



R. David Andrew, MSc, PhD  
Professor  
DEPARTMENT OF  
ANATOMY AND CELL BIOLOGY  
Botterell Hall, Ninth Floor  
Queen's University  
Kingston, Ontario, Canada K7L 3N6  
Tel 613 533-2860  
Fax 613 533-2566

November 12, 2008

Dear Nico,

I want to briefly review my assessment of the ability of ultrasound (US) waves (approx 20 kHz) to stimulate the brain, based on various papers I've read and our face-to-face discussion last week.

As I understand it, your US transducer is designed to provide a spatially generalized input to the whole brain as well as detect feedback in three dimensions that continuously modulates the input.

The idea is that the 20 kHz input provides a harmless, low energy "stimulus" to the entire brain in the form of ultrasonic waves that could, for example, be used to break up plaques in Alzheimer's Disease or to specifically kill tumor cells in cancerous tissue. You suggested that it may also be possible, by modulating the ultrasound input, to induce or entrain brain waves such as those exhibited by patients during sleep. Such waves are detected routinely using an array of electroencephalogram (EEG) electrodes placed on the surface of the scalp. Obviously, all three examples noted (plaques, tumors, sleep waves) have radically different physiology that generates the targeted event. From your description, the potential strength of the transducer is that each region of the brain receiving the ultrasound can be monitored second to second and the output adjusted accordingly.

As a research neurophysiologist who also teaches neuroanatomy and neuropharmacology, I can confidently state that most brain researchers would initially have some basic questions for you regarding whether your device is capable of stimulating brain cells, as we discussed last week.

1) How do neurons react to ultrasound? There are a number of published investigations using isolated nerve fibres (axons) and the findings appear to be mixed. There can be some excitation of axons, but this could depend on the orientation of the nerve fibre with respect to the source of the ultrasonic waves. There is also much variability as to the strength and frequency of the ultrasonic stimuli that are employed. The published results are also variable when using live brain slices. Tyler et al. (2008) show that sodium and calcium channels in neurons open in response to US stimulation. They theorize that the oscillating membrane is stretched by US, thereby opening channels. Regardless whether that is the exact mechanism, channel opening is a very broad and non-specific response. Activating some nerve cells will stimulate the brain while activating others (particularly many interneurons) will actually inhibit the brain's activity.

2) Is there a relationship between the activated neurons' orientation and the direction of the stimulating ultrasonic wave propagation? This is important because there is likely a preferred orientation to the ultrasound at which the neuron will be maximally activated. The brain consists of millions of neurons arranged in many three-dimensional arrays. Holding a US transducer under the chin may activate different regions than when holding it beside the ear.

3) Can the US stimulation be focused onto a small region within the brain? This is where "deep brain stimulation" derives its strength: neurosurgeons can implant an electrode in the brain permanently to stimulate a volume of tissue about the size of a pea. This technique has major benefits for Parkinson's disease and depression (for example) but the electrode must be placed at an exact site and emit a very discrete amount of electrical energy to disable the neuron's discharge without activating nearby nerve cells.

4) If the stimulus is generalized across the brain (i.e., not focal), what is the evidence that a suspected benefit occurs? If there is no evidence, then a research specialist needs to be convinced to gather evidence that US induces a specific response in the tissue. Initial studies using lab animals to show that 20 kHz US dissolves Alzheimer plaques or specifically kills cancerous cells will require a few hundred thousand dollars worth of experiments. I am certain that showing that 20kHz US can entrain brain waves by monitoring subjects with EEG would be substantially less costly. To show that cultured cancer cells (i.e. cells in a dish) are more susceptible than regular cultured cells would probably require funding an established cancer lab to set up the cell cultures and then expose them to ultrasound. A source of money is essential to initiate any of this work because it will be difficult (if not impossible). This is because agencies such as the CIHR provide support only with some dramatic positive results that support a `proof of principle` showing feasibility. There would need to be at least some partial answers supplied to the four questions I have noted above.

I think you will find it difficult to convince researchers who already have funded projects `on the go` to shift their focus and help you explore the possibilities of your technique. This is because so little is known about the basic physics of ultrasound and how it alters (or not) brain activity. Your company would need to find funds for consulting fees and travel expenses, as well as fund initial experiments that at least partially answer some of the questions I have noted. Funding agencies want hard experimental evidence that a given approach is feasible.

Sincerely,

David Andrew  
Professor