Transcranial focused ultrasonic stimulation to modulate the human primary somatosensory cortex

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***Abstract*— Transcranial focused ultrasound stimulation (TFUS) recently gained momentum as new neuromodulation technique used in humans for research as well as for medical treatments. Compared to other methods such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation, TFUS might induce more focal effects, reduce confounds related to concomitant peripheral stimulation, and prevent contamination of electrophysiological recordings by electromagnetic artefacts. We will present our observations about the time course of the effects of TFUS over the human primary somatosensory cortex (S1) using somatosensory-evoked potentials (SEPs) elicited by transcutaneous electrical stimulation of the median nerve (MN).**

Keywords—neuromodulation, SEPs, TFUS, ultrasound

I. INTRODUCTION

Transcranial focused ultrasound stimulation (TFUS) offers new perspectives for neuroscientists. According to earlier research, it allows to overcome some drawbacks of neuromodulation techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (TDCS). In contrast to TMS and TDCS, TFUS offers the possibility to modulate deeper brain structures with a greater spatial resolution [1, 2].

In the present study, we characterized the effects of TFUS applied over the primary somatosensory cortex (S1) using concurrently-recorded somatosensory-evoked brain potentials (SEPs) in human volunteers. Furthermore, to assess a possible cumulative neuromodulatory effect of TFUS, SEPs were elicited by stimulation of the median nerve presented 100 or 200 ms after TFUS onset, and 500 ms before TFUS onset which served as control condition.

As preliminary step, we characterized the ultrasound beam profile generated by our focused transducer, including trial-by-trial and session-by-session variability of sonication intensity.

II. MATERIALS AND METHODS

A. Sonication setup

Our sonication setup was similar to the setups described in previous studies [3, 4]. A function generator, a power amplifier and a matching impedance network were used to drive a single-element focused transducer (GPS-350-D25-P50, Ultran, USA). Ultrasound sonication consisted of bursts having a frequency of 350 kHz and repeated at a frequency of 1 kHz. The frequency, the amplitude of the driving voltage and the number of cycles of each burst was set on the function generator. A digitizer (NI PXI 5105, National Instruments, USA) was used to trigger the function generator, thus controlling the onset of the TFUS sonication and the pulse repetition frequency of the stimulation.

Prior to the experiment conducted in volunteers, we performed measurements in a deionized water tank, using a calibrated 1 mm needle hydrophone (Precision Acoustics, UK) aligned with the transducer and a data acquisition card to characterize the spatial profile of the ultrasound beam. The grid of measurements was defined in a longitudinal plane passing through the revolution axis of the transducer. Its size was 100 * 50 mm², in steps of 1 mm in both directions. The full-width half-maximum area had the shape of an ellipsoid. Focal area was 9 mm wide and 60 mm long. The focal distance, defined the distance between the active face of the transducer and the point of maximal pressure peak in the measurement plane was equal to 24 mm.

B. Driving Voltage Selection

We evaluated the sonication pressure waves and its trial-by-trial and session-by-session variability according to the amplitude of the voltage set on the function generator. We developed a calibration prototype to allow for quick alignment between the needle hydrophone and the transducer. Moreover, the distance between the tip of the hydrophone and the active face of the transducer can be adapted. We performed the measurements with the calibration prototype in a small deionized water tank. The measurement distance was set to 24 mm, corresponding to the focal distance of the transducer.

One trial corresponded to the measurement of an ultrasound burst generated at a fundamental frequency of 350 kHz, composed of 126 sinusoidal cycles, with a driving voltage amplitude set on the function generator. One session of measurements was composed of 20 trials having the same driving voltage amplitude set. During one session of data

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acquisition, the trials were generated consecutively and recorded in separate files for later analysis. Finally, one set of measurements was composed of several sessions, depending on the number of different driving voltage set. One set of data was different from another depending also to the manipulation of the prototype.

