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TITLE:

Functional MRI in Conjunction with a Novel MRI-Compatible Hand-Induced Robotic Device to Evaluate Rehabilitation of Individuals Recovering from Hand Grip Deficits

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KEYWORDS:

MRI, fMRI, brain, motor function, robots, neurological disease, stroke, rehabilitation

SUMMARY:

We performed functional MRI using a novel MRI-compatible hand-induced robotic device to evaluate its utility for monitoring hand motor function in individuals recovering from neurological deficits.

ABSTRACT:

Functional magnetic resonance imaging (fMRI) is a non-invasive magnetic resonance imaging technique that images brain activation in vivo, using endogenous deoxyhemoglobin as an endogenous contrast agent to detect changes in blood-level-dependent oxygenation (BOLD effect). We combined fMRI with a novel robotic device (MR-compatible hand-induced robotic device [MR_CHIROD]) so that a person in the scanner can execute a controlled motor task, hand-squeezing, which is a very important hand movement to study in neurological motor disease. We employed parallel imaging (generalized auto-calibrating partially parallel acquisitions [GRAPPA]), which allowed higher spatial resolution resulting in increased sensitivity to BOLD. The

combination of fMRI with the hand-induced robotic device allowed precise control and monitoring of the task that was executed while a participant was in the scanner; this may prove to be of utility in rehabilitation of hand motor function in patients recovering from neurological deficits (e.g., stroke). Here we outline the protocol for using the current prototype of the MR_CHIROD during an fMRI scan.

INTRODUCTION:

Appropriate imaging metrics may monitor and predict the likelihood of therapy success in individuals better than clinical assessments and provide information to improve and individualize therapy planning. We have developed experience with patients recovering from chronic stroke¹⁻⁸. Developing optimal individualized strategies that focus on how motor training can influence incremental improvement either in reorganization of neural activity and/or motor function is still challenging. Insights into the underlying structural remodeling and re-organization processes for functional recovery in the brain after neurological disease can allow us to evaluate the relationship between distributed topographic patterns of neural activity and functional recovery via functional neuroimaging methods and brain mapping. Success will facilitate developing personalized treatment strategies optimized to yield improvements in grip strength in broad population with neurological conditions based on magnetic resonance imaging (MRI) metrics⁹.

Here we present a protocol that employs a newly re-designed robotic hand device that provides a controllable resistance force against which a subject grips and releases a handle in synchrony with an oscillating visual stimulus. The MR-CHIROD v3 (MR-compatible Hand-Induced RObotic Device) is a system for presentation of adjustable forces against which gripping and releasing motions are performed, while measuring and recording applied force, grip displacement and timestamps for each data point (**Figure 1**). The device was engineered to provide reliable assessments of brain activation images during fMRI (functional Magnetic Resonance Imaging), which can be used to evaluate blood-oxygen-level dependent (BOLD) changes in brain responses of patients recovering from neurological disorders. MR-compatibility is achieved through the use of entirely non-ferrous/non-magnetic components for the structure and pneumatic actuator elements and shielded sensor/electronic components that are positioned on the scanner's bed. **Figure 2** shows the device attached to an MR scanner bed, and with a subject in the magnet bore grasping the handle of the MR-CHIROD v3 (**Figure 3**). Interface and control components are positioned outside the MR scanner room (**Figure 4**).

The device is used simultaneously with brain imaging methods to assess relevant brain activations. The primary use of the system is to provide a motor task that generates activations of the brain's motor areas, which are detected using fMRI. Brain activation while using the MR-CHIROD during imaging can assess neuroplasticity in neurological disease. By tracking changes in activations in the course of and after motor training using the MR-CHIROD, progress of motor rehabilitation following any neurological disease that leads to motor deficits (e.g., stroke) may be observed.

The MR-CHIROD v3 can also be table-mounted, for use in intra-scan training exercises, in which the subject grips and releases in response to suitable visual stimuli for periods of 45 min, three

89 times per week during the study. Our experience with robotically delivered training, monitored
90 with imaging, suggests that the recovery window for stroke patients for instance may never
91 close¹.

92
93 Our rationale for building and using an MR-compatible hand-grip robot is that robotic recovery
94 has the potential to produce a great impact on impairment due to its easy deployment,
95 applicability across various motor impairments, high measurement reliability, and capacity to
96 deliver high intensity training protocols¹⁰. Our MR-compatible robot can: (a) be set for subject-
97 specific ranges of motion and be programmatically adjusted to apply subject-specific force levels;
98 (b) control, measure and record force and displacement parameters through a host computer;
99 (c) remotely adjust control parameters without requiring interruption of scanning for access to
100 the MR scanner room or repositioning of the subject; and (d) provide therapy via training
101 exercises precisely and consistently for extended periods.

102
103 We are aware of no commercially available recovery robotic device that can be used with an MR
104 scanner to measure the subject's hand grip force and displacement while applying computer-
105 controlled time-varying force. Tsekos et al.¹¹ have reviewed a variety of primarily research-based,
106 MR-compatible robotic and rehabilitation devices, including earlier iterations of the MR-CHIROP
107 series of devices. Other devices were designed for studying wrist motion, finger motion, isometric
108 grip strength, and multi-joint movements. For devices that actively provide resistive or other
109 forces, a variety of MR-compatible technologies have been employed including hydraulics,
110 pneumatics, mechanical linkages and electrorheological fluid dampers. Some devices include
111 multiple degrees of freedom, including another extension of the earlier MR-CHIROP versions
112 added a rotational degree of freedom and hydraulic force application, however it was not
113 adapted for MR-compatibility¹².

114
115 Our hand-grip-specific device has the advantages of portability (it is regularly transported
116 between the MR facility and office-based training sites), and capability of producing large,
117 computer-controlled, time-varying resistive forces. Current use of pneumatic technology in the
118 MR-CHIROP avoids the need for high voltage sources necessary for electro-rheological fluid-
119 based systems, the potential for leakage of hydraulic fluid, and complex cable/linkages linking
120 the interface mechanism with external power and control components.

121
122 The MR-CHIROP was the first device that was demonstrated to function in conjunction with fMRI
123 for brain mapping in stroke patients¹. Importantly, the MR-CHIROP v3 is particularly useful for
124 home- or office-based training, as the system and its software were designed for use without
125 expert clinical support and with motivational elements ("gamification"). Relative to physical
126 therapist-facilitated training in a hospital, office- or home-based training is less expensive and
127 more convenient, making it easier for patients to adhere to daily therapy. The device, already
128 relatively inexpensive relative to some of the other research-based devices, can be reengineered
129 to improve the cost-to-benefit ratio. Virtual reality and gamification of training, both of which
130 are compatible with the MR-CHIROP v3, can engage patients, increase their attention during the
131 task, and improve motivation, thus increasing the effectiveness of recovery¹³.

PROTOCOL:

All experiments were approved by the Institutional Review Board at Massachusetts General Hospital and performed as approved at the Athinoula A. Martinos Center for Biomedical Imaging.

