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An fMRI-compatible system for targeted electrical stimulation

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ABSTRACT

Background: Neuromodulation is a rapidly expanding therapeutic option considered within neuropsychiatry, pain and rehabilitation therapy. Combining electrostimulation with feedback from fMRI can provide information about the mechanisms underlying the therapeutic effects, but so far, such studies have been hampered by the lack of technology to conduct safe and accurate experiments. Here we present a system for fMRI compatible electrical stimulation, and the first proof-of-concept neuroimaging data with deep brain stimulation (DBS) in pigs obtained with the device.

New method: The system consists of two modules, placed in the control and scanner room, connected by optical fiber. The system also connects to the MRI scanner to timely initiate the stimulation sequence at start of scan. We evaluated the system in four pigs with DBS in the subthalamic nucleus (STN) while we acquired BOLD responses in the STN and neocortex.

Results: We found that the system delivered robust electrical stimuli to the implanted electrode in sync with the preprogrammed fMRI sequence. All pigs displayed a DBS-STN induced neocortical BOLD response, but none in the STN.

Comparisons with existing method: The system solves three major problems related to electric stimuli and fMRI examinations, namely preventing distortion of the fMRI signal, enabling communication that synchronize the experimental conditions, and surmounting the safety hazards caused by interference with the MRI scanner.

Conclusions: The fMRI compatible electrical stimulator circumvents previous problems related to electroceuticals and fMRI. The system allows flexible modifications for fMRI designs and stimulation parameters, and can be customized to electroceutical applications beyond DBS.

1. Introduction

Electroceutical therapy is a rapidly expanding therapeutic option used across diverse medical specialties to treat patients with disorders not controlled by medicine. Single interventions with cardiac defibrillators and electroconvulsive therapy are renowned tools, while long-term stimulations are best known in forms of cardiac pacemakers, bionic implants and replacements as well as numerous types of

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neurostimulators. Such devices for electrical modulation of brain function when no other effective treatments are available for brain disorders is a new frontier of medicine also known as *neuromodulation* or *neural electrochemical therapy*.

Although the therapeutic effect of electrochemical therapy is well-established for a broad range of neuropsychiatric conditions (Holzheimer and Mayberg, 2011) and chronic pain (Moisset et al., 2020), and also in, e.g., cardiac disorders, the underlying physiological mechanisms behind these treatments remain unclear. Since bioelectronic medicine target individual nerve fibers or specific brain circuits to treat a condition, a perspicuous step towards development of electrochemical therapy is to map neural circuits associated with disease, and then identify the candidate anatomical sites of intervention and transmission patterns associated with health so that these can be replicated (Famm et al., 2013). Such fingerprints can provide clinicians with a very important tool to fast track and personalize bioelectronic medicine with the potential to set optimal stimulation parameters at once, thereby saving the patients for numerous visits in the outpatient clinic for tedious adjustments and risk of proceeding therapy on suboptimal settings.

One way to achieve such insights is by combining electrical stimuli with feedback from functional magnetic resonance imaging (fMRI) to measure neural activity in terms of induced changes in cerebral blood flow and metabolism. Although such experiments are likely to make an important contribution to the understanding of how electroceuticals work in the brain, progress has been hampered by the lack of technology to accurately conduct such experiments. Delivering an electrical stimulus to a subject during fMRI is problematic for a number of reasons. Firstly, *distortion* of the fMRI signal is imposed by emission of radiofrequency (rf) radiation from the electronic device. Secondly, proper *communication* that synchronizes the electrical stimulus with the fMRI design and initiation of the scanner sequence is needed, and thirdly, there are potential *safety hazards* can occur from interference of the powerful magnetic field with the electronic device and electrode.

The RF emission transmitted from external sources coupling into connecting cables increases noise and artifact of the obtained fMRI data signal, causing a characteristic pattern of straight lines (Georgi et al., 2004). The image quality can also be disrupted by susceptibility artifacts proximate to natural interfaces or implanted hardware, which is of particular importance if the signal loss coincides with the area of expected activation.

Electrochemical therapy is generally applied in a continuous form of frequency, pulse width and voltage/amplitude, ramping at start of stimulation, and can be switched ON and OFF using a manual control unit. Accordingly, fMRI experiments have often been conducted in a block design with a ON vs OFF mode. The switching between ON and OFF states of electric stimulation in a block design requires an automated control to avoid time-delay which otherwise will disrupt the data.

