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The importance of acoustic output measurement and monitoring for the replicability of transcranial ultrasonic stimulation studies

Dear Editor,

We are writing about what we believe are important considerations for ensuring high standards and replicability of experiments using transcranial ultrasonic stimulation (TUS). TUS is a technique in its infancy, yet its potential is widely recognized. For the first time in humans, neural activity can be modulated non-invasively and with millimetre precision in deep brain regions. This opens up possibilities for therapeutic interventions in psychiatric and neurological brain disorders where current treatments include invasive deep brain stimulation or ablation. However, despite an estimated several hundred TUS users world-wide [1,2], there are still hurdles, for individual researchers, for controlled, effective and reproducible applications in humans.

Here, we discuss three considerations which can help ensure consistency and replicability across studies: first, understanding and accurately characterising the acoustic field produced by a TUS device; second, using this information to correctly define the field in an acoustic simulation; and third, ensuring consistency of the acoustic output of the device over time.

These points are important because (a) standards, protocols, hardware and software for TUS are constantly under development and changing rapidly [3,4]; (b) most devices on the market come without regulatory approval (CE marking in EEA, FDA-required labelling within the HHS) and associated guarantee of compliance with safety and measurement standards; (c) typically, TUS users in clinical/research settings are not trained in ultrasound engineering, but recognize the need for acoustic simulations to estimate in situ exposure and plan sonications.

Similar considerations are perhaps less critical for some other neurostimulation techniques, such as transcranial magnetic stimulation (TMS). The effectiveness and intensity of TMS device output can be established in each individual based on their motor evoked potential (MEP [5]). Recorded MEPs provide a direct check of the device output and major device issues would become immediately apparent. Currently, for TUS, such a direct check of the intensity or focal position in situ does not exist. TUS has not been shown to directly evoke motor or sensory readouts (like MEPs) in humans. Thus, its efficacy cannot be established in a given individual prior to the start of an experiment - although indirect ways of showing target engagement post-sonication do exist (e.g., using magnetic resonance imaging [6–8]). We believe the three considerations related to acoustic output and device operation outlined here (Fig. 1) could reduce variability in this rapidly expanding field, as well as reducing the possibility of null or non-replicable results, or inadvertent exceeding of biophysical safety recommendations [3].

First, to quantify the acoustic field produced by a given device, the field should be measured in water. This serves as a reference for the device output and behaviour before any estimation of the in-situ field is performed. For the device settings used in studies, the pressure amplitude at the focus, the spatial size or profile of the focal region and its location relative to the transducer should be measured. The spatial-peak pulse-average intensity (I_{SPPA}) can also be calculated from the pressure. These quantities can then be compared across studies by users of the same or alternative devices.

Obtaining accurate free-field pressure measurements can be complex [9,10], requiring equipment typically available only in specialist labs: a suitable calibrated hydrophone, a water tank large enough to avoid reflections, a stable mount to hold the ultrasound transducer, automated scanning and alignment of the hydrophone or transducer in three dimensions, and an oscilloscope to acquire and digitise waveforms from the hydrophone. Precise alignment during measurements, and careful postprocessing of the data is required to avoid errors. Consequently, typical TUS users may not have the know-how, equipment, time, or expertise to obtain acoustic field measurements themselves without further training. However, information can be obtained from another source, such as the manufacturer, another calibration/characterisation provider, or measurement expert. Because not all devices come with regulatory approvals (e.g., CE marking) currently, manufacturers do not have to show compliance with standards. Thus, individual researchers may decide to obtain additional measurements for verification. We recommend that characterisations are performed during the course of use of a device, for example prior to starting a new study, and that the users familiarise themselves with the generated fields, the associated uncertainties and expected variability on the pressure values [9], and with how these fields can change with the range of operating parameters.