1. Subject preparation

NOTE: Inclusion criteria are: (i) right hand dominance, (ii) ability to give written informed consent. Exclusion was implemented on the basis of screening for contra-indicators in the magnetic resonance environment such as the following: (a) Routine MRI exclusion criteria, such as the presence of a pacemaker or cerebral aneurysm clip and metal implants or metal content in body; (b) history of seizures (c) claustrophobia; (d) pregnancy.

1.1. To obtain informed consent, read the consent form to the volunteer. Both the volunteer and investigator sign in the appropriate locations on consent form in duplicate. Leave one signed copy of consent form in an appropriate location for the investigator records. Keep the second copy of consent form for the participant's records.

1.2. Screen the volunteer for MRI (magnetic resonance imaging) contra-indications. Fill out the MRI contra-indications list and inquire about each item on the list, checking off boxes as appropriate.

1.3. Do not proceed with the scan if participants have (or potentially have) any contra-indications, including surgical aneurysm clips, cardiac pacemaker, prosthetic heart valve, neurostimulator, implanted pumps, cochlear implants, metal rods, plates, screws, hearing aid or transdermal patch.

2. Setup

2.1. Perform initial setup in the scanner room.

NOTE: All necessary training must be obtained by the investigator in advance of the procedure. Precautions relevant to the MR facility must be taken at all times.

2.1.1. Bring the MR_CHIROD (Magnetic Resonance-Compatible Hand Induced Robotic Device) into the MRI scanner room and place it near the penetration panel. Insert the 3/8-inch pneumatic tube into the pass-through tube in the panel into the adjacent MRI support room.

2.1.2. Connect the MRI scanner room force sensing and encoder cables to the 9-pin D-shaped (DSUB) connector on the scanner room side of the panel.

2.2. Setup the MRI support room.

2.2.1. Plug the air compressor into a 110VAC wall outlet. With the compressor's internal regulator turned to the off/minimum pressure position and the ball valve in off-position, turn on compressor and allow it to come to full internal pressure (~4 min).

2.2.2. Connect the support room force sensing and encoder cables to the DSUB connector on the external side of the penetration panel.

2.2.3. Connect the 3/8-inch pneumatic tube fitting, emerging from the penetration panel pass-through to the outlet of the interface/power unit pressure regulator outlet. Connect the 4 mm pneumatic tube to the outlet of the compressor and the inlet of the air filter on the interface/power/regulator unit.

2.2.4. Connect the interface/power/regulator unit to the micro-USB connector of the USB cable/repeater assembly and lay the repeater cable out to the host PC/laptop in the MRI control room. Plug the interface/power/regulator unit into a 110VAC wall plug in the support room, and then turn on power switch.

2.3. Position MR-CHIROP v3 with the patient.

2.3.1. Fully extend and lower the MR scanner bed. Attach the bottom half of the head coil and guide the volunteer to lay down, making sure that the volunteer is resting comfortably and has extended their arms comfortably.

2.3.2. Loosely install the MR_CHIROP on the side of the patient opposite to that of their brain lesion using the corresponding bed-slot. With the volunteer's elbow resting on the table to support the weight of their arm, move the MR_CHIROP handle to the webbing between thumb and forefinger and guide the volunteer to grab the handles of the MR_CHIROP.

2.3.3. If the MR_CHIROP is on the opposite side of the table from the penetration panel, position the cables and the pneumatic tube so that they pass under the table rather than over the patient.

2.3.4. Make sure that the grip position is proper for squeezing. Instruct the volunteer to squeeze and push or pull the MR_CHIROP until they have the most comfortable position for squeezing.

2.3.5. Secure the MR_CHIROP firmly in place by tightening the plastic nuts using an MR-compatible wrench.

NOTE: No scan is being performed at that time. When positioning the MR_CHIROP, the volunteer is resting comfortably on the MR scanner bed outside the magnet. The door to the magnet room may be open.

2.4. Set up the control laptop in the MR control room (adjacent to scanner and support rooms), check and calibrate it.

2.4.1. Turn on the laptop and start the data acquisition/analysis software. Connect the USB cable/repeater assembly to laptop. Turn on the MR scanner room projector. Connect the laptop video output port to the projector connector and set monitor to extend screen onto projector. Connect scanner USB HID trigger cable to the laptop to receive trigger signals from the scanner.

2.4.2. Run the custom user interface (UI) / control / stimulus program for the MR_CHIROD. Automatically set MR_CHIROD pressure to the (minimal) “setup” level to push the handle to the end-stop, verifying display of motion and force waveforms.

2.4.3. Instruct the volunteer that the next few squeezes will be to calibrate for maximum strength of squeezing and hence will be difficult.

2.4.4. Set force level, for example, to 30 N and instruct the volunteer to completely squeeze 2–3 times with a period of approximately 2 s. Observe whether the volunteer can complete a squeeze at that force level.

2.4.5. Gradually increase the force level and repeat squeeze attempts until the volunteer cannot complete a squeeze. This measurement serves as a maximum of the volunteer’s grip strength. The UI automatically calculates 60%, 40%, and 20% of maximum force levels for use during testing.

3. Enter volunteer data and calibrate the MR scanner

3.1. Enter the volunteer’s de-identified data as per hospital policy in accordance with HIPAA (United States Health Insurance Portability and Accountability Act of 1996) regulations on the scanner console.

3.2. (In MR scanner room) Provide ear plugs to the volunteer for acoustic noise reduction.

3.3. (In MR scanner room) Attach the head coil and small foam pads to immobilize the head.

3.4. (In MR scanner room) Attach pillows around the volunteer’s gripping arm at the level of the arm and elbow, to minimize vibrational coupling to volunteer’s own body and to the walls of the MR scanner.

3.5. (In MR scanner room) Attach the communication ball on the volunteer’s chest, instruct them on how to use it and confirm that the communication ball works well before starting the scans.

3.6. (In MR scanner room) Move the table and the participant into the scanner and position at isocenter.

4. Run fMRI session

4.1. Observe the volunteer through the window between the control and scanner rooms and communicate with the volunteer to obtain the participant's permission to start the fMRI protocol. Instruct them not to hold the MR_CHIROD handle to allow it to rest at the fully open position.

4.2. Shim the magnet and run a localizer scan. Open the fMRI protocol and set slices to cover the volunteer's brain.

4.3. Instruct the volunteer that the fMRI session is about to begin.

4.4. Using the UI, set the MR_CHIROD to apply the first force level (20% of maximum). The UI program will display a set of instructions on the video projector for the volunteer to remind them how to respond to the visual stimulus. The UI will wait for the scanner to provide a trigger signal to continue.

4.5. Start an echo-planar-imaging protocol for fMRI. Use imaging program MR_CHIROD from folder USERS. Acquisition and reconstruction parameters are already set in the imaging program and should not be changed. The following parameters are employed: in-plane 192 x 192 or 256 x 256 acquisition matrices; TR (repetition time) in the range of 2–3 s; a 30 ms TE (echo time); 5 mm slice thickness, and a spatial resolution of ~1 mm x 1 mm.

NOTE: The UI/data acquisition/stimulus program will wait to receive a trigger pulse from the scanner corresponding with initiation of pre-fMRI scans in the scanner program. The visual stimulus will remove the instructions and show a "fixation cross" that the volunteer will focus on. When the fMRI scan TRs begin, a visual metronome display, in the form of a growing and shrinking circle will be displayed. The volunteer will completely squeeze and release the handle synchronously with the stimulus. Rest periods will separate stimulus periods, during which time the fixation cross will be redisplayed.