There is ample level of evidence to support the safety of inactive or disconnected neurostimulators during diagnostic MRI examinations at lower strength fields (Georgi et al., 2004). The hardware does not affect structural MR-imaging, except from susceptibility artifacts close to the electrode, and it works properly when switched back on after imaging (Georgi et al., 2004). However, safety concerns emerge, when the electrode is connected to an active electric stimulator switched on and off during an fMRI examination. The RF emission and fast switching gradients, such as used in fMRI sequences, can induce a voltage, which may increase the temperature in the electrode, evoke an unintended neurotransmission if the amplitude is high enough, or increase the intensity of the delivered stimulus (Georgi et al., 2004). Moreover, if there are loose connections or defective leads, all energy will be deposited at site of the increased resistance, causing hazardous heating or even sparking (Georgi et al., 2004).

This study describes a system that allows for delivering an adjustable electrical impulse to a subject while placed in an MR scanner, without disrupting or altering the delivered electrical signal or interfering with the obtained MRI signal.

2. Materials and methods

2.1. Description of the developed system architecture

The patented system (EPS 17195244.3 – 1666, October 2017) consists of two modules (Fig. 1), the Main unit and the MRI unit (Fig. 1), connected by optical fiber via wave guides into the MRI scanner room. The Lead Unit is placed outside the scanner room and coupled to a computer, which enables the programming of stimulus settings and fMRI design by use of E-prime® (Psychology Software Tools, Sharpsburg, Pennsylvania, USA). Also, it is connected to the MRI scanners trigger unit which serves to timely initiate the stimulation sequence at the start of the scan. The Lead unit consists of the following: Signal generator to produce the voltage-driven electric stimulation signal; oscilloscope monitors to record the electric stimulation signal transmitted back from MRI unit for quality assurance (QA) and; and two optical modules for transmitting the electric stimulation signal and QA signals to and from the MRI unit. The MRI unit has two corresponding optical modules and optical signal converters. The electronics in the MRI scanner room are shielded by use of caging and cable traps.

The system works as follows: When the MRI scanning is initiated, the Control unit receives an input trigger signal from the MRI scanner which initiate the pre-programmed stimulation sequence (fMRI design) and settings (volt, pulse width and frequency). The Lead unit converts the electric stimulus to an optical signal that is transmitted through wave guides to the MRI unit inside the scanner room. Here, the optical signal is converted back to an electric stimulus, which is then looped back to the Lead unit for QA before transmission of the electric stimulus to the implanted electrode in the pig brain during scan.

2.2. System adverse test (dry runs)

2.2.1. Image quality

To ensure that our device does not generate RF noise, which could cause image artifacts, we employed the RF Noise Spectrum sequence, which can be utilized to locate the source of an external RF interference. The RF Noise Spectrum sequence is comparable to that of the TIM TRIO sequence for RF noise and spike check developed by The Martinos Center for Biological Imaging and involving Massachusetts General Hospital, Harvard and Siemens, as detailed in [http://cbs.unix.fas.harvard.edu/science/core-facilities/neuroimaging/facilities/noise_spike](http://cbs.unix.fas.harvard.edu/science/core-facilities/neuroimaging/facilities/noise_spike).

The RF Noise spectrum sequence does not use any RF transmitter or gradient pulses, but performs simply by opening the MRI receiver during scan. The sequence runs for 30 s and makes 50 measurements in 10 kHz frequency ranges around the central frequency of the scanner [0 ± 500 kHz], creating a noise summary image of the mean signal intensity of all the frequency bands. The results are showed as a graphical display in the patient browser, or it can be viewed in real time via the inline display. RF noise is detected as sizeable spikes of the particular frequency band in sight.

We conducted noise scans with our stimulator connected to DBS electrodes placed in a phantom, in the following conditions: (A) Stimulation ON, (B) Stimulation OFF, (C) Stimulator not present in the scanner room, (D) Noise (doors open), and (E) Alternating stimulation ON (15 s) vs OFF (15 s).

To eliminate other potential sources for external RF emission, we also ran the test without the coil placed on the electrodes, and with lights turned both on and off during scan.

All conditions were compared to control by visual inspection for spikes and dissimilarities in the RF noise on the graphical display, but also in the active measurement output given as the maximum single measurements as well as the average mean of all 30 measurements.