Second, characterisation of the device in free-field should be used to inform the definition of the source in any subsequent simulations performed for in situ field estimation during planning. The behaviour of most real ultrasound transducers differs from that of an ideal source, due to e.g. cross-talk, physical construction and edge effects. For example, simulating the source using the nominal shape and size of the transducer, with any phase settings used for steering taken directly from the device, may result in a different field shape and focal position to that generated by the real transducer (Fig. 1a and b). However, these parameters can be optimised through small adjustments to find an 'equivalent' source which more closely recreates the measured field [11]. In some cases, manufacturers are working with researchers and developers of simulation software to provide matched source models. In any case, before simulating acoustic fields in any complex medium (e.g., the human head), researchers should verify that the measured field can be accurately simulated in water (Fig. 1b).

Finally, as studies are carried out, it is important to check that the transducer/device is reliable over time to ensure consistency between

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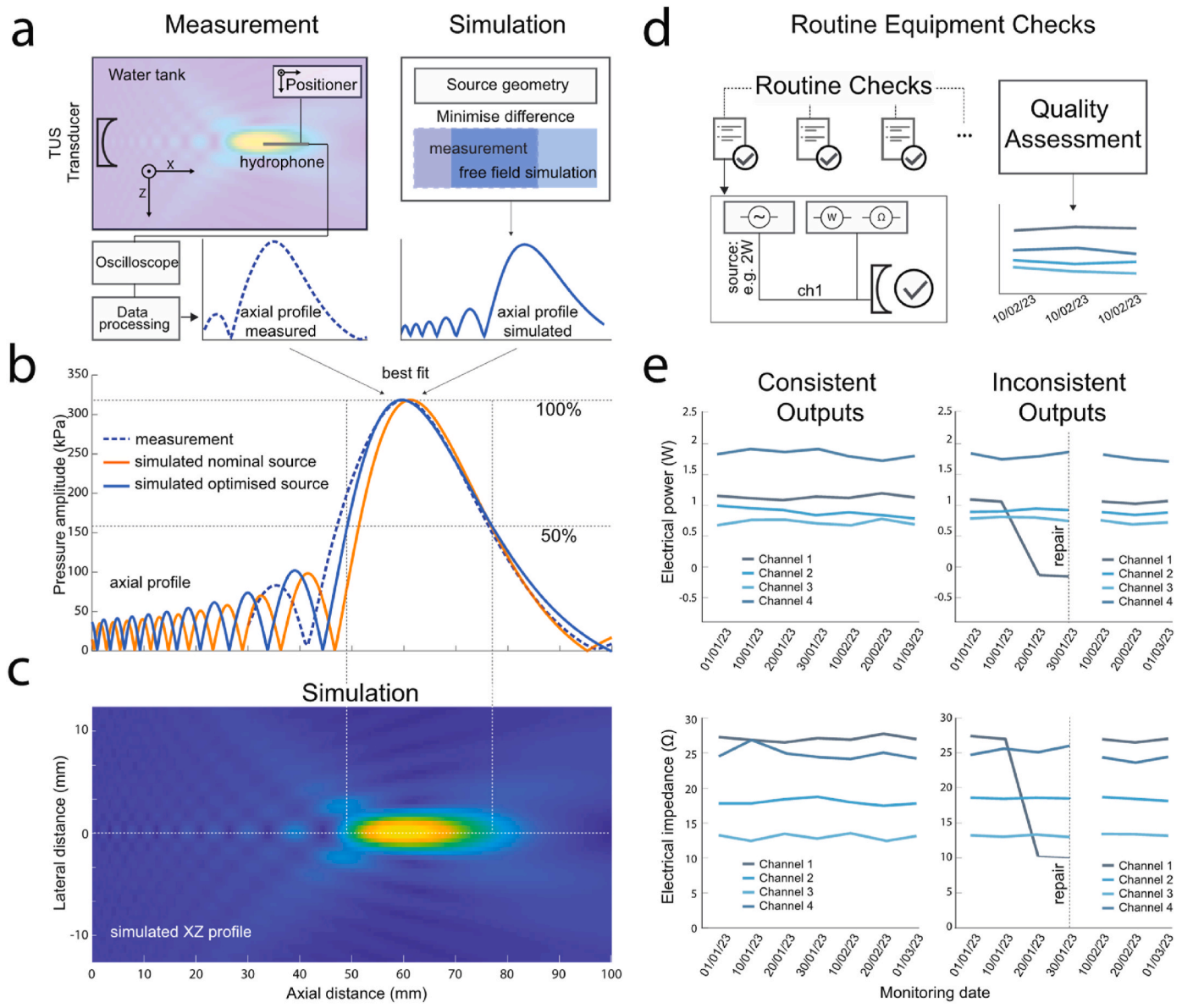

