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# Surgery-free brain stimulation could provide new treatment for dementia

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Temporal interference (TI) is non-invasive and delivers electrical stimulation through electrodes placed on the participant's head. Credit: Imperial College London

Scientists at Imperial College London are leading on the development and testing of the new method of stimulating the brain, which could provide an alternative treatment for brain diseases such as Alzheimer's, and its associated memory loss.

Known as temporal interference (TI), the non-invasive method works by delivering electrical fields to the brain through electrodes placed on the patient's scalp and head.

By targeting the overlapping electrical fields researchers were able to stimulate an area deep in the brain called the hippocampus, without affecting the surrounding areas—a procedure that until now required surgery to implant electrodes into the brain.

The approach has been successfully trialed with 20 healthy volunteers for the first time by a team at the UK Dementia Research Institute (UK DRI) at Imperial and the University of Surrey.

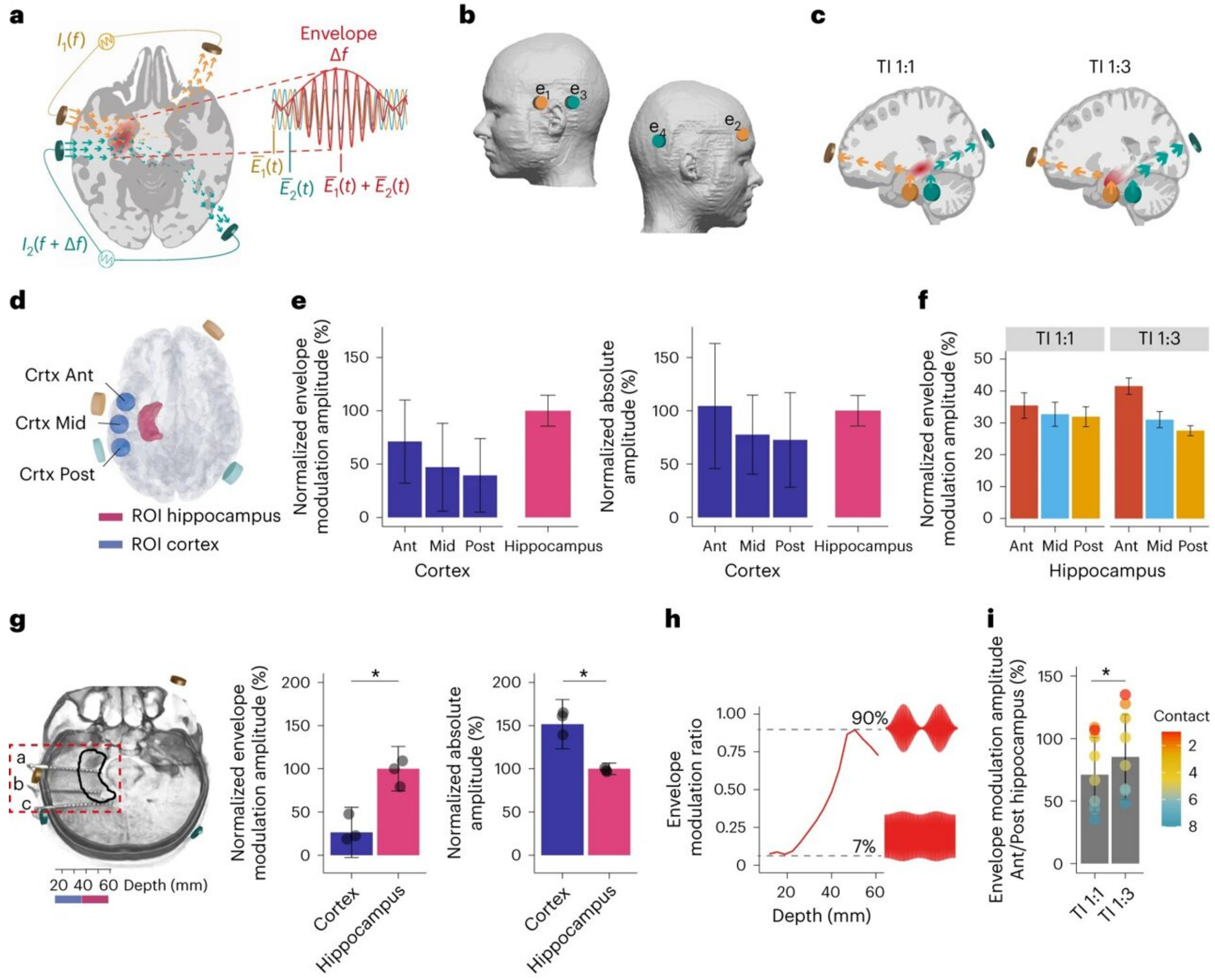
Their initial findings, published in the journal *Nature Neuroscience*, show that when healthy adults perform a memory task while receiving TI stimulation it helped to improve memory function.

The team is now conducting a clinical trial in people with early-stage Alzheimer's disease, where they hope TI could be used to improve symptoms of memory loss.

Dr. Nir Grossman, from the Department of Brain Sciences at Imperial College London, who led the work said, "Until now, if we wanted to electrically stimulate structures deep inside the brain, we needed to surgically implant electrodes which of course carries risk for the patient, and can lead to complications.

