Understanding the mechanisms by which low intensity focussed ultrasound is able to modulate neural activity

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Summary

Low intensity focussed ultrasound stimulation is an emerging neuromodulation technique that offers improved accuracy and penetration with potentially fewer side effects compared to conventional neurostimulation methods. There are already a surprising number of devices for sale and companies aim to market them for personal use (health benefits) and medical research (including rehabilitation settings). An improved understanding of the mechanisms by which stimulation can alter brain function would complement these efforts. Our project developed a flexible, affordable system way to adapt a commercial device to deliver repetitive neurostimulation to rodents (without anaesthesia). The main outcome is the ability to perform mechanistic driven research in animal models. Additional outcomes include using animals to test optimal stimulation parameters, dosing regimes, and therapeutic windows. This could inform the design of future human work that may ultimately benefit patient populations.

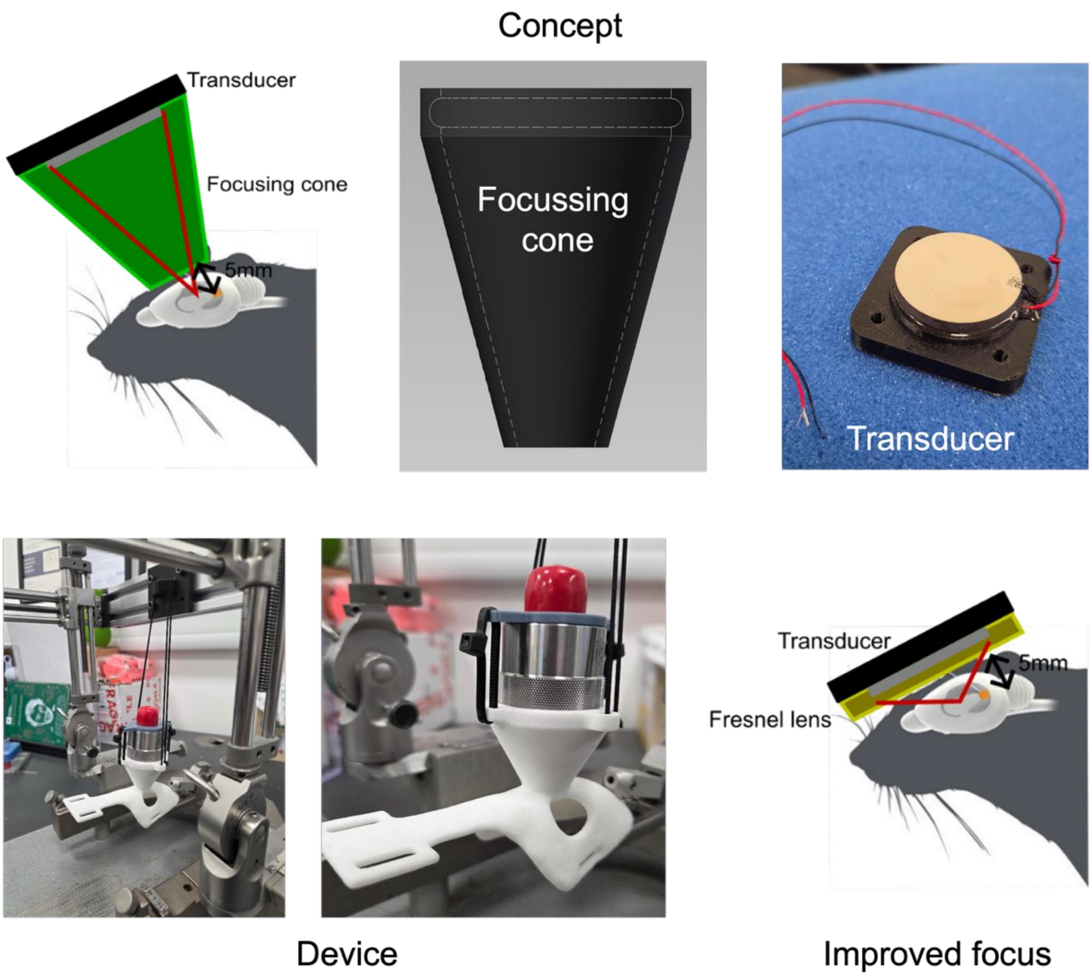
Methodology

A great deal of time was spent with the concept. We systematically reviewed the literature to obtain an overview of rodent specific devices. Publications tended to employ a handful of commercially available systems developed for human use. As such, focusing cones tended to be large and cumbersome. This meant anaesthesia was necessary, and this would make implementation of multiple stimulation sessions challenging.

Our concept was comparable, but we aimed for a much smaller transducer (>4mm) and focussing cone that would facilitate flexible multi-session delivery and have the capacity to target deeper brain structures After investigating multiple transducer designs, we approached NeurGear for a custom transducer (0.5MHz). We also applied for a University of Nottingham Knowledge Exchange Fund to compensate the engineer for the time to develop the transducer. Unfortunately, the final smallest diameter possible was 25mm, and the lead time was unexpectedly long.

Different focussing cones were manufactured with final diameters of 5mm and recesses were adapted to host an O ring that would support a watertight seal to protect the transducer from the cone gel. Modelling suggested the focal point of the stimulation would be approximately 5mm below this, enabling targeting of deeper brain structures. We also used MRI scans and castings of male and female rats to 3D print soft and comfortable 'helmets' with generous openings for the ears and the potential to attach a chin strap to help secure the helmet. The opening for simulation and cone attachment can be varied to target different brain regions. The designs for the helmets and cones can be made available. We also developed a rig to suspend the device from a typical stereotactic frame for rodent neurosurgery. This would facilitate an initial experiment to obtain a precise stimulation location. But more importantly, once the helmets were adapted for stimulation location, the attached cone and transducer can be suspended by elastics to bear the weight of the device and prevent pressure on the rat head. We do anticipate some training would be required for rats to become amenable to the helmet.

To improve the focussing power and precision (down to 1mm), we also designed a Fresnel lens for the transducer. The first attempts were not of sufficient quality, but the design exists.



Impact of the project

The outcome of the project is the flexible, affordable, customized ultrasound system to facilitate repetitive preclinical rodent neurostimulation research. All design templates can be made available, though we anticipate some further optimisation will be required. The equipment is currently located within the University of Nottingham, which has a strong group of researchers interested in neuromodulation. While the project lead and co-lead have now left the University, we have made sure to keep the preclinical neuromodulation researchers informed and updated, and indeed, they were helpful with suggestions that impacted the design.

Furthering network aims

Our Flexible Fund Project has supported the aims of the Neuromod+ network quite well. It has brought together a multi-disciplinary team of senior and early career investigators. We have diverse backgrounds in life sciences, engineering, manufacturing, as well as a neurologist to help advise future work. The common interest was neuromodulation and we were all particularly interested in promoting repair and recovery after stroke. We also established a new collaboration with NeurGear. Professor Kaiser works closely with NeurGear and is helping evaluate the Zenbud device. We obtained supplementary funds from the University of Nottingham to enable NeurGear to develop a custom transducer for rodents. It is possible this could be further developed and marketed.