4.6. During execution of a task, monitor force output and whether the participant is performing the task correctly (i.e., fully completing grips and releases and maintaining synchrony with the visual metronome) by observing live plots of force and displacement on the UI.

4.7. Once the first run is over, confirm continuation of the experiment on the UI, which will change force level to second of three levels. Repeat from step 4.5. Similarly, when the second run is over, confirm continuation to run the final run at the third force level.

4.8. After the third run, the UI will automatically set MR_CHIROD pressure to the low "setup" level.

5. Complete the MRI session

5.1. Instruct the participant to relax and to let go of the handle. Collect a series of anatomical scans.

6. Take-down

6.1. Remove the participant from the MR scanner room, follow the setup steps in reverse, and proceed to shut down and disconnect the parts of the MR_CHIROD. Transfer MR data to the database and to disk and close the session.

REPRESENTATIVE RESULTS:

The methodology outlined in the protocol allows the collection of fMRI images while the volunteer is performing the task in real-time in the magnet. Experiments were performed in the Bay 1 facility of the Massachusetts General Hospital Athinoula A. Martinos Center for Biomedical Imaging, using a 3T full-body magnetic resonance scanner. **Figure 2** and **Figure 3** show the placement of the MR-CHIROD on the table and the patient in place operating it. In **Figure 3**, a volunteer is in the scanner bore with his/her head placed at the isocenter of the magnet, which is the correct position for brain imaging. **Figure 4** shows a schematic of the system components and connections, which are set up during the initial phases of the process. During an fMRI session, not only are the images collected, but also a real-time trace of the actual strokes of the device as the person in the magnet bore is operating it are obtained. Typical results are shown in **Figure 5**. The use of controlled pneumatic pressure allows precise control of the constant reaction force provided by the MR-CHIROD v3.

Figure 5A–C shows typical areas of activation during gripping/releasing of the device, using the results of the BOLD technique during fMRI scanning. Red arrows show activation in the M1 region (primary motor cortex) and green areas show the SMA (supplementary motor cortex). **Figure 5D** shows the measured displacement during gripping/releasing, which was performed against the MR_CHIROD's resistance force. **Figure 5E** shows activation over time at a single voxel, chosen from within the somato-sensory area. The response corresponds with the subject's activity, elevated activation occurring during gripping/releasing, and reduced activation when the subject is resting.

FIGURE AND TABLE LEGENDS:

Figure 1: The parts of the MR_CHIROD v3 device. (1) Fixed handle; (2) Sliding handle; (3) Force sensor; (4) Position encoder; (5) Glass-graphite cylinder-piston unit; (6) Shielded load cell amplifier; (7) MR table mounting slot (mockup); (8) Ball bearings with acetyl races and glass balls.

Figure 2: View of the MR_CHIROD v3 securely attached at the scanner bed. This configuration allows the person to operate the MR_CHIROD without supporting any of its weight. The device may be positioned for left or right hand. Shielded cables are grounded at penetration panel, pneumatic tube exits via a pass through tube in the penetration panel.

Figure 3: View of the MR_CHIROD v3 relative to a patient. A volunteer is resting with his hand in position near the handles of the device. The volunteer is placed in the correct position at magnet isocenter for brain imaging.

Figure 4: Schematic diagram of MR_CHIROD set up for operation in an MR scanner room. The shielded cables carrying the signals for the position and velocity data and for the force sensor, as well as the pneumatic tubing pass through the penetration panel which serves as the grounding reference level.

Figure 5: Typical results from performing a motor task (squeezing the handles of a MR_CHIROD). Shown are (A) the fMRI brain activations, superimposed as blobs on an outline of the brain, (B) as pseudo-color on a three-dimensional cross-sectional view of the volunteer's anatomical brain scan, and (C) as pseudo-color rendered on a brain template. M1: Primary motor cortex. SMA: Supplementary motor cortex. (D) Actual force output, measured in units of force (Newton, N) as a function of time. The force output is the actual record of the volunteer's squeezing and is recorded in real time by the MR_CHIROD. (E) The single-voxel time course of activation is shown, chosen from a voxel at the somatosensory area at the location of the cross-hairs in (B). Black bars in (D) and (E) correspond with a 60 s stimulus/rest period.

DISCUSSION:

We present fMRI of a motor task using the latest version of a novel robotic device, the MR_CHIROD^{1,2,8}. The MR_CHIROD has been designed to execute a hand-squeezing grip task which has can be performed by chronic stroke patients and has been studied previously^{1-6,8}. The device is further used as a dynamometer, measuring the patient's maximum grip force, against which experimental force levels are normalized. Activation of the motor cortex is elicited in relation to the force level set during experiments. Further, maximum force is tracked over the course of the study to show improved grip strength. Our earlier iterations of the MR_CHIROD have already proven to be useful in studies showing evidence for neuroplasticity and rehabilitation of chronic stroke patients^{1,6}. We are currently combining the use of the MR_CHIROD with an imaging protocol allowing high sensitivity for fMRI of motor tasks⁷. Our approach combines functional MRI with a novel MRI-compatible hand-induced robotic device for hand motor function rehabilitation.

The device can be easily used or adapted for use in other MR facilities. Physically, the power/interface/regulation unit and air compressor need to be placed into a support/mechanical room with penetration panel access to the MR scanner room, with a suitable data pass-through and a physical pass through for the compressed air tubing. Connection between the unit and the host computer is currently made using a USB cable with a powered repeater to accommodate an approximately 10 m separation between the two elements. Lastly, the scanner must have an associated projector or similar visualization system to present the instructions, fixation cross and visual metronome to the subject, as well as a means to provide TR trigger information to the UI.

This version of the MR-CHIROD was specifically developed to support our experimental protocol in the MR scanner and convenience of use by researchers and subjects in a non-MR suite environment. In both sites, the subject grips and releases the handle of the device against a constant restoring force, which can be changed between experimental runs. As such, the pneumatic system was adopted, which allows for presentation of continuous resistive force to

the subject (compared with earlier and alternative viscous-braking systems using electro-rheological fluids that present zero force when the subject is not actively gripping or releasing and do not provide a restoring force). The earlier MR-CHIROP iterations and other systems are specifically designed to allow for rapid force changes in response to user interaction and rely on ER fluids to allow for the rapid response^{2,14}, however the cost and complexity of such systems was determined to be undesirable for this application.

The protocol presented represents the now stable version in our research. Results collected to date have shown no unexpected findings that will require alteration of the protocol. Future improvements may be required as needed and might include faster imaging and adaptation of our motor paradigm. In addition, the hardware selected supports not only adjusting control parameters via the serial USB connection without requiring interruption of MR scanning, but also doing so for remote updates of home-based training settings using the microprocessor's WiFi module.