Fig. 1. **A,** (top) schematic diagram of the setup for free-field measurements with superimposed 2D profile showing the axial-lateral pressure distribution. The source used in simulations should generate a field in water that matches the measurement as closely as possible, minimising differences between measured and simulated free field axial beam profiles (bottom). **B**, Differences are observed between the measured beam profile (dashed blue line), and that generated using the nominal dimensions of the source (orange line), which can be minimised by adjusting the source geometry (aperture diameter, radius of curvature), or relative phases in simulation (solid blue line) **C,** The corresponding simulated axial-lateral profile matching the measurement shown in (a, b). **D,** Routine equipment checks are critical in ensuring the consistency and stability of device output across studies, for example, by tracking electrical power and impedance over time. **E,** Example of consistency checks of transducer electrical power and impedance for one case where the transducer was functioning consistently over time (left) and for another case where one channel developed a fault (right). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

sessions and participants. This also helps detect any changes or damage to the device at the earliest opportunity. A simple way to perform such monitoring or consistency checking is to regularly (e.g., weekly or before study sessions) measure and log electrical parameters such as the electrical power or transducer impedance (Fig. 1d), rather than acoustic quantities which can be more complex to obtain. Large changes in these electrical quantities, that exceed the normal variability established at baseline, may indicate some change in the acoustic output of the transducer and therefore potential damage, which could lead to disrupted or shifted ultrasound foci and thus unintended exposure. This should be reported to the manufacturer (Fig. 1e).

We believe free-field measurements, correct measurement-based definition of the source in subsequent simulations, and output consistency checks performed over time are three vital components for ensuring the replicability of TUS experiments. We hope taking these steps will increase consistency across sites, devices, protocols, experiments, and ultimately medical applications. TUS has incredible potential, and its use in human research and clinical applications is increasing. We hope awareness of the three considerations outlined here will help an exciting field of research produce more reliable and robust outputs and thus ultimately increase TUS' therapeutic potential.

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CRediT authorship contribution statement

Miriam C Klein-Flügge: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Elsa F Fouragnan:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Eleanor Martin:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Miriam C Klein-Flügge[1,*]
Wellcome Centre for Integrative Neuroimaging (WIN), Department of Experimental Psychology, University of Oxford, Oxford, UK
Wellcome Centre for Integrative Neuroimaging (WIN), Centre for Functional MRI of the Brain (FMRIB) and Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford, UK
Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK

Elsa F Fouragnan[1]
School of Psychology, Faculty of Health, University of Plymouth, Plymouth, PL4 8AA, UK
Brain Research and Imaging Centre, Faculty of Health, University of Plymouth, Plymouth, PL6 8BU, UK
E-mail address: elsa.fouragnan@plymouth.ac.uk.

Eleanor Martin[1]
Wellcome/EPSRC Centre for Interventional and Surgical Sciences, University College London, London, WC1E 6BT, UK
Department of Medical Physics Biomedical Engineering, University College London, London, WC1E 6BT, UK

[*] Corresponding author.
E-mail address: miriam.klein-flugge@psy.ox.ac.uk (M.C. Klein-Flügge).

[1] These authors contributed equally to the work.