The first set of measurements we performed was composed of 52 sessions involving two different driving voltage amplitudes, 0.4 and 0.6 V peak-to-peak. Between two sessions, the prototype was disassembled, and the hydrophone was repositioned. The second set of measurements we performed was composed of 140 sessions involving five different driving voltage amplitude varying between 0.2 and 0.6 V peak-to-peak, by steps of 0.1V. The system was switched on the day of measurements, the hydrophone and the transducer were soaked for at least one hour before starting an acquisition. Several sessions were acquired on the same day, separated by at least 3 h. The calibration prototype was disassembled between each day of measurements. At the end of each day the water was replaced, and the hydrophone as well as the transducer were left to dry out. The room and the water temperature were measured before acquiring a new set of measurements. The adjustment of the distance between the hydrophone and the transducer were not changed during the acquisition of the 140 sessions. Finally, we conducted an additional set of measurements, composed of 175 sessions. The only difference between these sessions and the preceding sessions was the positioning of the calibration prototype using a landmark to reposition the transducer and hydrophone in the same angle relative to each other.

Based on the recorded pressure waves, we computed the maximum pressure peak (P), the spatial-peak pulse-averaged intensity (Isppa), the spatial-peak temporal-average intensity (Ispta) and the mechanical index (MI). Using these repeated measurements, we calculated the 90th percentile of the exposure indices. We selected a driving voltage for which the 90th percentile would not exceed the safety limits for Isppa, Ispta and MI defined by the International Electrotechnical Committee (IEC) [5, 6], which are 190 W/cm², 3 W/cm² and 1.9, respectively. To compare our free-field measured values with the IEC safety limits, we computed non-derated pressure peak values for those limits by taking into consideration the attenuation coefficient of the skull bone reported in previous studies targeting S1 in humans [3, 4, 7].

C. Participants

The local ethical committee (Commission d'Ethique Biomédicale Hospitalo-Facultaire of UCLouvain) gave its approval for all the experimental procedures conducted in human volunteers. Seven participants (20-24 years old), five females, gave their written informed consent to participate in the study. The participants received financial compensation for their participation.

D. Experimental design

Participants were seated in a chair, both forearms in supine position. TFUS was delivered over the left S1 during 500 ms. SEPs were elicited by transcutaneous electrical stimulation of the right median nerve (MN) at the level of the wrist. MN stimuli were delivered in three different conditions: 100 ms after TFUS onset, 200 ms after TFUS onset, and 500 ms before TFUS onset (control condition). 250 stimuli were delivered for each condition. The order of the conditions was randomized across trials. Inter-stimulus interval varied randomly between 4-5 s. The stimuli were divided in five blocks with a five minutes break between each block. Participants were instructed to attend a fixation cross during the entire duration of each block. Using a pair of earbuds, white noise was played to the participants to cover any noise made by the experimenter. During the break between blocks, participants were asked to report discomfort or sensations felt in the body.

E. TFUS

For the experimental setting, the emitter was introduced within a Plexiglass cylinder, its active face was covered with an echography probe cover filled with deionized water. The probe protection and deionized were changed for every participant. The cylinder was held against the scalp at the position corresponding to CP3 (see section EEG recordings). Acoustic gel was used to ensure acoustic coupling between the probe cover and the scalp of the participants.

Ultrasound sonication consisted of bursts of 126 cycles at a frequency of 350 kHz repeated at a frequency of 1 kHz for 500 ms. The selected driving voltage was 0.2 Vpp (see Figure 3). Based on our measurements performed in deionized water with the calibration prototype, the sonication had the following parameters the median pressure peak (P) was 542 kPa (90th percentile: 582.2 kPa), the median Isppa was 9.4 W/cm2 (90th percentile: 10.3), the median Ispta was 3.2 W/cm2 (90th percentile: 3.72) and the median MI was 0.95 (90th percentile: 1.01).

