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Articles

An MRI and MEG Compatible Device for the Study of Somatosensory Information Processing.

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In previous publications we have reported methods for applying multi-site vibratory stimuli to the fingertips. Typically, this involves the use of multiple, individual vibrotactile stimulator and limitations of such an arrangement include difficulty with both positioning the stimuli as well as ensuring that stimuli are delivered in a synchronized and deliberate manner. The device that we reported is a significant improvement on multiple independent stimulators (Holden et al, 2011), and due to both the success of that stimulator and the consequent need to validate a number of findings that have been made with both that device and the precursor of that device (Tannan et al, 2007a), we designed and fabricated a four-site stimulator that could be used in MRI and MEG compatible environments. The device can stimulate four independent skin sites and is primarily designed for stimulating the digit tips. The device is similar to the previously reported device in that it is portable and is ergonomically suited for delivering stimuli to the finger tips, but it has the advantage of being MRI and MEG compatible. However, the fundamental mechanisms of the device are significantly different from the device that we recently reported since the device is piezo-based rather than VCA based. The device was tested in both MEG and MRI environments and demonstrated that no detectable signal (or noise) was introduced by the stimulator in those environments. To demonstrate the reliability of the device for delivering tactile stimulation in a magnetic field, tactile stimuli were presented in an MRI to a single individual. The study produced results that were consistent with prior studies that produced activation of cortical ensembles.

Introduction

For the past several years, our research group has been working towards the development of a portable tactile stimulator that could effectively be used to study changes in sensory information processing in clinical and clinical research venues across a diverse spectrum of neurological disorders. Thus far, we have gone through several iterations in the development of this stimulator and the protocols that can be delivered with that stimulator. The current design of the stimulator – as described most recently in Holden et al, 2012 – is optimized for the delivery of vibrotactile stimuli to the finger-tips. This optimization was done in order to take advantage of the well-known somatotopic relationships with the concept in mind that delivering stimuli to adjacent digit tips would evoke cortical activity in adjacent and/or near adjacent cortical regions, and that the interactions that result from such stimulus evoked activity will be robustly impacted by alterations in cortical information processing.

The first prototype of the system (Tannan et al., 2005a) was used to demonstrate changes in spatial acuity with repetitive stimulation. A subsequent report described that this change did not occur with individuals with autism, strongly suggesting a lower-than-normal inhibitory response (Tommerdahl et al., 2007a). A second iteration of the device (Tannan et al., 2007a) was much more portable as well as more robust and reliable in its ability to deliver well-controlled vibrotactile stimuli to the skin. The device proved extremely useful, and a number of studies were conducted with it that demonstrated the ability to reliably and reproducibly obtain metrics of neuro-adaptation (Tannan et al., 2007b), temporal order judgment (TOJ) and the impact of synchronized conditioning stimuli on TOJ (Tommerdahl et al., 2007b), the absence of the impact of those same conditioning stimuli on TOJ in individuals with autism (Tommerdahl et al., 2008), the relationship between spatial acuity and amplitude discrimination (Zhang et al., 2008), a method for the study of tactile-thermal interactions (Zhang, 2009), a reliable means for measuring amplitude discriminative capacity and a robust near-linear relationship between duration of repetitive conditioning stimuli and the impact of that conditioning on amplitude discriminative capacity (Tannan et al., 2007b), the below-normal adaptation metrics in autism (Tommerdahl et al., 2007), the impact of NMDA receptor block on adaption metrics (Folger et al., 2009), a demonstration of Weber’s law (Francisco et al., 2008; Holden et al., 2012) and a robust relationship with neurophysiological data (Francisco et al., 2008), and differences in timing perception in Parkinson’s Disease (Nelson et al., 2011). A more portable and ergonomic model of the device, which was much more suited for a clinical or clinical research environment was then developed, and is capable of delivering vibrotactile stimuli to four fingers: the index (D2), middle (D3), ring (D4), and little (D5) fingers (CM4; Holden et al, 2012). The utility of that device has been demonstrated in a report of phenotypic differences within a spectrum of patients with chronic pain (Zhang et al., 2011a; Nguyen, et al, 2013), in a report that described stability of cortical plasticity across a wide age spectrum (Zhang et al, 2011b), in a paper that describes its utility for describing phenotypic differences within the autism spectrum via modulating vibrotactile stimuli (i.e., sinusoidal stimuli that dynamically change in amplitude; Francisco et al, 2011) and in a report describing it’s utility for evaluating concussed individuals (Tommerdahl et al, 2016). Most recently, a two-point vibrotactile stimulator was developed (the Brain Gauge) that is much more portable (approximately the size of a computer mouse) and has been used in multiple studies to date (King et al, 2018; Hanley et al, 2019; Favorov et al, 2019; Tommerdahl, A. et al, 2019; Tommerdahl, M. et al, 2019; Pearce et al, 2019; 2020).

