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BX Pulsar 1002

User Manual

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1.0 Overview

The BX Pulsar 1002 is intended as a **Research Use Only** device. Currently, use of the BX Pulsar 1002 is limited by an Investigational Device Exemption (IDE) from the FDA. Users must be trained in operation of the device. The operation of the device is limited to pre-set ultrasound pulse sequences provided by BrainSonix, and may be used in conjunction with functional magnetic resonance imaging (fMRI). Advanced mode operation is only possible with a license from BrainSonix, which allows for more fine-grained control of the device.

The ultrasound based BrainSonix device is a novel, non-invasive alternative to direct neural stimulation. Capitalizing on non-invasive high-intensity focused ultrasound, BrainSonix, using an animal model, found early evidence of selective suppression of regional neural activity in the brain. Importantly these effects were non-thermal and reversible. Low-Intensity Focused Ultrasound Pulsation (LIFUP) differs from high-intensity ultrasound because the intensities of ultrasound used are an order of magnitude lower than high-intensity focused ultrasound. Also, whereas ablative high-intensity focused ultrasound is administered continuously, LIFUP is administered in short pulses, which reduces energy deposition. Our data and those of others have demonstrated that administration of ultrasound as LIFUP causes a significant, but reversible, neuromodulatory effect, without causing tissue damage (Gavrilov et al. 1996, Tyler et al. 2008, Min et al. 2011, Yoo et al. 2011).

2.0 Device Description

The Brainsonix BX Pulsar 1002 was designed to deliver low-intensity focused ultrasound pulsations (LIFUP) to the human brain, and to be safe for simultaneous use with magnetic resonance imaging (MRI) and functional MRI (fMRI). The BX Pulsar 1002 consists of two main elements: the transducer and the ultrasound console (Fig. 1).

The other element of the BX Pulsar 1002 is the transducer. The transducer itself and the housing for it went through several iterations in order to be compatible with an MRI environment. This also allowed

Figure 1. BX Pulsar 1002



Fig. 1. A) Transducer, housing and head strap. B) Ultrasound console.



for a good connection with the scalp. An outer housing was designed to attach the transducer firmly to the head above the temporal window, and to allow it to be moved side to side to accurately target intended structures.

3.0 LIFUP Safety Studies

The BX Pulsar 1002 is not an FDA cleared device, and is appropriate only for use in IRB approved studies. The technology does have an excellent safety profile, and the device itself has passed the required safety testing.

A more complete coverage of the safety of LIFUP is available and previously published in peer-reviewed journals (Bystritsky et al. 2011, Bystritsky and Korb 2015). The following summarizes our safety findings.

LIFUP has demonstrated the ability to safely modulate neural activity in humans and in animal models (Bystritsky et al. 2011, Bystritsky and Korb 2015) and is compatible with fMRI technology (Yoo et al. 2011, Korb et al. 2014, Ai et al. 2016). LIFUP relies on low energy sound waves that pass through the skin and skull. The skull absorbs much of the ultrasound energy, while the shape of the focal region is preserved (Lee et al. 2015), and thus the ultrasound wave can be focused with precision in three dimensions in any brain region. While this focal volume is small relative the size of the brain ($< 0.2\text{cm}^3$ or approximately 0.01% of total brain volume), it can stimulate tens of thousands of neurons within the focal region. This is an acceptable stimulation level for producing fMRI signals that can inform scientists on dynamic communications between different brain regions.

Focused ultrasound is a means of delivering mechanical energy to tissue. The concept of using sound waves to modulate neuronal activity has been under investigation since 1958 (Fry 1958). Since then, the neuromodulatory effects of focused ultrasound have been demonstrated numerous times in multiple animal models (Bystritsky et al. 2011, Bystritsky and Korb 2015). Recent animal studies have shown that focused ultrasound is capable of stimulating auditory nerve responses (Foster and Wiederhold 1978); down-regulating nervous conduction (Hynynen et al. 1997), and inducing reproducible excitation of neuronal circuits in the motor cortex in excised rodent brain (Tyler et al. 2008) and in live animals (Tufail et al. 2010).