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1. RF (radiofrequency), STN (subthalamic nucleus).
were inspected by a veterinarian and allowed to acclimatize for 1 week. The pigs were housed in groups in adjacent pens. Experimental Medicine at the University of Copenhagen, the animals (Landrace, Yorkshire and Duroc, acquired from an agricultural herd) guidelines (www.nc3rs.org.uk/arrive-guidelines).

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logging of the electric signal delivered to the electrode to ensure time-

– 2.2.2. Time accuracy, signal stability and functionality of the device

For quality assurance, we designed the device with a back-loop and logging of the electric signal delivered to the electrode to ensure time-

– accuracy and constancy of stimulation parameters following the signal

conversions in the MRI environment. The back-looped signal was displayed on two systems. First, a two-channel digital oscilloscope was used to (i) monitor the amplitude, frequency and pulse width of the back-

looped electric stimulus and (ii) the MRI trigger signal for the TR pulse. Moreover, we also monitored the back-looped signal using a color-coded screen of green (stimulation ON) and black (stimulation OFF) and used a time-clock to test that the duration of the blocks (ON and OFF) was in accordance with the preprogrammed fMRI paradigm. Finally, we monitored the functioning of the device for unintentional stops during scan, such as reported in previously DBS-fMRI studies (Georgi et al., 2004) using cables led via waveguides.

2.3. Animals, housing and anesthesia

All animal experiments were performed in accordance with the European Communities Council Resolves of 22 September 2010 (2010/63/EU) and approved by the Danish Veterinary and Food Administration’s Council for Animal Experimentation (Journal No.1012–15–2934–00156), and is in compliance with the ARRIVE guidelines (www.nc3rs.org.uk/arrive-guidelines).

In this study, we used four female 9–10-week old pigs (crossbred Landrace, Yorkshire and Duroc, acquired from an agricultural herd) weighing 21 ± 1.5 kg (mean ± SD). After arrival to the Department of Experimental Medicine at the University of Copenhagen, the animals were inspected by a veterinarian and allowed to acclimatize for 1 week. The pigs were housed in groups in adjacent pens (3.8

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– 2.5. Animals, housing and anesthesia

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On the experimental day, fasting animals were premedicated by intramuscular (i.m.) injection of 0.14 mL/kg Zoletil® 50 Vet (Virbac, Kolding, Denmark) mixture with 6.25 Pt. xylazine (20 mg/mL) + 1.25 Pt. ketamine (100 mg/mL) + 2 Pt. butorphanol (10 mg/mL) + 2 Pt. methadone (10 mg/mL), weighed and intubated. Anesthesia was induced with 0.5–1 mL intravenous bolus injections of 10 mg/mL propofol (Fresenius Kabi AS, Halden, Norway), while maintaining spontaneous breathing during installation of catheters. Each animal had installed a bladder catheter, a peripheral venous catheter in both ears, one percutaneous femoral artery catheter (Arrow International Inc, Reading, PA, USA) and a small incision catheter in both mamillary veins. All incisions were preceded by local anesthesia given as a subcutaneous injection of 10 mL mixture; 1 Pt. 10 mg/mL xylocaine (AstraZeneca A/S, Copenhagen, Denmark) + 1 Pt. 5 mg/mL Bupivacaine (Amgros I/S, Copenhagen, Denmark).

After a short trolley walk to the scanner facilities, the animals were connected to a ventilator with 34 % O₃ and anesthesia was maintained with 1.5–2.5 % isoflurane (Scanvet Animal Health A/S, Fredensborg, Denmark) on all fMRI experimental days. On other non-fMRI experimental days, standard anesthetic was infusion with propofol 15 mg/kg/h. The animal was set up with a slow dripping infusion with isotope saline and monitored throughout by visual inspection, blink reflexes, blood pressure, heart rate, respiratory frequency, capnography, oxygen saturation and temperature.

2.4. Surgical planning and surgery

An MR compatible stereotaxic system for pigs (NeuroLogic, Aarhus, Denmark) was used for targeting and implantation of the DBS electrodes and microdialysis probes. The system is comprised of a stereotaxic localization box with 1) two MRI compatible detachable side plates containing a copper sulfate fiducial marking system that defines a Leksell stereotaxic space, and 2) one detachable arch-based frame for isocentric stereotaxy with a lead implantation device (LID) attached to the arch (Bjorkam et al., 2009, 2004).

