

# Noninvasive brain-stimulating ultrasound on the horizon

**Though acceptance of brain stimulation therapy is increasing, the devices used are not without their drawbacks. Madeleine Armstrong learns about a new technique that could overcome issues with deep brain and transcranial magnetic stimulation: low-frequency, low-intensity ultrasound**

Brain stimulation techniques are becoming more popular, with an ever-growing number of uses. The most established method, deep brain stimulation (DBS), has been available for several years for tremor and Parkinson's disease, but in February, the US FDA approved a DBS device in a psychiatric disease for the first time: Medtronic's Reclaim for obsessive-compulsive disorder (see *Clinica* No 1335, p 26).

However, DBS is limited by the fact that it is invasive – it requires surgery to implant the electrodes that send impulses to specific areas of the brain.

A noninvasive neurostimulation technique, transcranial magnetic stimulation (TMS), is available, but only targets superficial parts of the brain. The first such device to receive FDA approval was Neuronetics' Neurostar, which got the go-ahead in October 2008 for treatment-resistant depression (see *Clinica* No 1326, p 25).

However, a new noninvasive method, which uses low-frequency, low-intensity ultrasound waves, could overcome the disadvantages of both DBS and TMS.

## **Unlike DBS, ultrasound is noninvasive, and "almost as precise"**

"DBS and other related technologies require some type of surgical intervention to implant the electrode," Jamie Tyler of Arizona State University, Tempe, who is developing the ultrasound technology, told *Clinica*. "TMS represents a paradigm shift towards truly noninvasive techniques, but the advantage with ultrasound is that it can go much deeper than TMS, and it can have more precise targeting – almost as precise as DBS."

In January, Prof Tyler founded a company, SynSonix, to develop the ultrasound technique. The firm is initially evaluating it for three uses: Parkinson's disease, neuropathic pain and traumatic brain injury.

Prof Tyler's group is currently carrying out animal studies, and he hopes to start clinical trials in humans by 2011. "We think a product will probably be available about three years after that – so in four or five years in total."

SynSonix plans to initially develop a device for functional brain mapping; as ultrasound is already approved for other diagnostic uses, a 510(k) approval would be easier than getting the device approved first for neurostimulation. "And once it's approved for one indication, it's easier to gain approvals in others."

### **Unlimited uses?**

Although he is currently focused on three clinical areas, Prof Tyler explained that the low-frequency, low-intensity ultrasound technology's potential could be infinite. "Technically, I think it's best to initially test it in diseases that occur in well-identified brain circuits, such as Parkinson's, tremor and neuropathic pain. But eventually it will become useful in disorders like depression and Alzheimer's, as the scientific community finds out more about them – these

diseases are more widely distributed throughout the brain, and aren't localised at one specific circuit.

"On the flip side, it will be useful in traumatic brain injury, as we think we can activate neuroprotective pathways to reduce the secondary injury, by stimulating the release of protective neurotrophic factors," he said. This would involve widespread stimulation of the brain, instead of limiting it to specific areas, and the approach could also be used to rehabilitate stroke patients.

"Also, in epilepsy it's just been shown that widespread stimulation of the brain will inhibit seizures. And it doesn't have to be in the exact location of the seizure – it can be anywhere in the brain."

Moreover, the technology's utility is not restricted to the brain. "Once you learn how to control ion channel activity in cells, you can control any excitable cells, not just neurons," Prof Tyler said. "But for now we're focused on the brain applications. We can't possibly go after them all."

The ultrasound frequencies that the group has been using are well below those for diagnostic imaging. "For imaging, people typically use 2-3 megahertz or higher. We use lower frequencies, about 0.5 megahertz. This is because, to get through the skull, you need lower frequencies – high frequencies don't get through very well.

"And as for intensity, we're below most of the cut-off limits the FDA has set for diagnostic ultrasound. The maximum output for diagnostic ultrasound is 720 milliwatts for ophthalmic imaging. And we're having success at around 100 milliwatts."

This is a world away from high-intensity ultrasound techniques that are currently used, for example, to destroy uterine fibroids. "Some companies are working on high-intensity systems to ablate brain tumours. They're using low frequencies, but they're putting about 1,000 watts per cm<sup>2</sup> into the brain, compared with our 100 milliwatts. It's really, really dangerous."

### **"Completely safe"**

He is convinced that the low-frequency, low-intensity version is completely safe – so much so that the thought of using himself as a guinea pig has crossed his mind a couple of times. "I still think about it from time to time. I just don't know if the transducers I have will put up enough power to get through the human skull."

But right now, Prof Tyler is concentrating on building up SynSonix. "We're looking to raise \$6m over four years. And as soon as we get that funding we're going to build our company somewhere around Boston – hopefully in Cambridge, Massachusetts. We've filed two patents, and have a good scientific advisory board so far."

And although he has high hopes for the technology, he cautions that it will have to find its place among the other neurostimulation techniques: "We're basically looking at this as a way of replacing all current electrical methods. But it may be that we still need DBS to treat certain diseases, and TMS and ultrasound for others. There isn't a magic bullet."