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● *Original Contribution*

DOES EXPOSURE TO DIAGNOSTIC ULTRASOUND MODULATE HUMAN NERVE RESPONSES TO MAGNETIC STIMULATION?

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Abstract—Ultrasound (US) at diagnostic frequency and power is known to alter nerve potentials; however, the precise mechanism of action is unknown. We investigated whether US alters resting nerve potential to lower the threshold for magnetic nerve stimulation. Seventeen healthy subjects were recruited. For each subject, a 1.5 MHz US imaging probe was placed onto the elbow with the beam directed at the ulnar nerve. The probe was coupled to the skin using standard acoustic coupling gel as would be done for a routine clinical US scan. Ulnar nerve stimulation was performed simultaneously with magnetic stimulation (MS). Successful magnetic stimulation of the ulnar nerve was confirmed with nerve potentials measured by electromyography. There was no significant change in electromyography signal when MS was performed during US exposure. US at the diagnostic frequency and power tested does not alter nerve thresholds with MS. Testing at other frequencies is required, however, before US is negated as a technique to modify MS thresholds. (E-mail: neilwbailey@gmail.com) © **2016 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Ultrasound, Magnetic stimulation, Electromyography.**

INTRODUCTION

A number of electromagnetic techniques are currently available for treatment of psychiatric disorders, such as trans-cranial magnetic stimulation (TMS), deep brain stimulation, trans-cranial direct current stimulation and electroconvulsive therapy. However, each has significant limitations, such as invasiveness, lack of specificity, poor spatial resolution or inability to focus on deep brain structures. By contrast, ultrasound (US) is a focal and non-invasive tool that can be applied with high spatial resolution to influence nerve activity and possibly the potential to affect even deep brain structures (Ang et al. 2006; Bystritsky et al. 2011; Hameroff et al. 2013). The effects of US have been attributed to high-frequency mechanical vibration, although the precise mechanisms are as yet unknown (Fowlkes and Holland, 2000). A continuum mechanics hypothesis of US neuromodulation has been proposed by which US produces effects on the viscoelastic neurons and their surrounding fluid environments to alter membrane conductance (Tyler 2011). The effects of low frequency US upon neurons are reversible and make neuronal excitation and inhibition possible (while cavitation and thermal alterations have also been described, these are not explored in this study) (Bystritsky et al. 2011). As such, US is a potential form of focal and non-invasive neuromodulation. In addition to the stimulator used, the design of the probe (a piezoelectric transducer) governs the intensity as well as the focality and depth of the US wave. For example, phased array probes allow for fine control over how and when energy is deposited into a medium (Casper et al. 2012). That is, the arrangement of elements is critical to the efficiency, focality, depth, and thermal distribution of the US wave. Furthermore, the intensity, duration and pulse width of the delivered US determines physiologic and pathologic effects.

Hameroff et al. (2013) recently reported that 8 MHz trans-cranial US applied close to the temporal window of the skull can affect mood in humans. The authors suggested that the mode of action was *via* the induction of

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resonance in neuronal microtubules within the exposed area of brain. Tufail et al. (2010) reported that US triggered neuronal activity without increasing brain temperature in mice and that trans-cranial US can be used to disrupt electrographic seizure activity (Tufail et al. 2011). Kim et al. (2014) reported that focused US can non-invasively stimulate the rat brain at minimum threshold acoustic intensities of approximately 5 W/cm^2 at 350 kHz. Earlier, they had shown that focused US can stimulate the abducens nerve of a rat with no signs of blood–brain barrier disruption or damage to nerves or adjacent brain tissue (Kim et al. 2012). In another study, Yoo et al. (2011) used focused US to modulate focal brain activity with no sign of tissue damage. Another group reported that stimulation success increased as a function of both acoustic intensity and duration of exposure to US, and the response elicited appeared to be an all-or-nothing phenomenon, meaning that stronger stimulus intensities and durations increase the probability of a response without affecting the duration or strength of the response (King et al. 2013). In humans, Legon et al. (2012) found that pulsed US differentially stimulated somatosensory circuit, as indicated by electroencephalography and functional magnetic resonance imaging.

Although TMS is an effective tool for the treatment of refractory psychiatric illnesses such as major depression (Fitzgerald and Daskalakis 2011), it is not well tolerated by some patients due to sensations associated with scalp muscle and nerve stimulation, especially with stimulation at high intensity (Maizey et al. 2013; Rossi et al. 2009). A technique to achieve the same clinical response at lower power and therefore without such discomfort would be very useful. One possibility might be in combining TMS and US stimulation. The present study is thus a first step in determining whether US can be combined with magnetic stimulation (MS) to reduce MS stimulus thresholds.

Because TMS and US have not previously been combined, we decided to study the combination of both techniques at a peripheral nerve for safety reasons. For the sake of experimental simplicity, we opted to study the effect of US exposure to the ulnar nerve on motor thresholds during MS. Although the properties of peripheral nerves differ from the properties of neurons in the CNS, previous research has shown that stimulation of the peripheral nerves with both MS and US separately had an effect similar to stimulation of the CNS (Barker et al. 1987; Gavrilov et al. 1976; Gavrilov and Tsirulnikov 2012; King et al. 2013). Demonstration that US modulates peripheral MS thresholds would provide a proof of principle that the application of US could modulate responses to MS, providing justification for further research combining TMS and US for the stimulation of the nerves in the CNS.

METHODS

Participants

A total of 17 (five female) healthy control participants were recruited with community advertising. All participants were screened for TMS eligibility with the TMS Adult Safety Screen (Rossi et al. 2009). Participants were aged 21–41 y, with a mean age of 28.65 y (standard deviation = 6.284). Ethical approval for the study was obtained from the Alfred Hospital and Monash University's ethics committees, and all participants gave written informed consent.

MS coil and ultrasound probe positioning

A Magstim figure-of-eight coil (Magstim, Whitland, UK) was attached to the armrest of a chair with the handle of the coil aligned in the same direction as the participant's arm (palm down; Fig. 1). The arm was positioned so that the center of the coil was directly under the estimated position of the ulnar nerve as determined by palpating the olecranon notch. The participant's arm was also bent to provide posterior access to the olecranon notch for US exposure. The US probe was attached to a 2-cm rubber tube filled with US gel and shaped to fit the gap between the participant's elbow and the MS coil to ensure good acoustic coupling. Participants could not detect US output.

Motor evoked potential recording

Motor evoked potentials (MEPs) were recorded using electromyography (EMG) electrodes placed over muscles innervated by the ulnar nerve, which has projections into the flexor carpi ulnaris and the flexor digitorum profundus muscles. Pilot studies indicated these muscles showed the most reliable response to the TMS pulse; thus, the active EMG electrode was placed on the forearm above these muscles (in particular above the carpi ulnaris, which is more lateral and more superficial), and the reference electrode was placed on the radial section of the wrist between the distal end of the ulnar and the distal end of the flexor digitorum. The ground electrode was placed over the distal projection of the ulna (Fig. 1c).

EMG signals were digitized with a CED interface system (Cambridge Electronic Design, Cambridge, UK). The signal was amplified (by a factor of 1000), with a 500 μV range, 1 Hz high pass and 2 kHz low pass filter and was sampled at 5 kHz. Signals were recorded as epochs of EMG activity centered around each MS pulse from −100 ms to 200 ms.

Stimulation

Equipment setup. The MS figure-of-eight coil was connected to a Magstim 200 magnetic stimulation device (Magstim) with stimulation achieved using monophasic