With the pig placed in prone position and the head fixed in the stereotaxic localization box attached with the fiducial side plates and an adapted radiofrequency coil, structural T1/T2 MR images (Siemens 3 Tesla mMR hybrid PET-MR scanner) were obtained in each animal to visualize the fiducial markings and the subcortical target (Bjorkam et al., 2017a), followed by manual calculation, using Brain Lab® (BrainLAB AG, Germany), of the stereotaxic coordinates for targets sites and trajectories to the STN.

Next, the fiducial side plates were replaced with the arch-based frame followed by exposure of the sagittal and coronal sutures by a midline incision. Bilateral burr holes to the dura were made to target the medial prefrontal cortex (mPFC) according to a previously validated paradigm (Jørgensen et al., 2017) and to the MRI guided stereotaxic
entry point coordinates to the STN. Next, the guide tube with a blunt cannula was inserted to a location 5 mm above the target coordinate of the STN, where the blunt cannula was removed. The quadripolar (contacts labeled 0, 1, 2, and 3) DBS electrode with internal stylet (Model 3389, Medtronic Inc., Minneapolis, MN, USA) was inserted through the guide tube and gently advanced to the target and stabilized with a two-component surgical adhesive (BioGlue, CRYOLIFE International Inc., Kennesaw, GA, USA) before retracting the stylet and guide tube (Bjar- kam et al., 2008; Ettrup et al., 2011; Orlowski et al., 2017). The electrode was fixed with BioGlue to the skull and a frontally placed anchor screw, and the procedure was repeated on the contralateral side. Finally, the incision was sutured and the stereotaxic frame detached from the animal, leaving the electrodes externalized.

The animal was returned to the scanner and placed in the prone position, and the DBS electrodes were connected to the fMRI compatible animal, leaving the electrodes externalized.

Before continuing the experiments, preliminary confirmation of the correct position of the electrodes was confirmed by a postsurgical structural T1/T2 MRI scan.

2.5. Structural magnetic resonance images

The MR images were generated from a 3 T mMR Biograph (Siemens AG, München, Germany) whole-body scanner with a radiofrequency coil (four channels, receive-only, phased array coil) adapted to the pig head. Pre-and postoperative structural T1 and T2 weighted MRI scans were obtained for targeting and implantation of the DBS electrode and alignment of the fMRI scans during data processing and analysis. The postoperative MRI served as preliminary confirmation of the electrode placement in the cerebral target before proceeding with the experimental scans.

The protocol of the T1-weighted 3D magnetic MP-RAGE MRI was: frequency direction (FD), A >> P; slice number, 224, field of view (FOV), 250 mm; slice thickness (ST), 1 mm; repetition time (TR), 1900 ms; echo time (TE), 2.44 ms; inversion time (TI), 900 ms; flip angle, 9°; base resolution, 256; acquisition time (AT), 5.04 min.

The protocol of the T2-weighted 3D magnetic fast spin echo (FSE) MRI was: FD, A >> P; slice number, 240, FOV, 250 mm; ST, 1.00 mm; TR, 3200 ms; TE, 409 ms; base resolution, 256; AT, 6:26 min.

2.6. Stimulation parameters, fMRI design and BOLD protocol

The frequency, pulse width and voltage were set at 125 Hz, 500 or 200 µs, and 3 V (voltage) in a rectangular shape divided between two electrode levels (0–1) of the quadripolar Medtronic 3389 electrode (Medtronic Inc).

The fMRI paradigm was a classic block design, with stimulation turned on and off in a total of 5 cycles. After two volumes of discarded acquisitions to allow for scanner equilibrium, we acquired 375 volumes of alternating stimulus and rest: 60 DBS-OFF + 5 times (3DBS-ON + 60DBS-OFF).

The parameters of the gradient-echo, echo-planar imaging sequence sensitive to the blood-oxygen-level-dependent (BOLD) response were: FD, A >> P; slice number, 42, FOV, 192 mm; ST, 3.00 mm; TR, 2150 ms; TE, 26 ms; flip angle, 78°; base resolution, 64; spatial resolution 3 × 3 × 3 mm, AT, 12:07 min.