Due, in part, to the fact that we have experienced a great deal of success in demonstrating phenotypic differences between and within a number of neurological alterations, we determined that it would be useful to design and fabricate a magnet-compatible stimulator that had the same, or nearly the same, capabilities as the CM4. Such a device would allow for validation studies of a number of ideas that have been proposed by previous behavioral findings and would possibly elucidate the underlying mechanisms that lead to differential responses by different subject populations. In this report, a magnet-compatible version of the CM4 device, the CM-MAG, is described.

Magnet compatible stimulators are typically designed to use pneumatic or piezo-ceramic parts. Each has its own advantages and disadvantages. Pneumatic devices for use in magnetic environments are typically built with plastic and latex tubing, with the controlling electronics kept away from the magnets. These devices typically have a low frequency range with a maximum near 100Hz and require pressurized air to operate properly (Briggs et al, 2004; Golaszewski et al, 2002) was able to avoid using compressed air canisters by using a BP cuff and their use of a DC motor and pneumatic by-pass line gave a wider range (1-150Hz) and larger amplitude (up to 2mm) than most devices. The device designed by Briggs et al had the potential to support multiple probe tips, each with a different frequency, amplitude, and pattern, though the prior calculations were necessary to lower the risk of bursting the latex diaphragm. The one major disadvantage of any pneumatic device is the possibility of inexact and difficult to reproduce measurements (Briggs et al, 2004; Golaskzewski et al, 2002). Piezo-ceramics are the other typical option for use in a magnetic environment. These often have larger frequency ranges (up to 300Hz) than pneumatic devices (Harrington et al, 2000; Francis et al, 2000), with the ability to target a small frequency band such as the 16-34Hz band that Hegner et al (2010) targeted with precise frequency steps of 2Hz. Piezo-ceramics typically require large voltages to create a small amplitude (50V for 169um in Harrington et all, 2000; 100V for 400um in Francis et al, 2000). A work-around to get a large amplitude (though high voltages were still necessary) involves using piezo-ceramic wafers with multiple rods that can be individually controlled (Hegner et al, 2010). The high voltages required to move these amplitudes require that a non-conducting surface interacts with the subjects, such as plastic probe tips or non-conducting piezo-ceramic wafers. A piezo-ceramic stimulator offers more control than a pneumatic stimulator, though they are often more expensive and require large voltages. In this report, we describe our approach to implementing multiple piezoelectric devices in a single MRI/MEG compatible stimulator.

