Focused ultrasound stimulation of median nerve modulates somatosensory evoked responses

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Abstract—**Chronic pain can be alleviated using paresthesia caused by electrical stimulation of peripheral nerves. However, the implantation of electrodes is necessary to increase the specificity and efficacy of the treatment. Alternatively, focused ultrasound (FUS) can noninvasively and selectively modulate nerve function, which could potentially be an alternative to inducing paresthesia. Here, we show initial feasibility of FUS stimulation in the peripheral nerve of healthy human subjects. Somatosensory evoked potential (SSEP) elicited by electrical stimulation of the median nerve is demonstrated to decrease in amplitude while FUS is concurrently applied on the median nerve. The suppression of SSEP signals indicates the modulation of sensory signaling to the brain, which can potentially be used to reduce pain.**

Keywords—*Focused ultrasound neuromodulation, peripheral nerve, somatosensory evoked potential (SSEP)*

I. INTRODUCTION

Peripheral nerve stimulation is used to alleviate chronic pain, migraine headaches, epilepsy, depression and inhibition of hyperactive motor reflexes observed in spinal cord injuries, multiple sclerosis, and cerebral palsy (disorder of movement, muscle tone or posture). In this technique implanted electrodes deliver fast repeated electric pulses causing paresthesia [1]. The implantation of electrodes is necessary to increase the specificity and efficacy of the treatment.

Alternatively, focused ultrasound (FUS) can noninvasively modulate nerve function, which could potentially be an alternative to inducing paresthesia and treating pain. Our group has demonstrated in mice that nerve activation followed by tissue displacements of up to 423 μm can be achieved in the absence of heating using single short pulses [2], [3]. Conversely, repeated pulses (100 Hz) can introduce thermal effects (15.1 ± 1.6°C) that inhibits nerve activity [3]. Studies in the early 1970s [4] show the application of ultrasound in the context of pain for a variety range of frequencies (0.48, 0.88, 1.95, 2.67 MHz), intensity (0.01 - 7500 W/cm^2), and pulse duration (100 μs – 100 ms). Recent studies [5] have replicated these results and described findings on the elicitation of sensory responses by ultrasound. In summary, tactile sensations in human fingertip ("local touch", "slightly sensed stroke", and "slight push") increased with frequency and intensity using relatively long pulse duration (100 ms) [6]. When ultrasound was applied on skin, volunteers described sensations such as "warmth" and "cold", which disappeared for deeper targets. McClintic *et al.* 2013 [7] and Tych *et al.*, 2013 [8] demonstrated on rat pain models that neuropathic tissue is more sensitive than healthy tissue to FUS, which can be used for diagnosing purpose. In this case, pulse durations were up to 375 ms and the application of 30 pulses of 100 ms at 2000 W/cm^2 produced damages in rats. Similar conclusions were demonstrated on residual limbs of amputee patients [9]. In addition, high intensity FUS (up to 7890 W/cm^2) can reversibly or permanently block nerve conduction through focal heating achieved with long pulses and long sonication durations, which could potentially be used for analgesia or to treat chronic pain [10], [11]. Despite the promising results of these studies, a quantitative analysis of the FUS capability in modulating sensory signaling has not been performed yet.

Somatosensory evoked potentials (SSEPs) are presynaptic and postsynaptic responses generated along ascending sensory pathways in response to stimulation of peripheral sensory nerves. SSEP recordings are used to examine the integrity of somatosensory pathways and can be a quantitative method to evaluate sensory signaling to the brain. In this study, we examined the capability of FUS in modulating SSEP signals in humans. The goal was to evaluate quantitatively in humans whether excitatory and inhibitory effects could be achieved during FUS peripheral nerve stimulation.

II. MATERIAL AND METHODS

A. Ultrasound stimulation and imaging

FUS stimulation was performed using a 1.1-MHz transducer (SonicConcepts, USA) with single pulses and pulse duration of 5 ms at 2.0 MPa (mechanical index: 1.9). 3D displacement imaging was used for focus positioning on the median nerve located at the forearm of healthy volunteers using a P12-5 imaging probe (ATL, USA). An ultrasound research system (Vantage, Verasonics, USA) was used to drive both transducers, which were positioned using a robotic arm (Kinova, Canada).

B. Somatosensory evoked potential (SSEP) and electromyography (EMG) recordings

Electrical stimulation (300 μs using 2 to 7 mA) applied with bar electrodes on the skin over the median nerve at 2 cm

proximal to the wrist crease was used to induce motor responses on the three first digits. EMG responses from thumb and index fingers, as well as SSEP responses detected on the scalp and cervical vertebra (CP4/3, Fz, and C5S) were recorded using surface electrodes. Sets of 100 acquisitions were simultaneously acquired with electrical and FUS stimulations applied at a fixed rate of 0.4 Hz and compared with acquisitions with electric stimulation alone and FUS stimulation alone. Baseline acquisitions without stimulations were performed to record the background noise.

