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How does transcranial alternating current stimulation entrain single-neuron activity in the primate brain?

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In PNAS, Krause et al. (1) applied transcranial alternating current stimulation (tACS) in 2 macaque monkeys and measured the effect on neural entrainment in the hippocampus and basal ganglia. They delivered 2-mA tACS (4 mA peak-to-peak) through 2 scalp electrodes and measured average electric field strengths in the hippocampus and basal ganglia of 0.28 V/m in one monkey and 0.35 V/m in another monkey. They state that this setup gives a realistic model for human tACS, where the field on the neocortex may reach 0.8 V/m (2). Krause et al. (1) observed neural entrainment in the hippocampus and the basal ganglia and concluded that it was directly caused by the very weak fields in these structures. There is currently a lot of debate about what field strength is needed to cause neural entrainment. The conclusions of Krause et al. are controversial given that previous work in humans has shown that tACS could not entrain local field potentials (3).

In this letter we argue that the experimental design used by Krause et al. (1) allows for a valid alternative interpretation of their results. This is because of 2 caveats in the design. First, while the macaque is a useful model for studying human neuromodulation mechanisms, its head size is much smaller than that of humans. The macaque head volume is 10% of that of a human, while the brain volume is 6% (4, 5). Thus, as pointed out in a comparative modeling study (5), 2-mA tACS in a monkey will generate fields that are on average 3 times stronger than 2-mA tACS in humans. To make a realistic approximation of human tACS, amplitudes used in the monkey should be reduced by a factor of 3 (i.e., 0.66 mA instead of 2 mA). Second, Krause et al. report field strengths recorded at structures distant from the stimulating electrode. While complex high-definition montages may generate stronger currents in deep structures (6), the 2-electrode montage used by Krause et al. will always give the maximal electric field close to the stimulating electrodes (5, 7). Thus, based on modeling data (5), 2-mA tACS in the monkey will generate a field strength of around 3 V/m on the cortical surface under the electrode. It is well known that electric fields of this strength cause neural entrainment (8, 9). Therefore, we would expect strong neural entrainment in the neocortices just below the electrodes. It is also known that entrainment in the neocortex causes indirect entrainment in other brain structures such as the hippocampus (10). Thus, a valid alternative interpretation is that the stronger field just below the electrode caused neural entrainment in the neocortex, which then indirectly caused entrainment in hippocampal and basal ganglia neurons. Krause et al. did add a control where they mirrored the tACS montage and found reduced neural entrainment. However, this could be caused by weaker interhemispheric projections from the neocortex to the hippocampus. Single-unit data recorded from brain areas experiencing the strongest field (i.e., neocortex directly under the electrodes) are needed to establish the field strength required for tACS to cause neural entrainment.

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