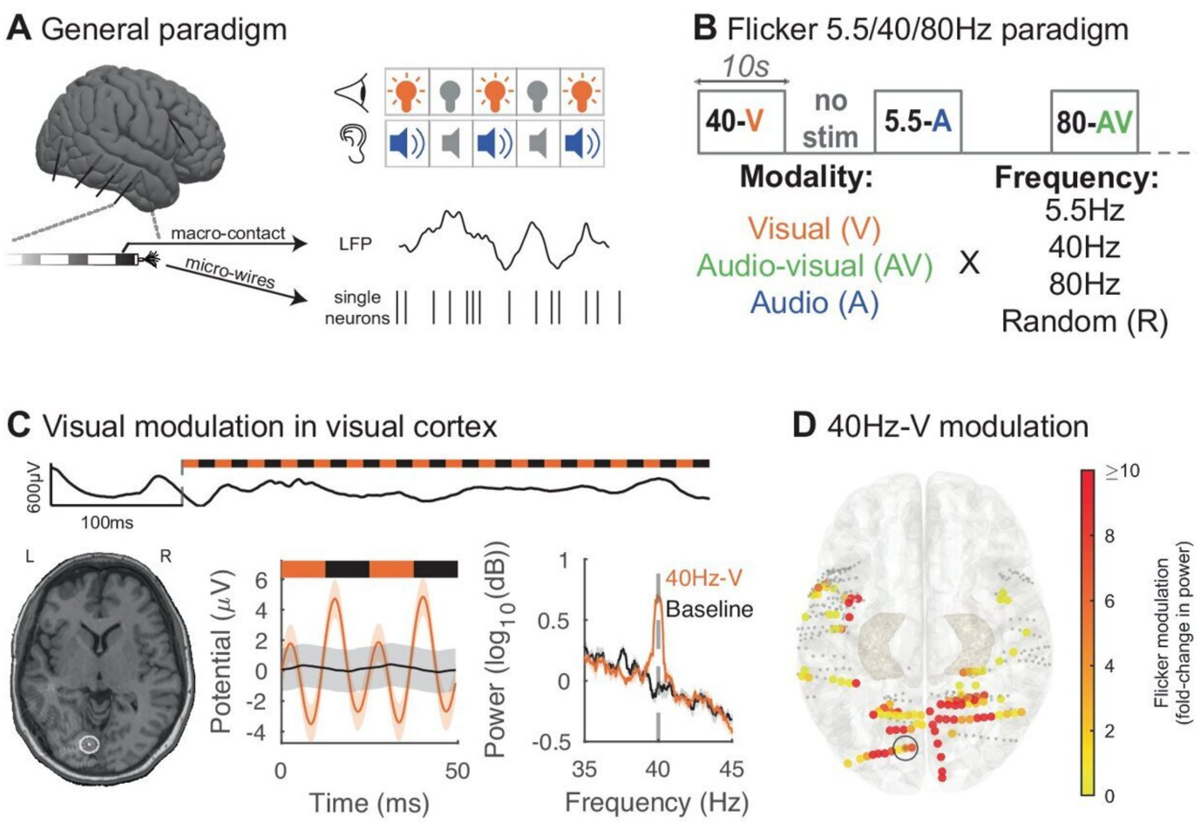

Auditory and visual flicker induce a steady-state evoked potential in human sensory regions. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-47263-y

Biomedical engineer Annabelle Singer has spent the past decade developing a noninvasive therapy for Alzheimer's disease that uses flickering lights and rhythmic tones to modulate brain waves. Now she has discovered that the technique, known as flicker, also could benefit patients with a host of other neurological disorders, from epilepsy to multiple sclerosis.

Previously, Singer and her collaborators demonstrated that the lights and sounds, delivered to patients through goggles and headphones, have beneficial effects. Flicker has been successful in animal studies and in early human feasibility trials, where it was tested for safety, tolerance, and patient adherence.

Now, thanks to a clinical trial for people with epilepsy, the researchers quantified flicker's effects with unprecedented precision. They also made an unexpected, but encouraging, discovery: The treatment reduced interictal epileptiform discharges (IEDs) in the brain.

These large, intermittent electrophysiological events are observed between seizures in people with epilepsy. They appear as sharp spikes on an EEG readout.

"What's interesting about these IEDs is that they don't just occur in epilepsy," said Singer, McCamish Foundation Early Career Professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. "They occur in autism, multiple sclerosis, Alzheimer's, and other neurological disorders, too." And IEDs disrupt normal brain function, causing memory impairment.

Singer and her team published their findings in *Nature Communications*.

The rhythm in our heads

Inside the brain are elaborate symphonies of electrical activity: brain waves, or oscillations, that compose our memories, thoughts, and emotions. Singer wants to modulate those oscillations for therapeutic purposes.

At specific frequencies of light and sound, the flicker treatment can induce gamma oscillations in mice. This helps the brain recruit microglia, cells responsible for removing beta amyloid, which is believed to play a central role in Alzheimer's pathology. Part of the work is in recording what's happening in the brain during treatment to verify how it's working.

The patients in the trial were under the care of physician Jon Willie at the Emory University Hospital Epilepsy Monitoring Unit. (Willie, co-corresponding author of the study with Singer, is now at Washington University in St. Louis.)

They were awaiting surgery to remove an area of the brain where seizures occur. Before that could happen, they had to undergo intracranial seizure monitoring—recording electrodes are placed in the brain to pinpoint the seizure onset zone and determine exactly which tissue should be removed. Then, patients and their care team wait for a seizure to happen. It can take days.

"In human studies, we've used noninvasive methods like functional MRI or scalp EEG, but they have real downsides in terms of resolution," Singer said. "Working with these patients was a game changer. These are people with treatment-resistant epilepsy, which means that drugs aren't working for them."

Pathway to healing

Singer's team recruited 19 patients. Lead author of the study, Lou Blanpain, a former Ph.D. student in Singer's lab and now a medical student at Emory, went from patient to patient with the flicker stimulation and recording equipment.

"Because these patients already had recording probes implanted for clinical reasons, we were able to record directly from the brain," Singer said. "We've never been able to get recordings of this quality during flicker treatment before."

As the researchers expected, flicker modulated the visual and auditory brain regions that respond strongly to stimuli. But it also reached deeper, into the medial temporal lobe and prefrontal cortex, brain regions crucial for memory. And across the brain, in regions Singer hadn't fully explored before, she found IEDs were decreasing.

"That has important implications for whether flicker is therapeutically relevant for people with Alzheimer's, but also in general if we want to target anything beyond the primary sensory regions," she said.

"All of this points to the potential use of flicker in a lot of different contexts. Going forward, we're definitely going to look at other conditions and other potential implications."

More information: Lou T. Blanpain et al, Multisensory flicker modulates widespread brain networks and reduces interictal epileptiform discharges, *Nature Communications* (2024). DOI: 10.1038/s41467-024-47263-y

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