2.7. Euthanasia and post-mortem handling

After the final scan, the pigs were euthanized immediately with an overdose of sodium pentobarbital (ScanVet Animal Health A/S, Frederensborg, Denmark) and moved for a post-mortem CT-scan (Dual Source Somatom Definition, Siemens, Munich, Germany) of the brain before removal of the brain and electrodes (Bjar-kam et al., 2017b). The CT scan was used as final validation of the correct position of the electrodes in target by co-registration to both the structural MRI and a modified pig brain atlas (Villadsen et al., 2018).

2.8. Data processing and analysis

After image acquisition, the time series data were processed to obtain maps of brain activation using the JIP analysis toolkit (http://www.nmr.mgh.harvard.edu/~jbm/jip/) customized with the modified pig brain atlas (Villadsen et al., 2018) to analyze pig fMRI data.

First, the images were pre-processed by a) Converting DICOM format to NIfTI files, b) Alignment of the structural scan to the modified pig atlas (Villadsen et al., 2018), c) Motion correction (only functional scans) and correction to the hemodynamic input function d) Alignment of the functional scans to the aligned postoperative anatomical scan, and e) Register and spatial smoothing (3 mm) of all fMRI data.

Next, we determined if there was a significant activation associated with DBS-ON compared to DBS-OFF in neocortex and in STN. Within-subject fMRI data analyses were performed using Generalized Linear Modeling (GLM) with terms to describe baseline drift plus a repetitive finite-impulse response triggered by stimulus timing. The average BOLD response magnitudes and errors for all subjects were used in a second-level analysis following the summary-statistics approach (Worsley et al., 2002). We employed a significance threshold of p < 0.001 (uncorrected) in BOLD response across all individuals, which corresponds to a statistical threshold of p < 0.05 with a Bonferroni correction appropriate for about 50 regions. The regional or focal BOLD response was displayed in a time-dependent fashion and averaged in relation to the event across all cycles for each pig.

3. Results

3.1. Functionality of the device

The RF Noise Spectrum scans (Fig. 2) show that the functioning device did not produce external RF emission and spikes which interfere with the image quality. Also, we did not observe any surge lines in the images.

To illustrate what noise looks like, we added a graphical display of a RF noise spectrum scan with doors left open during scan to compare with the stimulator turned on and off, or removed from the scanner room (Fig. 2). Moreover, we did not see any changes with lights turned on and off, or with removal of coils (not shown in figure).

Likewise, we showed with continuous oscillatory monitoring of the back-looped signal that the stimulation parameter (voltage, pulse-width and frequency) was constant throughout the scan. The accumulated propagation delay of all electrical stimuli during the 12-minute fMRI paradigm was 400 µs. Moreover, we did not experience unintentional stops of the device during any of the scans and observed an excellent time accuracy of the delivered stimulation compared to the pre-programmed paradigm.

3.2. fMRI Bold signal

With the electrode placed in target STN (Fig. 3) and the electrical signal back-looped for quality assurance, we found that the fMRI compatible stimulator delivered a robust electrical stimulus to the implanted electrode during the entire experimental period of 750 s. The electrical stimulus showed an excellent signal and time-stability in sync with the preprogrammed fMRI block design, which was initiated by a trigger impulse upon start of MRI volume acquisition.

When DBS-STN was turned on, we observed a neocortical BOLD response (Fig. 4), which was reproducible across stimulation cycles and between individuals. However, no BOLD response was observed in the target site for implantation and stimulation, i.e., STN. (Fig. 4).
4. Discussion

We here present a patented system, a fMRI compatible electrical stimulator, as well as the first proof-of-concept neuroimaging data in pigs obtained with a prototype of the device. The system enables generation of a predefined electrical signal to be delivered to an individual while undergoing fMRI examination. Importantly, the system can synchronize the stimulation and an automated fMRI design which is triggered upon start of the first fMRI volume acquisition. The system solves three major problems related to electrical stimuli and fMRI examinations, namely preventing distortion of the fMRI signal, communication that synchronize the experimental properties, and surmounting the safety hazards.