Methods

Hardware

The Cortical Metrics (CM-MAG; see Figure 1) stimulator was developed in our laboratories for use in a number of experiments at multiple sites that were subsequently published (described in Discussion). The principle driving design requirement for the CM-MAG stimulator system is to allow up to four vibrotactile stimulator mechanisms to interact with a test subject's fingertips while their cortex is being imaged in a magnet-based imaging system such as fMRI. The system was designed using state-of-the-art rapid manufacturing technology to allow multiple identical systems to be built and used in different locations. Also, the use of rapid manufacturing permitted very rapid design evolution, thereby facilitating the production of special fixtures and changes to geometry as needed for special applications. The device consists of two separate parts: the controller/power box and one, or in some cases two, detachable stimulator head unit(s) connected together by a 40-conductor shielded twisted-pair ribbon cable, 2 meters in length. The flat plates of all exterior housing and other components of approximately planar geometry are direct manufactured using laser-machined cast acrylic sheet, cut on a 120 Watt CO_2 laser engraving system, model number X660 (Universal Laser Systems, Scottsdale, AZ). The more complex housing and internal mechanism components are direct "3-D" manufactured from ABS plus thermoplastic material, by fusion deposition modeling (FDM) on a StrataSys Dimension1200es (StrataSys, Inc., Eden Prairie, MN). The four large cylindrical components forming the four movable disks of the stimulator head units are CNC machined from 1" thick Acetal (Delrin) plate. All housing and mechanism components and assemblies were solid modeled prior to fabrication using SolidWorks solid modeling software (SolidWorks Corporation, Concord, MA).