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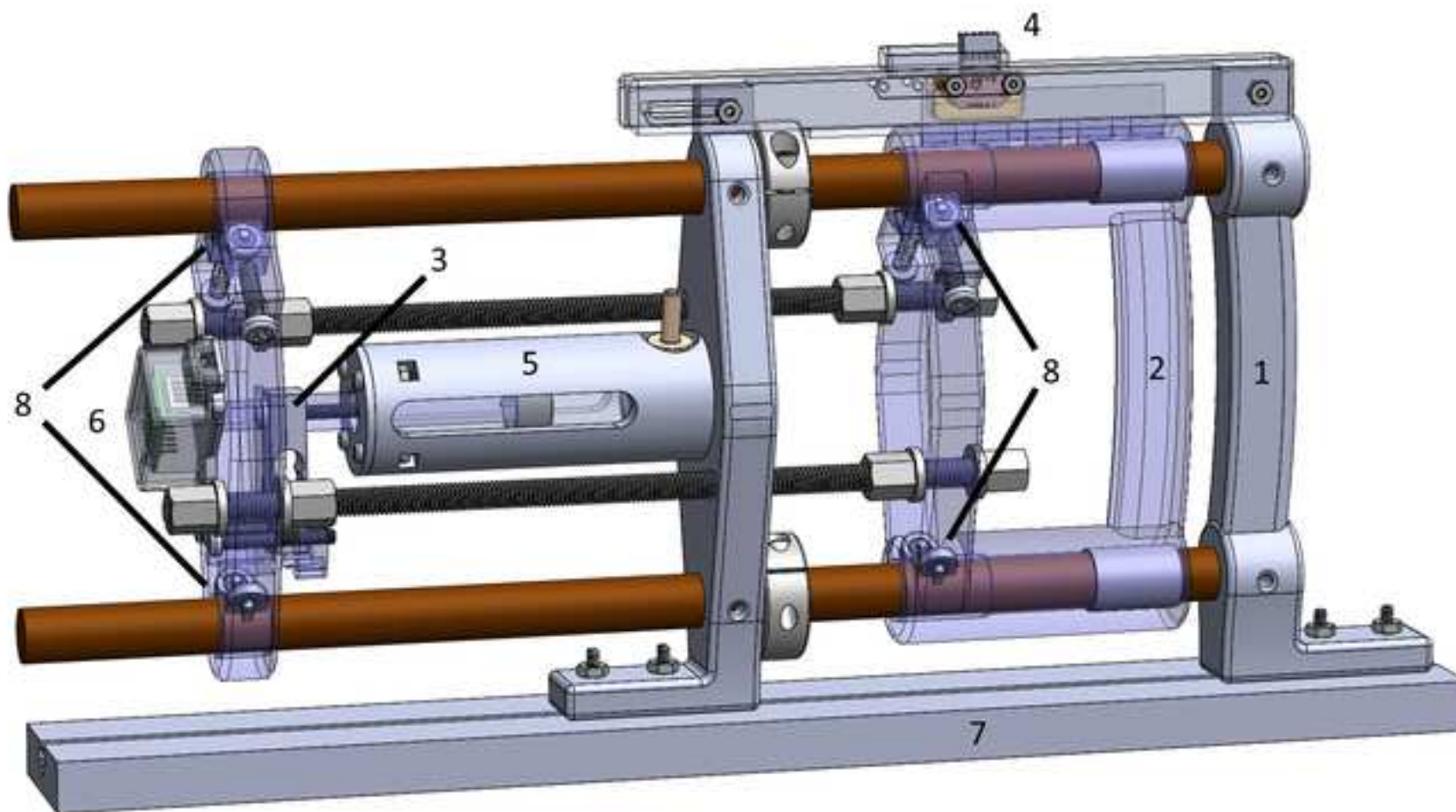
DISCLOSURES:

None of the authors have conflict to disclose.