F. Median Nerve Stimulation

Transcutaneous electrical stimulations (200 µs square-wave pulse) were delivered at the level of the wrist using a constant-current stimulator (DS7A, Digitimer, UK) and adhesive electrodes (Ambu BlueSensor NF - ECG electrodes, Ambu A/S, Denmark) to ensure that their position remained constant throughout the experiment. The cathode was positioned proximal relative to the anode. Stimulation intensity was set to 1.4X the threshold to elicit a visible motor response in the thumb.

G. EEG analysis

The EEG signals were analyzed offline in Matlab, using the Letswave toolbox (http://letswave.org). A linear detrend was used to remove slow drifts in the signals. In some recordings, spreading of the ultrasonic gel led to the creation of electric bridges across electrodes located close to the site of sonication. The signals from these electrodes were discarded from further analyses. An FFT notch filter was used to remove line noise at 50, 100, 150 and 250 Hz. The signal was then re-referenced against the frontal electrode Fz. A Principal Component Analysis was performed to remove artifacts due to eyeblinks and/or to TFUS stimulation. The filtered signals were then segmented into epochs from -800 ms to +400 ms relative to MN stimulation onset. The epochs were baseline-corrected (interval -10 ms to -4 ms). Signals from electrodes contralateral to MN stimulation, posterior to the central sulcus, were pooled together after visual inspection. Separate average waveforms were

computed for each participant and each experimental condition (100ms and 200ms after TFUS onset, and active sham).

The early-latency N20 and P27 components of SEPs were identified in each average waveform of each participant. Latencies and amplitudes were compared using a repeated-measures ANOVA and post-hoc paired-sample t-tests.

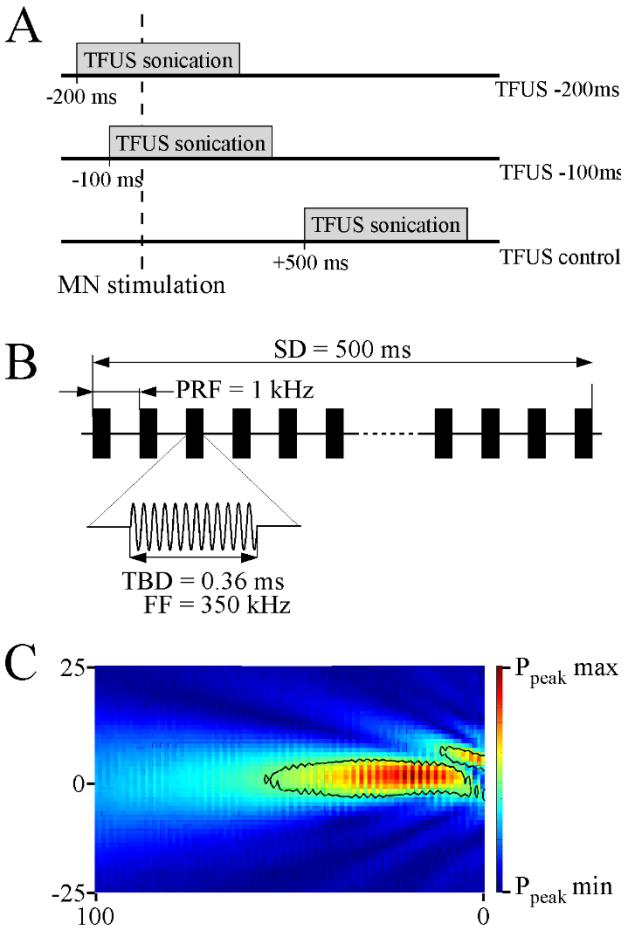

Fig. 1. Experiment overview. A. Representation of the three different conditions applied to human volunteers. The ultrasound stimulation started either 200 ms (TFUS -200ms) or 100 ms (TFUS -100ms) before the stimulation of the right median nerve (MN) or 500 ms after the median nerve stimulation (TFUS control). B. Representation of the sonication parameters. The sonication duration (SD), the pulse repetition frequency (PRF), the tone burst duration (TBD) and the fundamental frequency applied to the left primary somatosensory cortex of human volunteers. C. Acoustic pressure field measured in a longitudinal plan. The black line delimits the full-width half-maximum area, which corresponds to the focal area of stimulation.