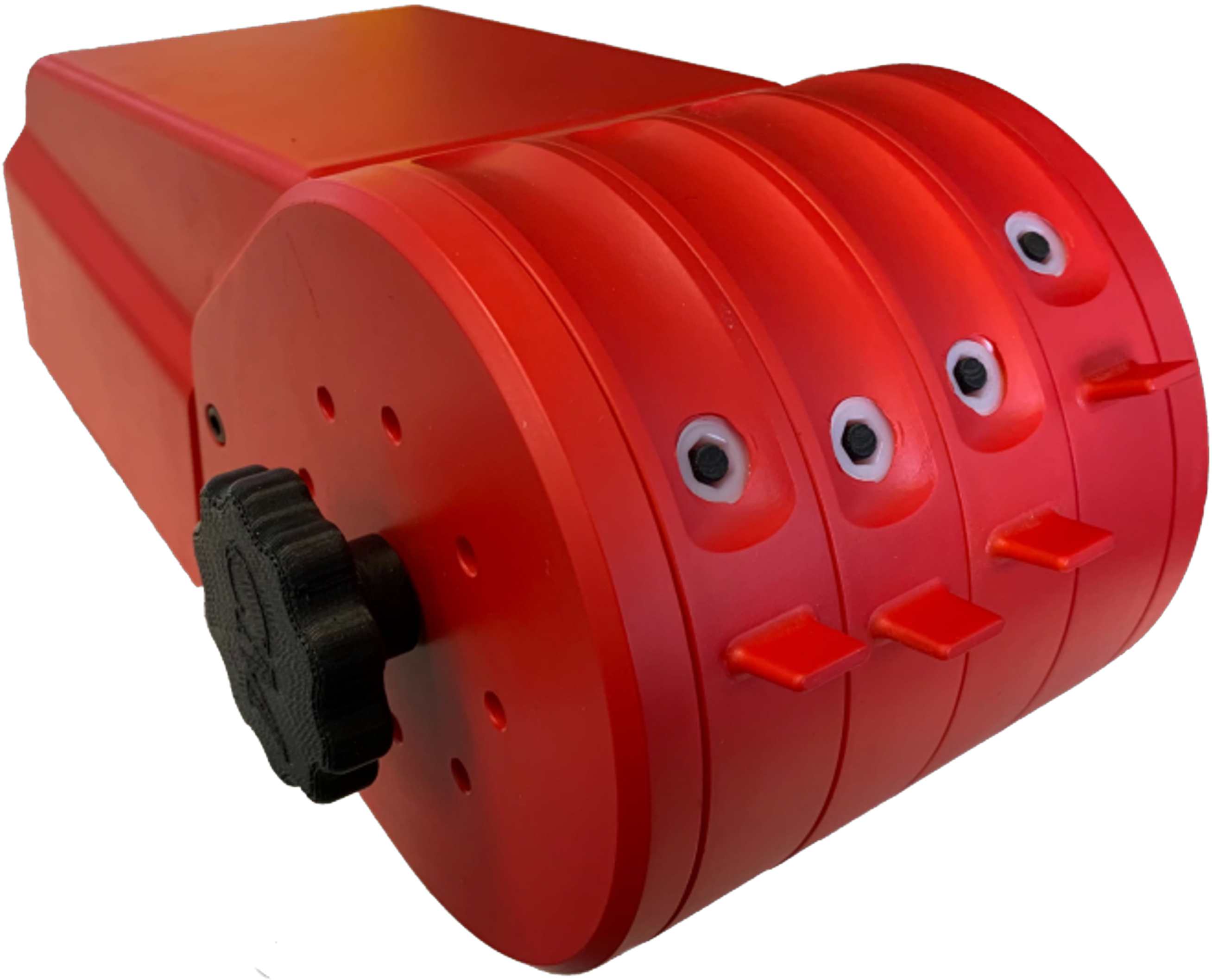

Figure 1. ***Four Site Vibrotactile Stimulator.*** *Each of the four probe tips is positioned by rotating the four independently-positioned drums to maximize contact between finger pads and the stimulator tips. During an experimental session, subjects place their hands on the device and the drums are rotated independently so that the finger-tips are positioned over the probe tips.*

The internal mechanism of the head unit is comprised of identical cylindrical disks placed sideways and four abreast coaxially (130mm in diameter, 24mm in depth) between two acetal side panels. Each disk can be independently rotated to adjust for differing finger lengths for each test subject. A servo mechanism comprising a non-metallic piezo bender actuator and a compliant four-bar link linear motion mechanism are mounted inside each disk. The piezo bender actuators (P/N: Q2C, formerly Q220-A4NM-303YB) are custom manufactured by Piezo Systems, Inc., in Cambridge MA. Each piezo bender is .5mm thick x 12.5mm wide x 32mm in length and requires approximately 200 to 300 volts for actuation. Each piezo bender is attached to a cylindrical plastic probe (5mm diameter) which slightly protrudes through a hole (7mm diameter) in the side of each 130 mm diameter acrylic disk, which serves to mechanically isolate the test subject from the internal piezo driver voltages. The amount of protrusion for each probe is independently adjustable as are the positions of the holes to accommodate the length of the subject’s fingers as he/she wraps their hand around the stimulator head unit. The piezo bender motion is converted into linear displacement by the four-bar compliant mechanism to drive the cylindrical plastic stimulator probe tips linearly into and out of each 130mm diameter disk in the stimulator head unit, according to prescribed sinusoidal waveforms. The moving components of the stimulator tips are directly manufactured from ABS “plus” material by 3-D FDM as a single compliant mechanism component integrating a mounting flange, a thin-beam four-bar linkage, coupling lugs for attaching one piezo bender into each actuator mechanism, and the extension to the mechanical stimulator tip. The compliant four-bar linkage mechanism allows the stimulator tip to be displaced vertically along a straight line for a distance of ± 1 mm. The 4-bar compliant mechanism also provides a very low hysteresis linear restoring force to center each tip vertically when no voltage is applied to the piezo benders. The entire four-bar mechanism is 5.3 mm in thickness, and is positioned such that the stimulator tips move along a radial line extending from the center of each 130mm disk, perpendicular to the outer circumference of each disk. The resulting linearized piezo bender mechanisms generate extremely linear force outputs as a function of drive voltage with very low hysteresis due to the "frictionless" nature of the single piece bearing-less four bar compliant mechanism. The position of the vibrating tips is not sensed for the CM-MAG units, unlike the optical position sensors in the previously reported CM4 systems (Holden et al, 2012). Care was taken throughout the design of the CM-MAG stimulator head to exclude magnetic and/or electrically conductive components that might interfere with or be damaged by the presence of strong external magnetic fields associated with modern magnet-based imaging systems.

The custom electronics were designed using free CAD software from ExpressPCB (www.expresspcb.com). The printed circuit boards were manufactured using the resulting CAD files, also by ExpressPCB. The hybrid circuit is interfaced via four parallel pin connectors (2 banks of 50 pins for digital signals and 2 banks of 34 pins for analog signals) to an internal NI-USB-6259 data acquisition (DAQ) board. The DAQ board then interfaces via a USB connection to any standard PC running Microsoft Windows 7 or later.