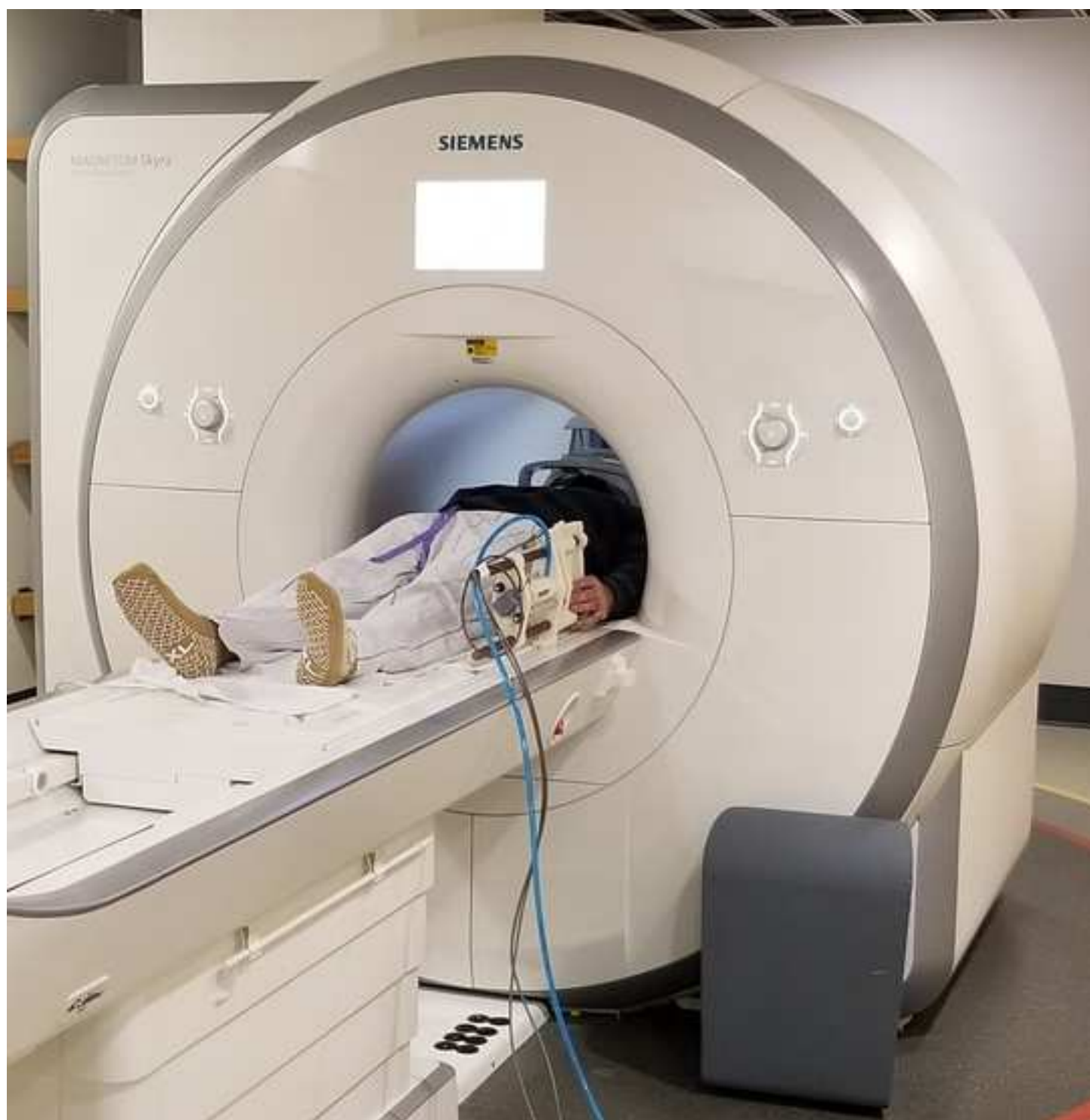
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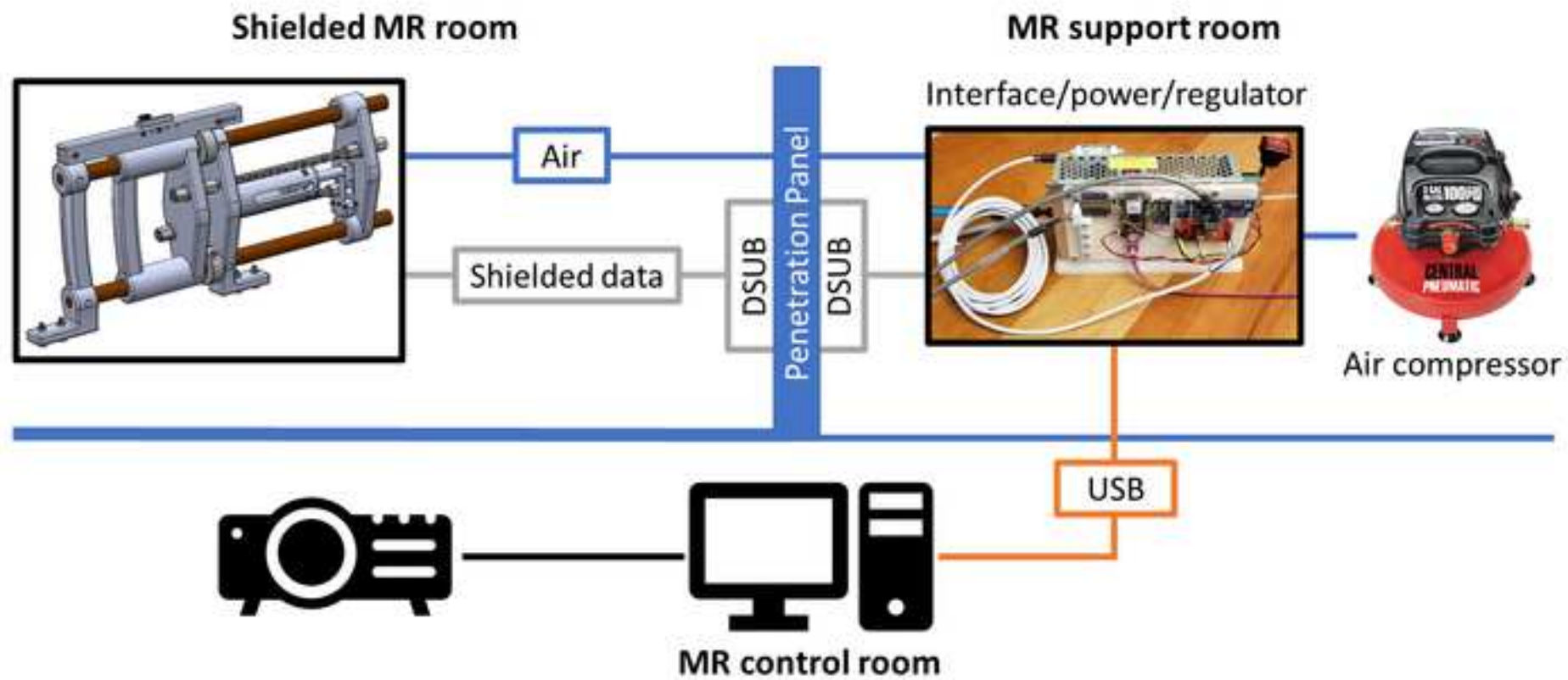
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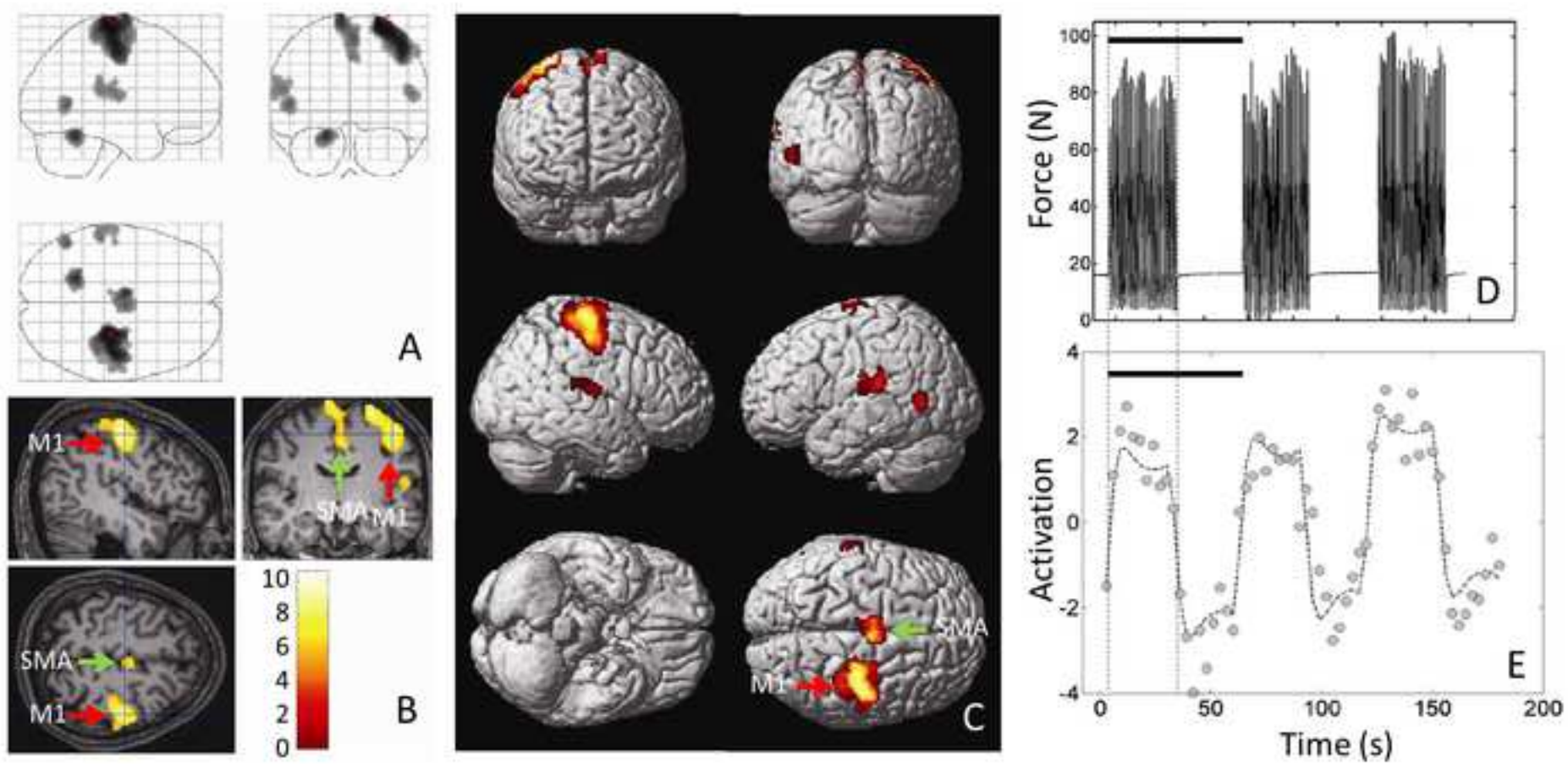
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Name of product	Company	Catalog number
Ball bearings, plastic with glass balls (8)	McMaster-Carr	6455K97
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Dual LS7366R Quadrature Encoder Buffer	SuperDroid Robots	TE-183-002
Feather M0 WiFi w/ATWINC1500	Adafruit	Adafruit 3010
Flanged nuts, fiberglass, 3/8"-16 (8)	McMaster-Carr	98945A041
Garolite rod, 3/4" dia, 4' long	McMaster-Carr	8467K84
Laptop	Various	
Load Cell (20kg)	Robotshop	RB-PHI-119
Load Cell Amplifier- HX711	Mouser	474-SEN-13879
MATLAB	MathWorks	
Magnetic resonance imaging scanner	Siemens	Skyra 3T
MR_CHIRODv3	fabricated in-house	
Op amp development board	Schmartboard	710-0011-01
Panel Mount Power Supply	Delta	PMT-D2V100W1AA
Plastic tubing & tube fittings	McMaster-Carr	various
Pyrex/graphite piston/cylinder module	Airpot	2KS240-3
Screws, 1/4"-20, nylon	McMaster-Carr	various
Shaft Collars for 3/4" dia shaft, nylon (2)	McMaster-Carr	9410T6
Shielded cables (2)	US Digital	CA-C5-SH-C5-25
Threaded rod, fiberglass, 3/8"-16	McMaster-Carr	91315A010
Transmissive optical encoder code strip	US Digital	LIN-2000-3.5-0.5
Transmissive Optical Encoder Module	US Digital	EM2-0-2000-I
PTFE sleeve bearings	McMaster-Carr	2639T32