Non-invasive LIFUP neuromodulation is feasible in the human brain (Bystritsky and Korb 2015). In one study, LIFUP focused ultrasound that targeted the hand area of the somatosensory cortex elicited both tactile sensation in the contralateral hand and relevant EEG evoked-potentials (Lee et al. 2015). In another set of studies targeting the same region during concurrent median nerve stimulation, LIFUP significantly decreased the amplitude of stimulus-evoked potentials (Legon et al. 2014) and altered the dynamics of intrinsic EEG activity (Mueller et al. 2014). This study showed that LIFUP can not only modulate brain electrical activity but affect perceptions and behavior as well.

The safety of focused ultrasound has been assessed in multiple experiments. In sharp contrast to high-intensity focused ultrasound, none of the studies using LIFUP suggest any



adverse effects from histological, blood-brain barrier or behavioral data. Several recent studies looked thoroughly for evidence of damage caused by LIFUP and found none (Tyler et al. 2008, Yoo 2008, S-S. Yoo 2010, Tyler 2010). Even with chronic stimulation of LIFUP for 48 hours, no alterations were seen in the fine structure of neuronal membranes (Tyler, et al, 2008).

The low frequency and low energy of LIFUP falls well below the threshold to induce damage. Even at high frequency (5.7Mhz) and high energy (280 W/cm²), tissue damage has not been observed (Foley et al. 2007, Foley et al. 2008), and the threshold for damage is likely much higher (Velling and Shklyaruk 1988).

In general, any potential ultrasound-induced tissue damage appears to be caused by heating, and for the proposed study an increase in temperature is not required to exert effects on neural activity (Tufail, et al. 2010).

Safety testing of the BX Pulsar 1002 was conducted according to IEC 60601-1, 60601-1-2 including basic safety, immunity testing, and radiated emissions. The device passed all safety testing (Appendix A).

4.0 Setting up the BX Pulsar 1002

The BX Pulsar 1002 is easy to use and quick to set up. This section will describe how to set up the BX Pulsar 1002. Contact BrainSonix with questions or for further information about your specific needs.