Software

A custom line-of-business application was developed for the Microsoft .Net platform using the C# programming language and Windows Presentation Foundation (WPF) framework to control the stimulator and administer the data collection protocols. The interface was designed to be intuitive, extensible, and aesthetically pleasing. The software needed to be extensible to facilitate the development of future protocols for a device as flexible as the CM-MAG. The core extensibility was achieved by using a "plugin" architecture with a shell application whose function is to discover, load and execute small plugins. The shell exposes a software contract (an inheritable C# class) that is consumed and extended by each plugin. Each task described in this paper represents one such plugin. Most traditional neuropsychological protocols using the standard X-alternative forced-choice (X-AFC) tracking method (Cornsweet, 1962) can be created with only a couple of dozen lines of C# code. While most plugins interact directly with the CM-MAG stimulator, this is not a requirement of the plugin contract. Plugins can, for example, be designed to collect arbitrary subject information pertinent to the given study (e.g. participant demographics, relevant medical history, various surveys, etc.). The net effect is not only a significant reduction in the amount of clinical paperwork that needs to be completed by each participant, but also a marked reduction in data-entry time for clinicians. All data collected by the application are stored in an encrypted (128-bit RC4) SQLite database in a user-specified location. Each database can be shared with multiple instances of the shell application, providing a mechanism for seamless networking of CM-MAG stations (Holden, et al, 2012). The software is also capable of storing, as well as creating and customizing, all relevant initialization information for each plugin, such that a given battery of protocols can be administered repeatedly and in a consistent manner, while maintaining flexibility for future projects. The batteries allow for greater reuse of each plugin, resulting in shorter development times a more efficient workflow throughout an experiment.

Results

Description of completed device

The device that was built and described in this report is a magnet compatible 4-point stimulator (see Figure 2). The device is a high voltage, piezoelectric stimulator that delivers tactile stimulation in and around strong magnetic fields. The device delivers up to four simultaneous vibrations 10Hz-500Hz, with a max peak-to-peak amplitude of 1mm at 25Hz. The system's dimensions are designed for easy portability. The head unit and controller system together fit in a Storage Case 18" x 15" x 8", with all necessary cables. Necessary cables include: a 50' HV cable, one USB A to min-AB cable, and a standard 110V power cable. The system can be configured to deliver 4 stimuli to one hand or 2 stimuli to 2 hands (Figure 3).

Figure 2. ***Complete magnet compatible stimulator system with electronic housing.*** *Electronics are connected via a shielded cable that reaches from outside the room housing the imaging system to the MRI or MEG.*