Comments
Any laptop with USB2.0 port(s) and MATLAB
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Title of Article:

Functional MRI of a rehabilitative motor task using a novel MRI-compatible hand-induced robotic device

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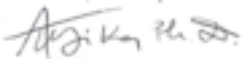
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Article Title:	Functional MRI of a rehabilitative motor task using a novel MRI-compatible hand-induced robotic device	
Signature:		Date: 20 November 2018

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JoVE

Dear Dr. Dsouza,

We are pleased to resubmit the revised version of manuscript JoVE9420, now entitled “Functional MRI in Conjunction with a Novel MRI-Compatible Hand-Induced Robotic Device to Evaluate Rehabilitation of Individuals Recovering from Hand Grip Deficits”

We thank you for your additional instructions, queries and recommendations for alteration. We have revised the content in response to those items, with descriptions of those specific alterations to follow. Figures have been rearranged to better align with the content adjustments. In addition, we have created a supplementary figure, a flow chart through the software’s sequence of dialog windows with screen shots of the typical data traces, to address the issue you raised regarding assistance to the script writer. However, we do not feel that this figure should be included in the manuscript itself, so it is not referred to in the body of the text.

We look forward to addressing any new items that may arise in response to the alterations.

Respectfully yours,

Mark P. Ottensmeyer, PhD.

Line references correspond with the revised document.

Line 2: Evaluate "what" is individuals exactly? Seems like a word is missing. "Evaluate recovery"?

The title has been revised to clarify this

Line 52: Please expand your Introduction to include the following:...

The Introduction has been expanded and revised to include elements addressing the JoVE guidelines for this section

Line 53: The introduction repeats the summary and abstract and the first paragraph sounds like another abstract.

We believe the expanded version of the Introduction now addresses your concern in this respect

Line 57 and other locations: Please re-order your references so that they are listed in the order of call-outs.

The references have been reordered and checked to ensure that they are listed in order of appearance

Line 64: Improvements in what?

The treatment aims in make improvements in grip strength and control. The Introduction now makes this specific.

Line 65 and other locations: Text marked in red font overlaps with previously published work and must be re-written using original language.

The relevant sections have been reworded and/or revised to substantially avoid repetition of previously published phrasing.

Line 69: Employs the device to do what exactly?

The description now explains that the device provides a resistance force against which the subject grips and releases the handle of the device.

Line 153: Have you tested this? It does not add value to state that it can be used in a VR environment unless you have performed some level of testing yourself.

A gaming application for our device has been developed but is not yet of a VR variety. Gaming/VR will be presented in a later publication, and the reference as such has been removed, presented instead by reference to other research.

Line 159: I have edited the protocol structure slightly to meet JoVE's style requirements.

We thank you for making the changes on our behalf.

Line 165: History of stroke or brain lesion?

This has been clarified as an inclusion criterion for non-control subjects.

Line 182: I have unhighlighted these steps due to low filmable content.

We appreciate your insight into the video production process.

Line 224: Check and edit

Thank you for catching the typo on the name of the device.

Line 230: <no text included>

We believe the term “brain lesion” is generic enough to cover a variety of conditions that would result in motor impairment that could benefit from use of our system.

Line 257: Is a script run for this? A screenshot of the software will be useful here to help the scriptwriter out.

A minor modification has been included to specify that the initial force level is set automatically. In addition, supplementary images showing the sequence of user interface dialogs and data displays have been included for the benefit of the script writer. We do not believe that these images would warrant inclusion as a separate figure.

Line 349: Please avoid product names in the manuscript. List this item in the table of materials instead.

The MR scanner vendor and model have been removed, specifying only that a 3T full body MR scanner system was used in our experiments. The scanner has been added to the equipment list.

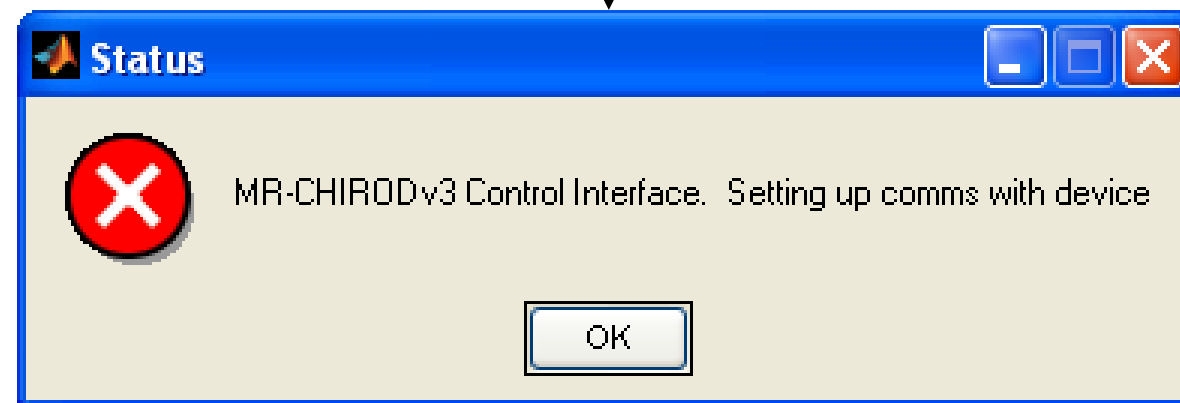
Line 359: Sentence is incomplete, please revise.