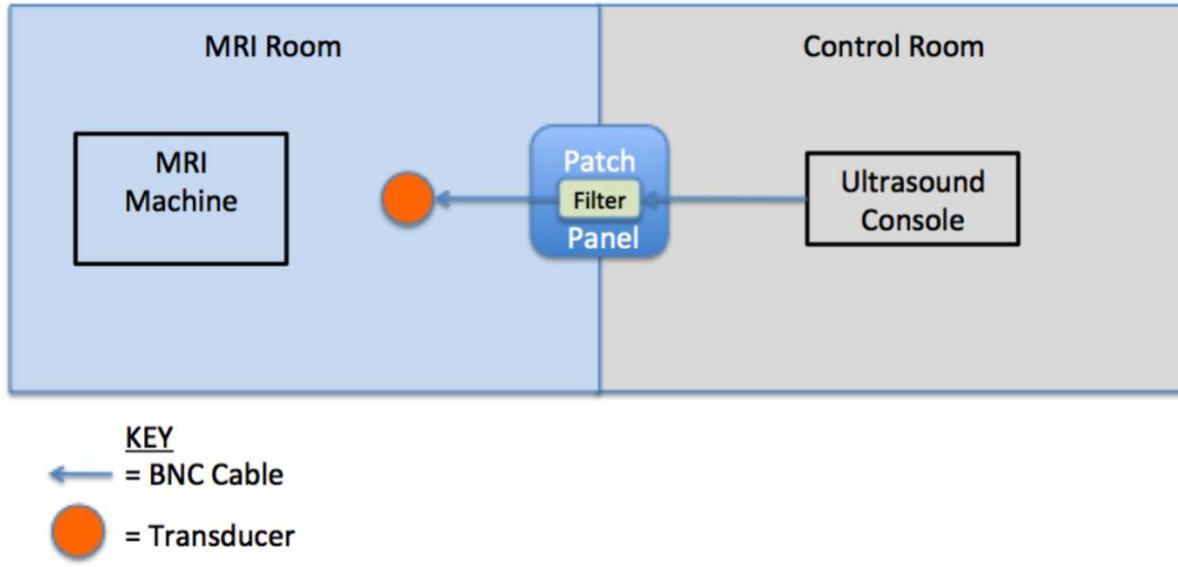
4.1 Setting up the System

Because the console or any other metallic object cannot be present in the room housing the MRI scanner, the transducer will be located next door in the MRI control room (Fig. 2). In order to properly set the system up there must be a BNC connector through the patch panel in the MRI control room. If this is not installed, the system cannot be used.

Plug the device into a standard 120V outlet. Connect a BNC cable from the console output to the penetration panel on the outside of the MRI room. Inside the MRI room, attach the RF filter to the penetration panel. Then connect one end of an MRI safe BNC cable to the filter and the other end to the transducer cable. **SAFETY NOTE: The cable used inside the MRI room must not be magnetic, and need to be calibrated with the system! Use the supplied cables only.**



Figure 2. Schematic of Device Setup



4.2 Synchronizing LIFUP to Image Acquisition

LIFUP may be synchronized to MRI acquisition in a variety of ways. Any triggering from the scanner should be optically isolated. You can utilize the optical trigger port, or if you have an optically isolated trigger that utilizes a BNC or USB connector, those can be used also.

4.3 Powering the System

To power on the system, press the power button on the back of the base of console. Then press the power button on the bottom of the monitor, which turns on the device. The startup process takes about 1 minute during which you'll hear a series of sounds.