4.1. Distortion

Two factors may disturb image quality, namely external RF emission and transitions in susceptibility. Like others who evaluate the effects between states of DBS during fMRI (Arantes et al., 2006; Georgi et al., 2004; Phillips et al., 2006; Rezai et al., 1999; Stefurak et al., 2003), we have placed the oscillating unit outside the scanner room in order to avoid problems with image quality caused by direct RF emission from the electronic device. However, this maneuver does not eliminate RF emission from external sources coupling into the connecting cables between the pulse generator and the electrodes, led through waveguides. Such external high-frequency electromagnetic power cause straight line surges across the electrode (Georgi et al., 2004), and this effect cannot dependably be omitted by shielding of the cables, which add unpredictability to the examination. Our system circumvents interference from external RF sources by converting the electric stimulus to an optic signal outside the scanner room and back to an electric stimulus inside the scanner room, easily and reliably led through waveguides.

Due to the small signal to noise ratio in GE-EPI and DTI sequences, susceptibility artifacts proximate to the electrode and lead are more...
**Fig. 3.** Electrode placement in STN. The top panel shows the placement of the tip of the electrode (yellow) relative to the DBS target in STN (blue-green). The bottom panel displays an overlay of additional cerebral regions. The figure is an overlay of the postoperative MRI scan of the pig brain co-registered to both the modified pig-atlas (regional overlays) and a postoperative CT scan (electrode). All the images show signal loss caused by susceptibility artifacts proximate to the electrode. The cross shows the coordinate in right STN for the three views.

**Fig. 4.** BOLD signal in neocortex and STN following DBS-STN. The DBS-STN induced fMRI response in four pigs (rows) are displayed for two cerebral regions, neocortex (left column) and STN (right column). The average BOLD signal changes across five cycles of DBS-STN with stimulation settings 130 Hz, 3 V and either 210 µs (n = 2) and 500 µs (n = 2). Time 0 indicates start of the stimulation period. The data (black) is given as the average percentual BOLD signal change ± SD for each pig, as well as the fitted data to the model (red).
prominent with fMRI than with structural imaging (Boutet et al., 2019). Except in the immediate vicinity of the electrode and lead (Georgi et al., 2004), the sequences are, however, still useful for data analysis. Still, this may limit the use of fMRI, particular if the susceptibility artifact occurs in the exact area of expected activation. Correspondingly, we observed a DBS-STN induced change in BOLD response in neocortex, but not in the cerebral target site for the implanted electrode and stimulus---so possible effects of DBS at stimulation site remain unknown. However, no stimulator system used in fMRI examinations, including ours, can overcome the difficulties with metallic susceptibility artifacts proximate to electrodes and leads, but future advances in carbon electrodes might (Zhao et al., 2020).

4.2. Communication

It is essential to ensure that the electric stimulus is properly synchronized with the block-designed fMRI examination, including the initiation of the scanner sequence. Moreover, this communication must not be disrupted by the RF emission from the MRI scanner. To respond to these requirements, our fiber optic system, back-looped for quality assurance, prevents a) human and systemic timing errors, b) unpre-

meditated changes in stimulation parameters imposed on the electric stimulator by RF pulses from the MRI scanner, and c) inconsistencies in the functioning of the oscillating unit placed outside the scanner room during the experiments. The system can run numerous pre-programmed stimulation parameters and fMRI designs, which facilitate fast and simple shifts between fMRI experiments.

First, manual switch of an impulse generating (IPG) unit between the two states, ON and OFF, is too imprecise to conform to the fMRI block-design paradigms and the MR volume acquisition because the person operating an IPG unit can induce a delay. A delay can also occur between pressing the control button and until the IPG unit switches. One study demonstrates (Fiveland et al., 2018), that even when the IPG unit is preprogrammed to the requested change in stimulation parameters, a time delay of six seconds accumulate during an fMRI experiment. Such time-delay is enough to wobble the block-design and subsequent data analysis, particular in block-designs with short stimulation periods which typically is used with BOLD paradigms to avoid attenuation during the fMRI sequence.

A limitation with previous approaches, including ours, designed to assess changes in fMRI signal between the two states, DBS ON and OFF, is the necessity for externalized electrodes. However, one study has developed a so-called custom electronics box (Fiveland et al., 2018), which has the ability to decode a preprogrammed stimulation pattern outside the scanner room, and once the individual is placed in the MRI scanner, the fMRI sequence is initiated by a trigger output signal with an absolute error of 100 ms. The system allows for fMRI experiments with internalized IPG units, but the IPG unit needs to be preprogrammed and running before placing the individual in the scanner, thereby rendering the fMRI experiment susceptible to attenuation of the data signal, and it does not allow investigations of de novo stimulation or sequential fMRI sequences.