We have modified the sentence slightly for clarification, but we believe the sentence was complete, in the form “Not only was X collected, but also Y”. We can revise it further if needed.

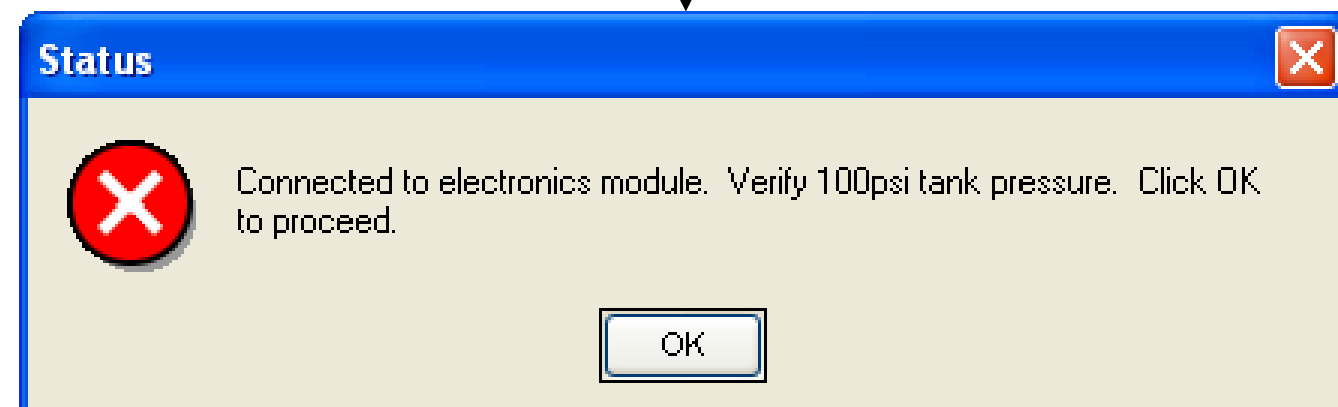
Line 403: Unclear what a glass brain is and why it is in quotes. Reference citations will be helpful.

“Glass brain” is a standard rendering method for presenting regions of excitation in the brain, as if the viewer is looking through a transparent body with opacity related to the excitation. As the specific phrase is of minimal importance, it has been removed in favor of a more generic description.