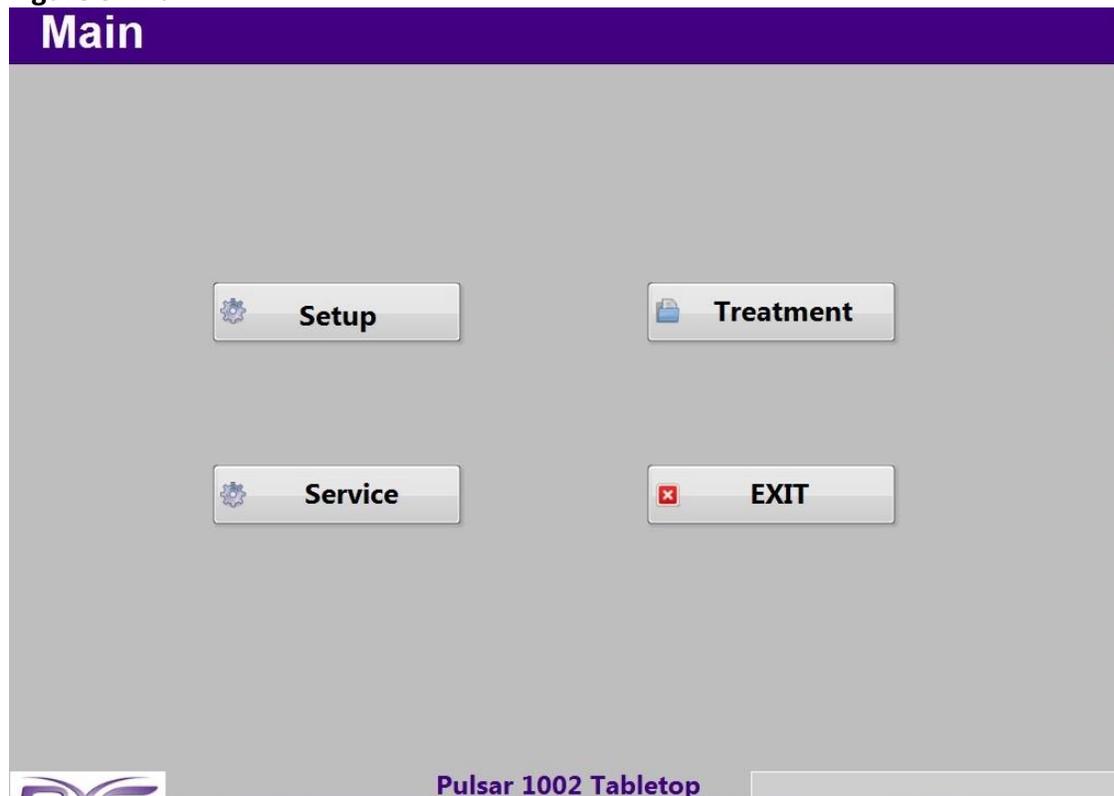
5.0 Using the BX Pulsar 1002

This section describes use of the BX Pulsar 1002 with a research participant.

5.1 Opening the BX Pulsar Software

The software should automatically open on start-up. If it does not, simply double-click the icon on the desktop for the BrainSonix software. The software begins on the main startup screen (Fig. 3). The options are “Setup”, “Service”, “Treatment” and “Exit.”

Figure 3. Main





5.2 Setting up a Treatment/Experiment

To setup up a treatment or experiment, click on “Setup”. This will take you to the setup screen (Fig. 4). This displays all the parameters of the currently selected sonication file. It also allows you to leave notes such as the Patient ID, Treatment ID, Operator, Location/Site ID, MRI Info and general notes. These are all optional, and can also be modified for each individual treatment. If you are satisfied with the sonication parameters, click “Return to Main Screen” to continue the experiment. NOTE: if Patient ID and Treatment ID are not entered, a popup will display a message “No value has been entered for Patient ID or Treatment ID.” These values are not required, so if you wish to proceed without modifying, then click “Proceed.” Otherwise click, “Cancel.”

Figure 4. Setup

Setup

System s/n: BSX10002 Transducer: 0518-5705F650 Frequency (KHz): 650 Transducer Connection: Direct Connection

Patient ID: Operator: dfg Location/Site ID: dfg MRI Info: dfg

Treatment ID: Notes:

Sonication Parameters

| | | | |
|-------------------|--------------------------------------|-------------------------|-----------------|
| Pr.0 (MPa): 0.234 | Ispta.0(mW/cm ²): 905 | Pulse Width (ms): 5 | PRF (Hz): 100 |
| Pr.3(MPa): 0.197 | Ispta.3(mW/cm ²): 640.47 | Duty Factor: 0.5 | XMT Volts: 4.04 |
| Pr.a (MPa): 0.129 | Ispta.a(mW/cm ²): 273.3 | Skull Thickness (mm): 4 | |

Skull attenuation modeled at 2 dB/mm

Sonication Duration (s): 30 Between (s): 30 Number: 8

Trigger Source: Optical (selected), Edge, Rising, Retrigger, Disabled

Trigger Enable: Sync Off (selected), Delay(ms): 480000, Sonication Indicator: On

Sonication File Name: josh_eegrest_DC50_100Hz.bsx

[Select Another Sonication File](#) [Modify Current Sonication File](#) [Return to Main Screen](#)

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Make sure you select the correct transducer, which can be identified by the serial number on the cable of the transducer. This ensures the system is properly calibrated.

It is also important to correctly indicate how the transducer is connected to the system under “Transducer Connection.” “Direct Connection” indicates that the transducer is plugged directly into the system (using a BNC adapter). This may be the case when the device is used outside of an MRI environment. If any cables are used, then only the provided cables should be used, otherwise the calibration will be off and the incorrect amount of energy will be delivered.