Moreover, even when placed outside the scanner room, RF pulses from the MRI scanner can interfere with an electric stimulator, regard-

less of shielding the cables between the electrode and oscillating unit. It has been shown that RF pulses can induce high voltage, which can lead to improper stimulation amplitudes or even cause the pulse generator to unintentionally switch off during examination (Georgi et al., 2004). Although the stimulation unit may easily be switched back on, such flaws require constant monitoring of the apparatus and make the data acquisition prone to human errors. The Mayo Clinic (Rochester, USA) has developed a Bluetooth based communication system, WINCS (Bledsoe et al., 2009), wherein wireless communication modules are used to communicate between inside and outside the MRI room. The WINCS system avoids direct interference from RF pulses on the electric stimulator, as there are no connecting cables led through the waveguides. One concern with the Bluetooth based system may be that the electromagnetic interference on wireless data transfer produced inside the MRI scanner imposes alterations in the delivered electrical signal. This is of particular concern to regulatory requirements in a clinical setting, when a Bluetooth based medical device is used to deliver an electroceutical therapy to an individual undergoing fMRI examination, as compared to a less critical Bluetooth function which monitors, e.g., ECG and pulse.

4.3. Safety hazards

The possible safety issues that exist for electroceutical systems used in fMRI examinations include interaction of the magnetic field and functional disruption of the device (Rezai et al., 1999). As previously mentioned, RF pulses from the MRI scanner can lead to improper stimulation or unintentional stops of the oscillating unit, even when placed outside the scanner room and shielding of connecting cables. This risk is eliminated with our stimulation system using optic fibers. Moreover, three potential mechanisms (Dempsey et al., 2001) caused by magnetic field interaction can induce voltage, current flow and heating in the lead and its electric circuit: 1) Electromagnetic induction heating, 2) Electromagnetic induction heating of a circuit in resonance, and 3) The antenna effect.

First, electromagnetic induction from switching gradients and RF pulses can cause: a) eddy currents to flow at the surface of any conductive material in the scanner room, b) voltage coupling into the lead with potential to increase the stimulation amplitude up to 30 % with risk of even trigger unintended neurostimulation if the amplitude is high enough, or c) resistance heating when induced currents dissipate as heat occurring in locations with high resistance, such as the electrode-tissue interface. In case of disconnections or defective electrodes and leads, a sudden increase in resistance can result in excessive heating or even sparks (Georgi et al., 2004). These effects can be minimized both by use of cable traps (Seeber et al., 2004) and by including a feed-back to the system when output saturation or high resistance is reached. The latter is measured by an impedance-meter. Although our system does not prevent RF emission from the MRI scanner to couple into the cable leading from the electrode to the MRI unit placed outside the 200-gauss line, the systems’ cables are shorter and does not extend outside the scanner room, which would add risk of picking up external RF emission.

Second, resonance heating occurs in the unlikely event when a conducting loop arranged perpendicular to the RF field magnetic field resonates at a frequency equal to that of the RF field, which increases the ability of the loop to concentrate current leading to excessive heating (Bennett et al., 2012; Moisset et al., 2020). Heating from large diameter loops can be avoided by placing the lead straight in the z-direction, in the center of the magnetic core and preventing direct contact between the cables and the individual undergoing fMRI examination.

Thirdly, the antenna effect occurs when the electric component of the RF emission, rather than the magnetic component, couples into a lead equal to half the length of the RF fields wavelength or multiples hereof, thereby producing a resonant standing wave with a maximum antinodal current and heating at the open end of the lead (Georgi et al., 2004). This effect can be eliminated by avoiding resonant lengths of cables.

4.4. Potential use of the system

fMRI is perfectly suited to investigate changes between states in electroceutical therapies, because the stimulation is steady, well-regulated, and with reproducible clinical effects, ideally suitable for fMRI block designs (Rezai et al., 1999).

fMRI can map changes in brain activity reflecting the underlying changes in regional brain metabolism. The combination of fMRI and electroceutical therapy can provide an important tool to investigate underlying mechanisms associated with the effect of DBS, optimize the
stimulation parameters coupled to a certain fMRI signal that reflects DBS clinical efficacy, and possibly distinguish responders and non-responders to therapeutic interventions. fMRI brain imaging of the effects of electrical stimuli in brain disorders where DBS is considered helpful can potentially provide the clinician with an important tool to improve therapy and potentially commence fast track and personalized medicine by prompt calibration of optimal stimulation settings, as compared to many hospital visits for tedious adjustments.