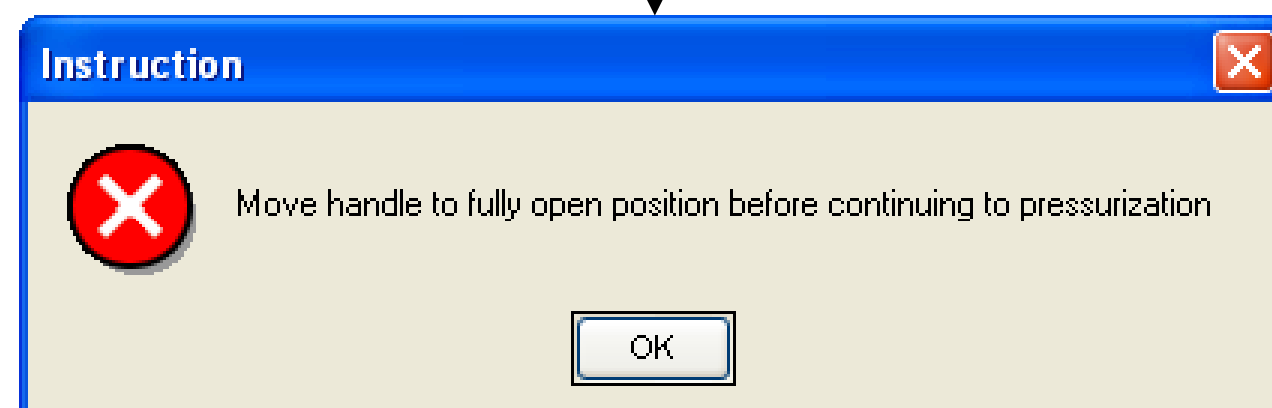
Start operator interface



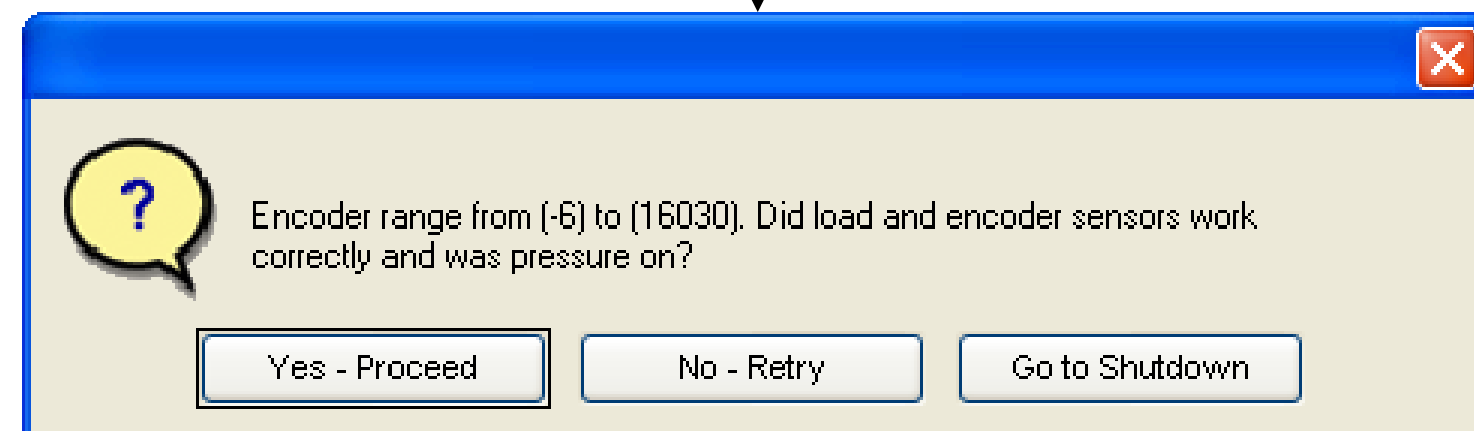
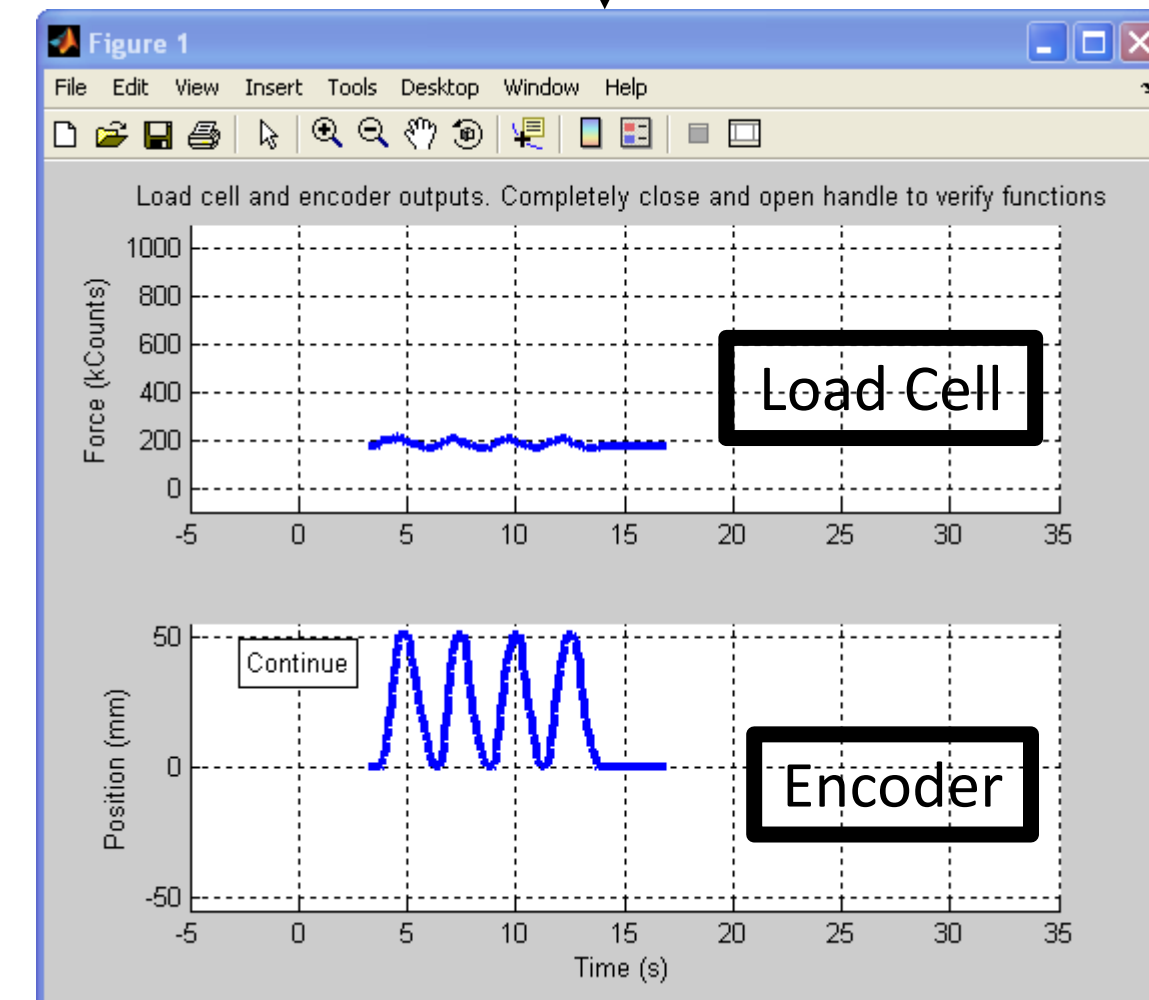
Connection successful?



Check compressor pressure



Minimal pressure applied,
verify sensor function



Sensor function/range verified?

?

Please confirm filename for this run as: data2019-04-30_12-18-40.txt

Yes - Proceed No - Use Alternate Go to Shutdown

Adjust filename if needed

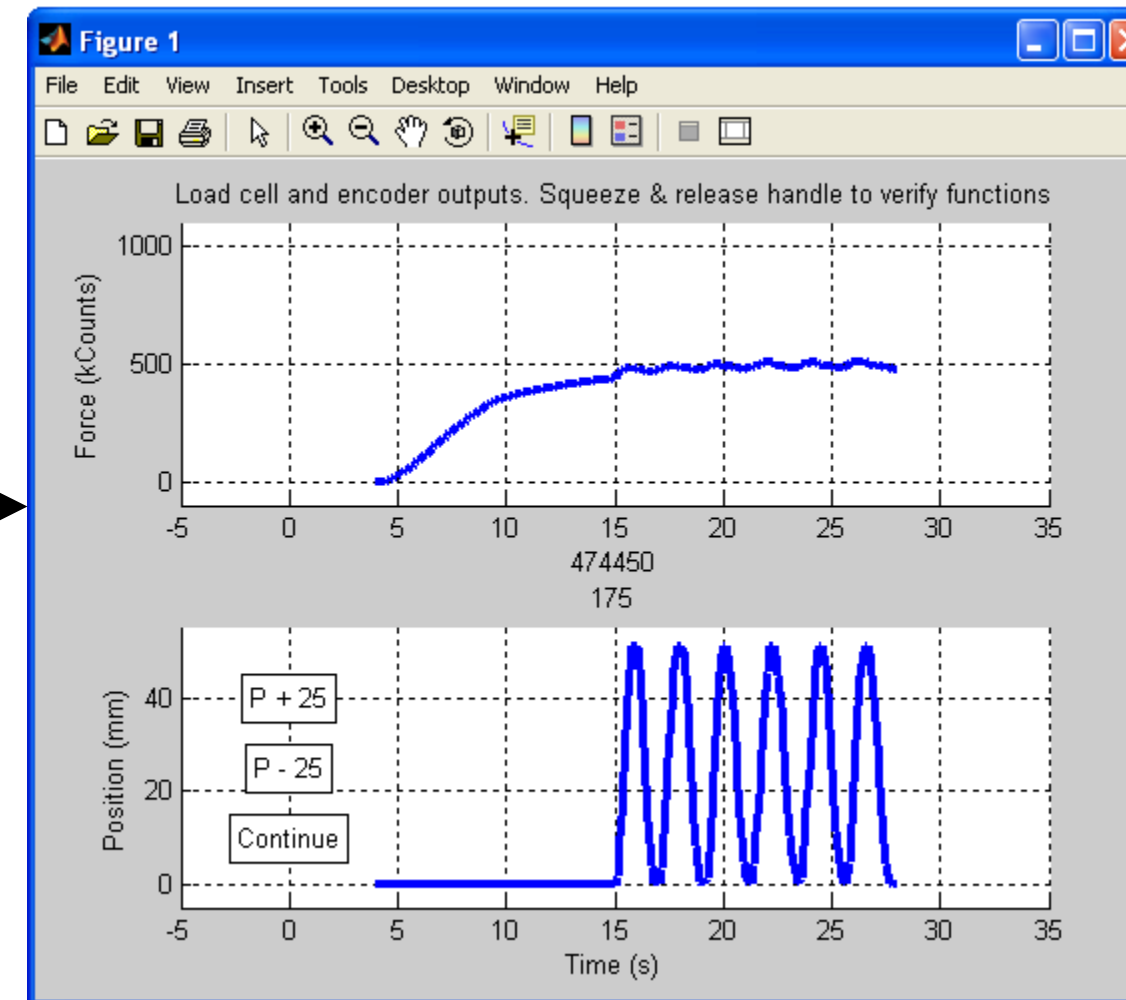
Instruction

✖

Instruct subject that grip force testing will begin now

OK

Automatically increase force to 5%



Subject reached maximum grip strength?

Increase force by
2.5% (25 counts)

?

Is 175 the desired maximum force level?

Yes - Proceed No - Test Again Go to Shutdown