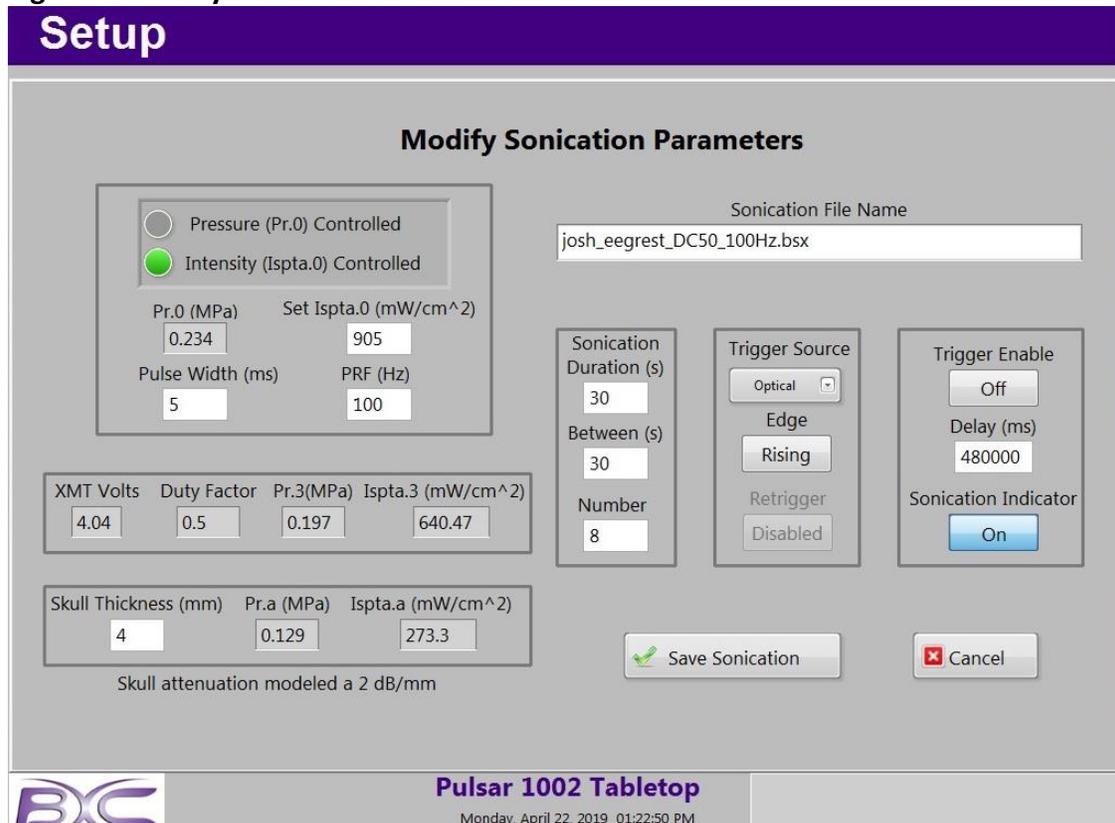
To select another sonication file, simply click the button labeled, “Select Another Sonication File.” This will open a file selector, from which you can choose the appropriate file.

To change the parameters in a sonication file, select “Modify Current Sonication File.” This is described further in the section below.

5.3 Modifying a Sonication File

To change the parameters in a sonication file, select “Modify Current Sonication File,” which brings up the following screen (Fig. 5).

Figure 5. Modify Sonication Parameters



You can define either the desired pressure (Pr.0), or the desired intensity (Ispta.0) and the software will calculate the other, and will also calculate the voltage and duty cycle based on the parameter values you provide.

Since some of the values are dependent on each other, it is important to have a good understanding of what these parameters mean. Pulse width, pulse repetition frequency, and sonication duration are illustrated in Fig. 6. The parameters in this sonication will be repeated the number of times indicated in “Number,” and be spaced apart by the time indicated in “Between (s)”. The example above shows a sonication with an intensity of 905mW/cm² $I_{spta.0}$ with a pulse width of 5ms and a pulse repetition frequency of 100Hz. This will be applied for the



duration of the pulse train (30s). This whole pulse train will be run a total of 8 times (i.e. Number) with 30 seconds in between each pulse train.

