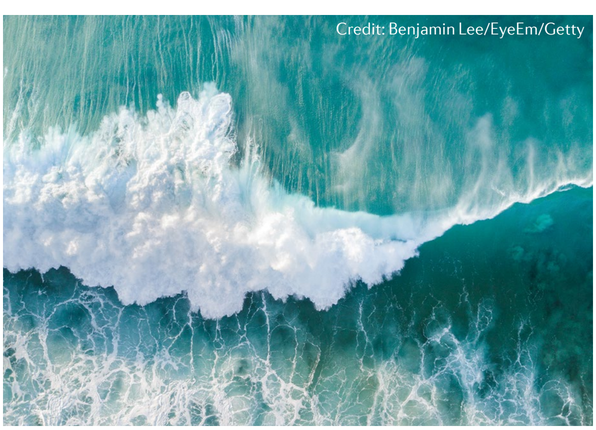
TECHNIQUES

Making waves with ultrasound

“TUS ‘sharpened’ the connectivity profiles of the targeted regions”

Transcranial ultrasound stimulation (TUS) has been proposed to be an effective technique for non-invasively modulating brain activity. However, whether the effects of TUS can last long beyond the stimulation period is unclear, and whether TUS can target structures deep within the brain with high specificity is not known. Now, two papers from the Sallet laboratory show in macaques that the effects of TUS on the functional connectivity profiles of targeted structures can last for up to 2 hours following stimulation, and that TUS can successfully modulate the functional connectivity profiles of subcortical or deep-cortical structures.

In both studies, the authors used a TUS protocol in which 250 kHz ultrasound waves were pulsed at 10 Hz for 40 s. To investigate the effects of TUS beyond the stimulation period (‘offline’), Verhagen et al. targeted TUS to either the supplementary motor area (SMA) or the frontal polar cortex (FPC) of three (anaesthetized) macaques. The authors imaged the resting-state functional connectivity of the targeted region in these monkeys before and 30 minutes after completion of the SMA TUS or FPC TUS protocol, using functional MRI (fMRI). In general, TUS ‘sharpened’ the connectivity profiles of the targeted regions: it increased the functional coupling of the stimulated regions with regions that were strongly or closely connected, but reduced coupling with regions that were more remote or weakly connected. Strikingly, these effects were observable for up to 2 hours after stimulation. SMA TUS had little effect on FPC connectivity, and vice versa, suggesting that the TUS of these regions had dissociable effects. Moreover, the authors replicated the effects of FPC TUS on FPC coupling in a further three macaques, supporting the reproducibility of these results.


Credit: Benjamin Lee/EyeEm/Getty

In the other study, Folloni et al. applied TUS to the amygdala (a subcortical structure) in four monkeys and the anterior cingulate cortex (ACC; a deep-cortical structure) in three other monkeys. Again, TUS modulated the connectivity profiles of these regions for tens of minutes, but did not affect the connectivity profiles of control areas, indicating that such stimulation can selectively target structures deep in the macaque brain.

Some previous research has attributed the effects of TUS on neural processing to acoustic artefacts. However, the authors reasoned that this would be unlikely here, because unlike in previous studies, the modulating TUS frequencies were outside the hearing range of macaques, and neuroimaging data were collected many minutes after stimulation. Moreover, stimulation of the SMA, FPC or ACC did not affect the functional coupling of these regions with the primary auditory cortex (A1). Although amygdala TUS affected the functional connectivity profile of A1, these effects were explained by the connections of A1 with the amygdala and regions strongly connected to the amygdala. Thus, these results suggest that the effects of TUS are independent of acoustic effects.

Verhagen et al. also investigated other possible confounds and potential deleterious effects of TUS. By retaining the fMRI signal from the so-called meningeal compartment around the brain (which is typically removed from fMRI analyses), the authors showed that when the TUS was targeted at the meninges, and only then, TUS gave rise to a widespread increase in ‘meningeal’ signal, independent of changes to neuronal activity, indicating that TUS might, under some circumstances, affect the vasculature in the brain. Computer simulations of TUS on 3D models of the macaque head estimated the maximum TUS-induced increase in temperature to be 0.5 °C, yet the authors did not observe any ‘tissue burn’. Furthermore, structural MRI and histological analyses revealed no overt signs of oedema or neuronal damage in the stimulated tissue.

Although the mechanisms that underlie the effects of TUS on neural function remain to be determined, and the safety of the technique should be further tested before use in humans, these results demonstrate the potential for TUS in non-invasively manipulating the connectivity of specific brain regions over longer time periods than previously considered feasible with this technique.

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ORIGINAL ARTICLES Folloni, D. et al. Manipulation of subcortical and deep cortical activity in the primate brain using transcranial focused ultrasound stimulation. *Neuron* https://doi.org/10.1016/j.neuron.2019.01.019 (2019) | Verhagen, L. et al. Offline impact of transcranial focused ultrasound on cortical activation in primates. *eLife* **8**, e40541 (2019)