C. Safety assessment

The nerve function integrity was evaluated by comparing the nerve conduction velocity before and after the experiments. EMG measurements at the distal palmar branch of the median nerve were acquired following electric stimulation performed at two different locations of the median nerve in the forearm (19.5 to 26 cm apart). The conduction velocity was determined by the ratio of the distance between the two stimulation sites by the onset time difference of both EMG measurements.

III. RESULTS AND DISCUSSION

The FUS transducer and the electric stimulator were maintained on the volunteer's arm throughout the experiment (Fig.1a). Stimulation sessions were performed with simultaneous FUS and electric stimulations (E+F) and with combinations of sham sessions where one or both methods of stimulation were not applied (B= sham FUS and sham electric stimulation, E= electric stimulation with sham FUS, F=FUS stimulation with sham E) (Fig.1b). Fig.1b presents the boxplots of the area under the curve (AUC) of EMG signals (top) and the AUC of EEG signals (bottom) across multiple acquisitions (shown in order of acquisition). Each session lasted 250 s with 2.5 s interval between stimuli and consecutively executed with minimal interval of about 30 s between sessions.

FUS alone (F) did not elicit detectable motor or sensory responses in EMG and EEG recordings, which were in the same range as baseline (B) acquisitions performed at the beginning of the experiments (Fig.1b). Based on our previous studies in mice, higher pressure levels are necessary to elicit motor responses. On the other hand, this demonstrates that FUS does not introduce any artifact to the measurements. Interestingly, multiple applications of FUS and electrical stimulation (E+F) generated a decline in somatosensory evoked responses (SSEP) (Fig.1b; bottom), despite the stable motor responses (EMG) observed in all sessions (Fig.1b; top). The SSEP reduction indicates the modulation of the afferent fibers signaling caused by FUS.

A sham sonication experiment where only electric stimulation was applied throughout sessions did not generate EEG decline across sessions. Thus, the decline in SSEP when FUS is performed concurrently did not result from signal variability or potential fatigue of the nerve.

Finally, temperature monitoring using thermocouples [12], [13] have shown negligible temperature increase on the skin (below 0.1°C). In addition, the conduction velocity measured before the experiment and after the experiment did not show significant difference across all volunteers (59.1±5.5 m/s),
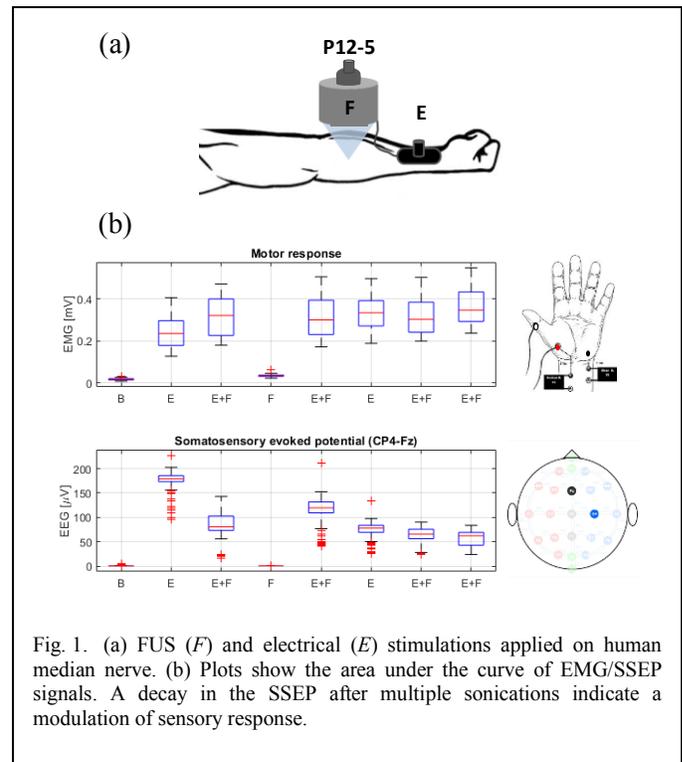

Fig. 1. (a) FUS (*F*) and electrical (*E*) stimulations applied on human median nerve. (b) Plots show the area under the curve of EMG/SSEP signals. A decay in the SSEP after multiple sonications indicate a modulation of sensory response.

which demonstrates nerve function integrity after stimulation by either electrical or FUS.

IV. CONCLUSION

This study presents preliminary quantitative evaluation of SSEP that shows the potential of FUS to modulate afferent signals. Repeated sessions of FUS decreased SSEP signals elicited by electric stimulation of the median nerve. The reduction in the sensory response EEG amplitude demonstrates the potential of FUS in alleviating chronic pain. Future studies will explore the effects of FUS peripheral nerve stimulation in pain patients.

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