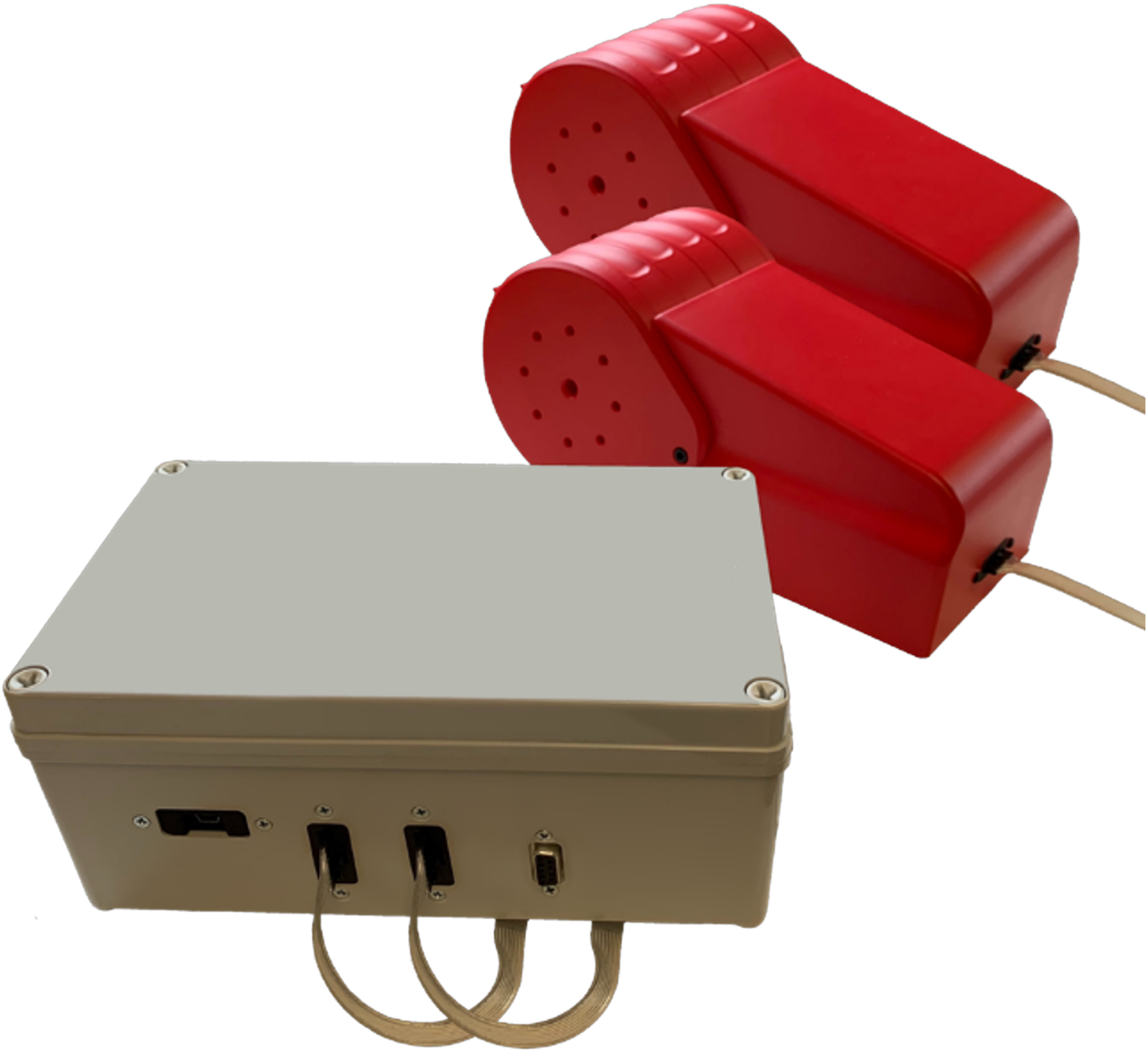

Figure 3. ***The CM-MAG can be modified to deliver stimuli bilaterally.*** *Note that the controller box delivers control signals to two stimulator units, each with the ability to stimulate 2 digits independently.*

The core system controller interfaces to a PC using a USB 2.0 connection. The system can be programmed to deliver customizable sinusoidal stimuli using a standard TSV format. Input and Output triggers with a 10kHz resolution allow the device to synchronize stimuli with imaging systems and other devices.

A high-voltage rated, 50ft cable allows for the controller system to stay near the host PC and a safe distance away from the magnetic field. The cable and head unit contain no steel or other ferric materials, ensuring that the device and signals remain unaffected by magnetic fields exceeding 5T. The same build design also ensures no adverse effects on the imaging system.

High voltage, low amperage piezoelectric actuators deliver stimuli to the skin in a safe manner. Internal protection features are provided to prevent high voltage power transmission when the device is idle.

Noise testing in the MRI and MEG environments

The CM-MAG has been used in several reported studies that were conducted in magnetic environments (described in the Discussion). Noise levels are determined prior to the beginning of the studies with data being acquired in four different setups: 1) no equipment in the scan room; 2) the CM-MAG on the scanner table; 3) the CM-MAG on the table and connected to the driving hardware in the control room, with no power; and 4) everything connected, and running. No significant differences were seen between any of the four setups, with no dominant noise spikes observed for MRI or MEG environments.