If you wish to trigger with a BNC input or Optical TTL, select the appropriate trigger source. To include a delay from the trigger or button press, enter a delay in milliseconds under “Delay (ms).” If you wish to trigger via a USB or clicking with a mouse, or pressing a button on the keyboard, be sure that “Trigger Enable” is set to “Off.” “Trigger Enable” is used only when triggering with BNC or Optical TTL.

“Skull Thickness” does not change any of the sonication parameters, but simply changes the estimates of the ultrasound pressure and intensity at the focus.

To save your parameters as a new sonication file, enter the file name in the “Sonication File Name” box and click “Save Sonication.” If you have entered the name of a file that already exists, it will ask if you want to overwrite it.

Figure 6. Pulse Diagram Description

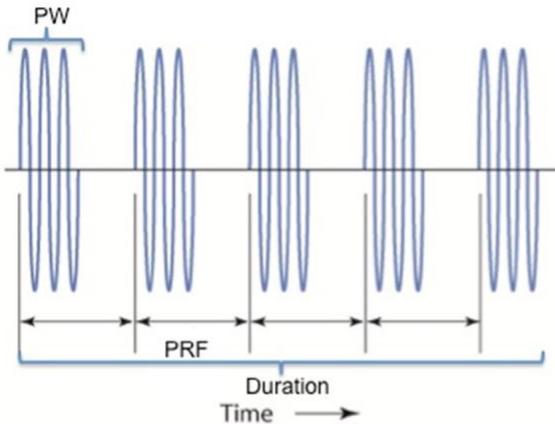


Fig. 5. This diagram shows a pulsed sine wave of ultrasound at 650kHz, which is the fundamental frequency of the transducer. The pulse width (PW) represents the time from when an ultrasound pulse starts to when it stops. The pulse repetition frequency (PRF) is the rate at which pulses are repeated and is equal to 1/period. The duration is the total length of the train of pulses.

Table 1. A Sample of Configuration File Parameters

| # | PW (ms) | PRF (Hz) | Ispta (mW/cm ²) | DC | Duration (s) | Sonications |
|---|---------|----------|-----------------------------|-----|--------------|-------------|
| 1 | 50 | 10 | 720 | 50% | 1 | 8 |
| 2 | 50 | 10 | 1440 | 50% | 1 | 8 |
| 3 | 50 | 10 | 2880 | 50% | 1 | 8 |
| 4 | 50 | 10 | 5760 | 50% | 1 | 8 |
| 5 | 0.5 | 100 | 720 | 5% | 30 | 2 |
| 6 | 0.5 | 100 | 1440 | 5% | 30 | 2 |
| 7 | 0.5 | 100 | 2880 | 5% | 30 | 2 |
| 8 | 0.5 | 100 | 5760 | 5% | 30 | 2 |

PW=pulse width. PRF=pulse repetition frequency. Ispta=derated spatial-peak temporal-average intensity. DC = duty cycle.

5.4 Preparing the Participant and Transducer



Because hair absorbs ultrasound, it is recommended to shave the head of the participant on the region where the transducer is placed. Place the straps over the participant's head and tighten to a snug, yet comfortable tension. Make sure the transducer holder aligns with the presumed target.

Apply approximately 1 teaspoon of ultrasound gel on the concave side of the gel pad and place it against the transducer. Press out any visible bubbles. Then place a similar amount of gel, or as much as is needed, onto the exposed side of the gel pad. The gel pad, and gel on both sides ensure good conduction of ultrasound from the transducer to the participant.

To place the transducer and pad into the holder, squeeze the grips on the back of the transducer, and slide them into the holder. Ensure that the transducer and pad are snug against the head, and are at the desired angle. You may need to pull the transducer holder away from the head slightly in order to get the transducer to clip in. Adjust the straps again if necessary.