III. Results

A. *Across-trial variability of sonication amplitude*

The maximum pressure peaks measured across trials and sessions are shown in Figure 2.

In the first 52 sessions, the ultrasounds bursts recorded at 0.4Vpp and 0.6 Vpp produced average pressure peaks of 977 ±130 and 1404 ±186 kPa, respectively (mean ±SD). Within each session, the average standard deviation across trials was 2.9 kPa. In the second set of 140 sessions, with a driving amplitude varying from 0.2 to 0.6 Vpp, and disassembling and reassembling the prototype using the same position to place the transducer and hydrophone prototype parts, the mean and standard deviation across sessions was 521 ±84, 769 ±124, 1005 ±161, 1231 ±193 and 1444 ±223 kPa. The average standard deviation across trials was 2.9 kPa. Finally, in the third set of 175 sessions, using a driving amplitude varying from 0.2 to 0.6 Vpp, and disassembling the prototype between two consecutive sessions. The mean and standard deviation across sessions was 502 ±71, 742 ±103, 971 ±133, 1187 ±162 and 1400 ±188 kPa. The average standard deviation across trials was 4.7 kPa.

Taking together all the 89 sets of measurements, the median and the standard deviation across sessions computed separately for the driving voltage of 0.2V, 0.3V, 0.4V, 0.5V and 0.6V were 542 ±77, 800 ±114, 1040 ±142, 1274 ±178, and 1489 ±200 kPa, respectively.

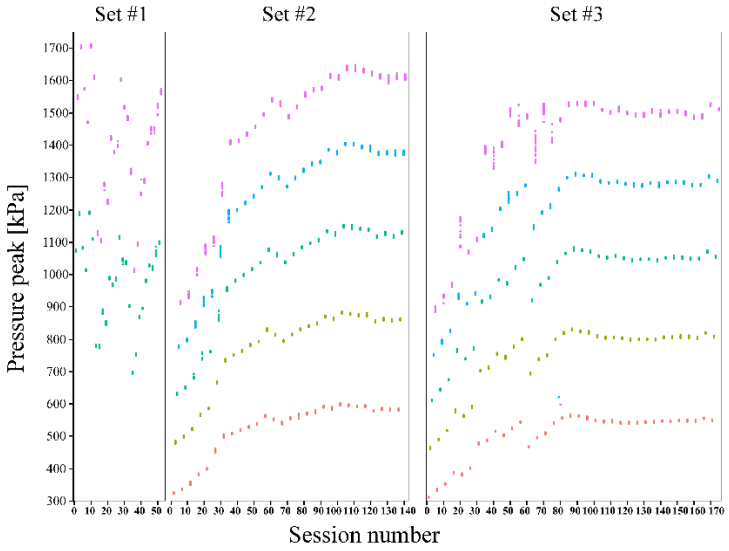

Fig. 2. Diagram of the pressure peaks recorded with the hydrophone. Each dot represents the maximum pressure peak extracted from a trial. The results were sorted according to the set of measurements they belonged to and according to the driving voltage used to generate the ultrasound burst.

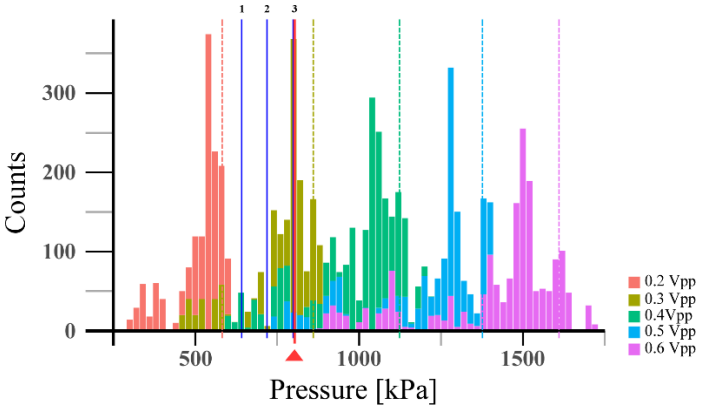

Fig. 3. Pressure histograms for the driving voltage selection. 367 sessions were classified according to the driving voltage used to generate the ultarsound bursts. In addition to the pressure distributions, the 90th percentile of each distribution is represented as a dashed line. The safety limit defined as the lower pressure equivalent of the IEC limits is represented in red. The values of pressure from the references [4],[6] and [3] are represented by the blue lines numeroted 1,2 and 3, respectively.