Discussion

Over the past decade, we have developed a number of measures to utilize in research that have demonstrated the capacity for CNS deficits across a wide spectrum of neurological disorders. These somatosensory based tasks have demonstrated sensitivity to alterations in neurological function in autism (Tommerdahl et al, 2008; Tannan et al, 2008; Puts et al, 2013; 2014; Francisco et al, 2009; Wodka et al, 2016*34567*), Tourette's (Puts et al, 2015), OCD (Guclu, et al, 2015), ADHD (Puts et al, 2017), Parkinson's (Nelson, et al, 2012; Kursun et al, 2013), chronic pain (Zhang et al, 2011a; Nguyen et al, 2013; Maeda et al, 2014))*15*, concussion (Tommerdahl et al, 2016; King et al, 2018; Favorov et al, 2019; Pearce et al, 2019; 2020)*1819*, aging (Zhang et al, 2011b), alcohol consumption history (Nguyen et al, 2013), early stage diabetes (Favorov et al, 2017) and amputation (Collins et al, 2017). Additionally, these methods were used to demonstrate sensitivity to pharmacological manipulation in healthy individuals (low dose of DXM; Folger et al, 2008), alterations in cortical information processing with TMS (Lee et al, 2013; Rai et al, 2012)*27* and different conditions of adaptation (Tannan et al, 2006; Jones et al, 2016).

The CM-MAG, described in this report, has been used in several behavioral studies such as those referenced above. Tavassoli and colleagues used the CM-MAG to demonstrate information processing differences in children with autism spectrum disorder (Tavassoli et al, 2015). This speaks to the resolution of the CM-MAG, as the study focused on static vs. dynamic thresholds which requires delivery of very low amplitude stimuli. These same behavioral tasks were also conducted by Bryant and colleagues (Bryant et al, 2019; Bryant, 2019). An investigation of bilateral versus unilateral conditioning utilized a bilateral CM-MAG that delivered stimuli to both hands (Ruitenberg et al, 2019) to investigate age-related tactile and motor inhibitory function.

The aforementioned studies were made possible by the utilization of a high precision tactile stimulator, and an important foundational concept of all of these studies is the underlying cortical-cortical interactions that are evoked with tactile stimuli and how percept is altered by these interactions. One way to validate the impact that the tactile stimuli utilized in these tasks have on cortical dynamics and brain function is to measure the neurophysiological response evoked by those tactile stimuli in magnetic environments. Several studies have delivered tactile stimuli in magnetic environments that yielded findings that paralleled the behavioral observations. Maeda and colleagues (Maeda et al, 2014) demonstrated cortical representations with fMRI that were consistent with the results from amplitude discrimination testing of individuals with carpal tunnel syndrome. Kahn and colleagues (Kahn et al, 2015) found results with MEG that were consistent with tactile based connectivity studies of individuals with autism (Tommerdahl et al, 2008). The CM-MAG has been utilized in several MRI and/or MEG based studies that have been reported. Bryant (2019) utilized the CM-MAG to demonstrate differences in adolescents with autism in a 7T MRI. The CM-MAG was used in a 3T MRI environment to demonstrate frequency representations in somatosensory cortex (Perez-Bellido, et al, 2017) and in similar fashion, to investigate multimodal frequency representations (Rahman et al, 2020). In the MEG environment, the CM-MAG was utilized to investigate conscious perception across sensory modalities (Sanchez et al, 2020).

The advantage of a tactile stimulator that can be used in an MRI or MEG environment is that functional imaging allows for a significant increase in the signal-to-noise ratio over. For example, studies that target functional differences between different neurological populations generate observations that are amplified by stimulus properties. Delivering high fidelity stimuli allows investigators to maximize differences between populations particularly if there are functional mechanistic differences that the stimuli can target. Non-human animal MEG or MRI studies can dosimetrically study the impact of a wide range of neurological insults in an fMRI or MEG environment and calibrate the responses evoked in human subjects under identical stimulus conditions to determine the degree of neurological impact. Future studies will report findings neurologically compromised individuals and how those findings correlate to ongoing non-human animal imaging studies.

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