The holder has grooves at 3 different levels that allow for 3 different angles of the transducer: 0°, 2.5°, and 5°. If the transducer tabs are on the groove at the same level, regardless which one, then the transducer will have an angle of 0°. If the groove level is off by one, then the angle will be 2.5°. If the groove level is off by two, then the angle will be 5°. It is recommended that the angle of the gel pad match the angle of the transducer. Although the gel pads allow for some compression for slight adjustments.

NOTE: For LIFUP to be safe and effective the participant must have a temporal window that is both not damaged and not too thick (i.e. <5cm). Ideally this should be determined via CT scan prior to the experiment.

When placing the participant inside the MRI scanner, ensure that the wire from the transducer does not create any loops. It should run straight along the body of the participant.

Make sure subject's head is comfortably immobilized inside the head coil.

5.5 Targeting the Transducer

Targeting the transducer is an iterative process. First, using landmarks on the head such as ears and eyes, the transducer is placed over the estimated region of the brain to be targeted. Place the participant in the MRI scanner and run the quick MPRAGE scan. Using the 3D feature on the scanner console, select the axis rotation tool (curved arrow) to align the axes with the fiducial markers on the transducer. The fiducial markers are aligned parallel to the transducer and perpendicular to the beam. A line that passes through the center of the transducer, perpendicular to the fiducial markers will point straight to the target.

Check if the axis of the beam passes through the area of interest and if the distance of the brain region from the surface of the transducer is within 1cm of the focal length of the transducer. When that occurs, the targeting is complete. If not, the direction and magnitude that the transducer must be re-estimated and moved in order to achieve accurate targeting. If re-targeting is necessary, the subject is removed from scanner gantry and remains on the scanner bed, while the operator adjusts the location of the transducer. This process is repeated as necessary. For most cases, accurate targeting can be accomplished in ≤ 3 iterations.



5.6 Running a Treatment/Experiment

From the Main screen click “Treatment.” This will take you to a confirmation screen to verify your selected parameters (Fig. 7).

Patient ID, Treatment ID, Operator, Site ID, MRI Info, and Notes are all auto-filled by the defaults provided in the sonication file. You can write or overwrite any of these that apply to this treatment or experiment only and it will not affect the defaults in the sonication file.

Confirm that the parameters match your expectations.

If you would like to make changes, by either selecting a different configuration file, or modifying the parameters, click the appropriate button. If you are satisfied, click “Confirm Setup.”

Figure 7. Confirm Setup

Main

Confirm Setup

Patient ID:

Operator:

Location/Site ID:

MRI Info:

Treatment ID:

Notes:

NOTE: Select Modify Setup to change values below

Transducer ID:

XDCR Connection:

Frequency (KHz):

Pr.0 (MPa): Ispta.0(mW/cm²): Pulse Width (ms): PRF (Hz):

Pr.3(MPa): Ispta.3(mW/cm²): Duty Factor: XMT Volts:

Pr.a (MPa): Ispta.a(mW/cm²): Skull Thickness (mm):

Sonication Duration (s):

Time between Sonications (s):

Number of Sonications:

MRI Sync Enable:

MRI Sync Delay(ms):

Sonication Indicator:

Sonication File:

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A window will pop up asking to verify that the Site ID, Patient ID, Treatment ID and Transducer ID are all correct. Click “Yes” to continue, or “No” to return and correct this information. Clicking “Yes” will take you to the treatment screen (Fig. 8).

The treatment is now ready to begin. If you would like to start the treatment manually then click “Start” at the moment that you want to start the treatment. The treatment will start with any delay that is specified in the configuration file, and then start LIFUP pulses. If the



treatment will be triggered via the optical or BNC port, and those options are selected, then clicking “Start” will arm the device and cause it to be ready to receive a trigger. If you will be triggering using a BNC or optical trigger, be sure not to click “Start” until you are ready to sonicate, since unintentional signals can initiate the sonication.