"With our new technique we have shown for the first time, that it is possible to remotely stimulate specific regions deep within the human brain without the need for surgery. This opens up an entirely new avenue of treatment for brain diseases like Alzheimer's which affect deep brain structures."

TI was first described by the team at Imperial College London in 2017 and shown to work in principle in mice.



Fundamentals of TI hippocampal stimulation and validation using computational modeling and cadaver measurements. Concept of TI hippocampal stimulation: **a**, Two current sources $I_1$ and $I_2$ are applied simultaneously via electrically isolated pairs of scalp electrodes (orange and green) at kHz frequencies $f_1$ and $f_2$, with a small frequency difference $\Delta f = f_1 - f_2$ within the range of neural activity. The currents generate oscillating electric fields E\bf E$_1(t)$ and E\bf E$_2(t)$ inside the brain (orange and green arrows, respectively). Superposition of these fields, E\bf E$_1(t)$ + E\bf E$_2(t)$, results in an envelope amplitude that is modulated periodically at $\Delta f$. The peak amplitude of the envelope modulation can be localized in deep brain structures such as the hippocampus (highlighted in red). **b**, Schematic of electrode configuration targeting the left hippocampus. Electrodes $e_1$ and $e_2$ formed one electrode pair (orange) and electrodes $e_3$ and $e_4$ another (green), corresponding to $I_1$ and $I_2$ in **a**. $e_1$ and $e_3$ were located at nasion plane of the left hemisphere, symmetrically above the anterior–posterior midline of the hippocampus (5 cm distance between electrode centers). $e_2$ and $e_4$ were located at a plane above the eyebrow on the right hemisphere (approximately 16 cm distance between electrode centers). Electrodes were 1.5 cm × 1.5 cm square with rounded corners for ex vivo and in vivo experiments and circular 2 cm diameter for computational modeling. **c**, Illustration of steering of the TI stimulation locus along the hippocampal longitudinal axis. TI stimulation with 1:1 current ratio ('TI 1:1') and stimulation locus in the middle region (left); TI stimulation with 1:3 current ratio ('TI 1:3') and locus in the anterior region (right). By reducing the current amplitude in one electrode pair and increasing it in the second while keeping the current sum fixed, the stimulation locus can be steered toward the electrode pair with the smaller current amplitude[14]. Computation of TI stimulation locus in a human anatomical model: **d**, Schematic of the ROIs in the left (stimulated) hippocampus and its overlying cortex; Ant, anterior; Mid, middle; Post, posterior. **e**, Left: fields' envelope modulation amplitude. Right: fields' absolute amplitude; for the ROIs shown in **d**. Values are median ± s.d. normalized to the hippocampal value here and thereafter (*n* indicates number of voxels (nvox) per ROI: Cortex (Crtx), Crtx Ant 48,103, Crtx Mid 43,247, Crtx Post 42,656, Hippocampus 50,349). For whole-brain electric field modeling, see Supplementary Fig. 1a. Note that the cortex ROIs are more heterogeneous than the hippocampus as these include gray matter with different folding and white matter tissue. **f**, Envelope modulation amplitude in hippocampal ROIs (for ROI schematic, see Fig. 2b) during TI 1:1 and TI 1:3 stimulations (*n* indicates nvox: Ant 22,651, Mid 17,718, Post 9,980); for additional current ratios, see Supplementary Fig. 1. Measurement of TI stimulation locus in a human cadaver ($I_1 = 2$ kHz, 1 mA; $I_2 = 2.005$ kHz, 1 mA): **g**, Left: CT head image with intracranial electrode leads a, b and c implanted in the left mesial temporal lobe. Each electrode consisted of 15 electrode contacts; black contour, approximate location of the left hippocampus; orange and green stimulation electrodes. Middle: amplitudes of the envelope modulation in the left (stimulated) hippocampus and its overlying cortex showing higher envelope amplitude at the hippocampus (LMM, two-sided paired *t*-test, $t_{(2)} = -5.515$, $P = 0.0345$, $n = 3$ electrodes). Right: absolute amplitudes in the left hippocampus and overlying cortex, showing higher absolute amplitude in the overlying cortex (LMM, two-sided paired *t*-test, $t_{(2)} = 7.051$, $P = 0.0195$). Dots represent individual electrodes. See Supplementary Table 1 for full statistics and Supplementary Fig. 2 for additional amplitude maps. **h**, Envelope modulation ratio versus depth for electrode b, showing increasing envelope modulation with depth. **i**, Anterior (Ant) to posterior (Post) envelope modulation amplitude for the TI 1:1 and TI 1:3 conditions, showing higher Ant/Post amplitudes for the TI 1:3 condition (two-sided paired *t*-test, $t_{(7)} = -7.765$, $P = 1.204 \times 10^{-4}$, $n = 8$ hippocampal electrode contacts); envelope modulation amplitudes in the anterior electrode a were normalized to the posterior electrode c. Dots represent individual contacts in the hippocampal region and are color coded by depth (cold colors for more superficial contacts and warmer colors for deeper contacts). Asterisks identify significant differences, $P$

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