Our system has a current controlled voltage source with flexible frequency and pulse width settings appropriate for deep brain stimulation, but can be moderated to applications using a current controlled current source or higher stimulation parameters appropriate for surface electrode stimulations. The system can apply electrical stimulation equivalent to implantable and external neurostimulators used to treat neuropsychiatric disorders, rehabilitation and chronic pain therapy, and may also be modified to new applications for electroceutical therapy within ophthalmology, otology, gastroenterology, urology, cardiology, and bionic replacements.

4.5. Comparator devices

The safety of internalized DBS systems for use in structural MRI sequences is well established, and the recent Medtronic (Minneapolis, MN, USA) label change now allows patients with specific systems to undergo approved structural MRI sequences also with stimulation turned on, but only when certain precautions are met. At present, three studies have also applied high gradient fMRI sequences to examine the effects of DBS on brain activity and neurocircuitry with internalized systems manufactured by Medtronic (Fiveland et al., 2018; Zhang et al., 2021) and Beijing PINS Medical Co (Beijing, China) (Shen et al., 2020). These recent progresses in fMRI scans with stimulation turned on contribute to the understanding of how DBS acts in the brain and support the safety in conducting future fMRI experiments. However, the deployed MRI conditional devices do not embody all the mechatronic characteristics of a fMRI conditional device, which both deliver, control and monitor an accurate and timely stimulus to an individual during an fMRI examination, and without presenting a risk to the individual or affecting the image quality (Hartwig et al., 2017).

4.6. Limitations

As previously discussed, it is difficult to assess if a fMRI signal in the stimulation target site is a real or observation or due to susceptibility artifacts from the implanted electrode (Fig. 3). Future technological advances, such as carbon electrodes, may resolve the issue.

The present prototype does not encompass current charge balance, an impedance-meter and a safety default system for immediate stimulation stop, but this will be included in our next generation prototype as an important safety precaution for clinical studies.

Finally, the system necessitates the electrodes to be externalized, which means that measurements can only be done in connection with the implantation or when the battery needs to be exchanged. Alternatively, indwelling models of chronic stimulation in animal models can be accomplished by encapsulating the externalized probe contacts within headset chambers (Arsenault and Vanduffel, 2019).

4.7. Conclusions

The presented fMRI compatible electrical stimulator delivers a pre-defined electrical stimulus during fMRI examination, synchronized with the fMRI design and triggered upon initiation of the fMRI sequence. The system, based on an optic fiber solution, circumvents previous problems related to DBS and fMRI, namely image distortion, improper communication and safety hazards. The system can be modified to elicit stimuli either voltage- or current-control and in addition, flexible stimulation parameters costumed to numerous electroceutical applications used within a broad range of medical conditions can be tuned. We anticipate that the system will be useful for DBS, spinal cord stimulation, cranial nerve stimulation, peripheral nerve stimulation, cortical multi-electrode stimulation, bionic replacements, cardiac pacemakers, retinal and corneal electric stimulation, cochlear implants, as well as surface-electrode stimulation in forms of auricular vagal nerve stimulation, neuromuscular electrical stimulation and transcutaneous nerve stimulation.

CRediT authorship contribution statement

All authors fulfill the criteria for authorship and appear on the author list. All authors revised and gave final approval of the manuscript. Following authors contributed to the conception (LMJ, AO, CT), drafting of the article (LMJ and GMK), design (LMJ, AO, CT, JHCS, AEH, BJ and GMK), acquisition of data (LMJ, AO, ANG, PW, BJ, PW, AEH and CT), and analysis and interpretation of data (LMJ, AO, JM, AEH, CT and GMK).

Declaration of Competing Interest

The University of Copenhagen, Copenhagen University Hospital - Rigshospitalet and Copenhagen University Hospital - Roskilde have in collaboration filed an international patent application entitled System for electrical stimulation during functional MRI published as WO 2019/068884 A1 with Anders Oikhues Baandrup, Louise Møller Jørgensen and Carsten Thomsen as the inventors. Thus, the institution and inventors have a financial interest in the patent and its developments. The other authors declare that they have no competing interests.

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