The treatment screen has a visual indicator, roughly showing the structure of the treatment. Light blue shows the delay before sonication (if any). Light green shows sonication periods, and dark green shows the time between sonications. Keep in mind that the length of the sonications are not always to scale, and short sonications may appear to have different timing. This is just a visual representation, and does not affect the timing of the actual pulses.

Figure 8. Treatment

Treatment

Ready To Start Treatment

Total Treatment Time: 15:30.00

15:30.0 Remaining

Legend:
Pre-Sonation (Light Blue)
Sonication (Active) (Light Green)
Inter-Sonication (Inactive) (Dark Green)

Buttons: Start, End Treatment, Test

| | | | | | |
|-------------------|-----------------|------------------------------|------------------------------|------------------|-------------------|
| Patient ID | Treatment ID | Pr.0 (MPa) | Ispta.0(mW/cm ²) | Pulse Width (ms) | Sonication Number |
| dfg | gdfgdgfdg | 0.21 | 905 | 5 | 8 |
| Transducer ID | Pr.3 (MPa) | Ispta.3(mW/cm ²) | XMT Volts | PRF (Hz) | Duration (s) |
| 0518-5705F650 | 0.176 | 640.47 | 4.28 | 100 | 30 |
| XDCR Connection | Frequency (KHz) | Sonication File | Duty Factor | Between (s) | |
| Direct Connection | 650 | josh_eegrest_DC50_100Hz.bsx | 0.5 | 30 | |

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5.7 Service Mode

Service mode is not required under standard usage of the device. If service mode is required, please contact BrainSonix for the password and further information.



5.8 Support and Troubleshooting

BrainSonix Corp. provides operational support through 310-943-6983 or alexk@brainsonix.com.

- If selecting the transducer on the system results in an error, contact BrainSonix to obtain replacement transducer file.
- If you see an error that says “Fault – XMT Supply too low” make sure that the cable configuration you’re using matches the one selected in the software. If that does not fix the problem, try restarting. If the problem persists, please contact BrainSonix.
- If signal dropout in the MRI is excessive, use a deeper transducer with a thicker gel pad to maximize distance between the participant’s head and transducer.
- If the transducer slips on the head too much, apply less gel or tighten the straps, but not so much as to cause excessive discomfort.
- If the software stops responding, restart the system. This may happen from the “Confirm Setup” screen if the header for the “Main” screen behind it gets accidentally clicked.
- If you notice that the system delivers an extra sonication, or does not shut off after the sonication period, hit the emergency stop button, copy the relevant log files, turn off the device, and contact BrainSonix immediately. Do not use the device until given “all clear” by BrainSonix personnel.
- If there appear to be electrical, hardware, or software issues, please unplug the device and contact BrainSonix before using.
- For other issues, please contact BrainSonix.



Appendix A. Safety Tests

The BX Pulsar 1002 satisfied the following safety requirements:

IEC 60601-1-2:2007 Medical Electrical Equipment – Part 1-2: General Requirements for Basic Safety and Essential Performance – Collateral Standard Electromagnetic Compatibility – Requirements and Tests

- Radiated Emissions CISPR 11, Class A
- Electro-Static Discharge Immunity Test IEC 61000-4-2 ed2.0 (2008-12)
- Radiated, Radio-Frequency, Electromagnetic Immunity IEC 61000-4-3 ed3.0 (with A1:2007+A2:2010)
- Electrical Fast Transient/Burst Immunity Test IEC 61000-4-4 ed3.0 (2012-04)
- Immunity to Surges IEC 61000-4-5 ed3.0 (2014-05)
- Conducted, Radio-Frequency, Electromagnetic Immunity Test IEC 61000-4-6 ed2.0 (with A1:2004+A2:2006)
- Power Frequency Magnetic Field Immunity Test IEC 61000-4-8 ed2.0 (2009-09)
- Voltage Dips/Interruptions Immunity Test IEC 61000-4-11 ed2.0 (2004-03)

Magnetic safety

- ASTM Standard F2052, 2006 *modified*
- ASTM Standard F2213, 2006 *modified*