B. *TFUS applied over S1 in humans*

None of the participants reported any sensation other than the one elicited by MN stimulation.

The group-level average waveform of the SEPs elicited during sonication (100 and 200 ms after TFUS onset) and the SEPs elicited before sonication (500 ms before TFUS onset) are shown in Figure 4. The average latencies and amplitudes of the N20 and P27 components are reported in Table $.

The magnitude of the N20 wave was significantly different across the three conditions (F=4.698, p=0.0358). Post-hoc comparisons showed that the magnitude of the N20 elicited by MN stimulation 200 ms after the onset of TFUS was significantly greater than the magnitude of the N20 elicited by MN stimulation in the control condition (t(6)=3.247, p=0.0175). No significant differences were observed for the latencies of the N20 component.

The magnitude of the P27 was significantly different across conditions (F = 6.470, p=0.0188). Post-hoc comparisons showed that the magnitude of the P27 elicited by MN stimulation 200 ms after the onset of TFUS was significantly decreased as compared to the control condition (t(6)=3.157, p=0.0196).

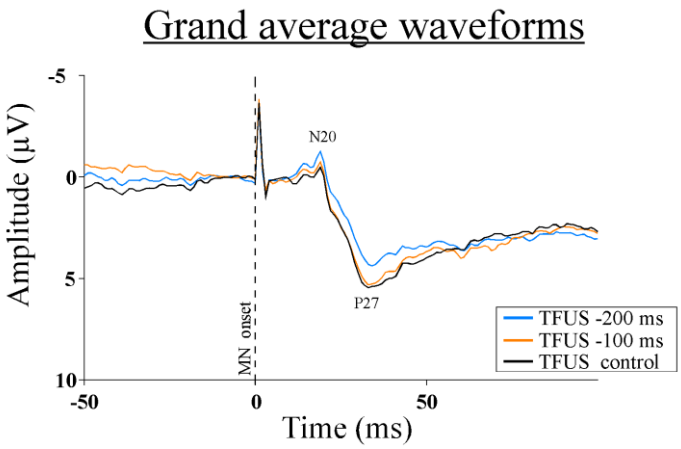

Fig. 4. Grand average waveforms (N=7). EEG waveforms evoked by MN stimulation are represented in blue when TFUS onset was 200 ms before the MN stimulation, in orange when the TFUS onset was 100 ms before MN onset and in black when TFUS onset was 500 ms after MN onset (control).

IV. Discussion

An unexpected observation during calibration was that the intensity of sonication varied significantly from one measurement session to the other (approximately 15% variation of the mean maximum pressure peak across sessions). In contrast, within each session, variations across trials were very small (0.3%). We were unable to relate this between-session variability to variations in temperature, transducer and hydrophone positioning, or time since switched on). This led us to select a driving voltage taking within safety guideline limits that took into account this variability. For this reason, the median sonication intensity used in this study was lower than what has been used in most previous studies.

Nevertheless, our results suggest that TFUS sonication over S1 modulated the EEG responses elicited by stimulation of the contralateral MN. As compared to the active control condition (onset of TFUS 500 ms after MN stimulation), the amplitudes of the N20 and P27 components recorded when TFUS onset started 200 ms before the MN stimulation were significantly increased and decreased, respectively. In a similar experiment, Legon et al. [3] observed an amplitude reduction of the N20-P27 complex. On average the N20-P27 complex was also decreased in the present study, but this difference was not significant.

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