Safety of Transcranial Magnetic Stimulation for Parkinson's Patients with Deep Brain Stimulators

Abstract

The purpose of this experiment was to determine if transcranial magnetic stimulation (TMS) is safe for use in patients with implanted deep brain stimulators. Patients with Parkinson's Disease have struggled with controlling movements, and extreme cases cannot be treated with oral medication, prompting the use of deep brain stimulation (DBS). Although this reduces many symptoms, preliminary research suggests the use of TMS directed to the primary motor cortex to resolve remaining issues. However, TMS may induce high levels of current in implanted DBS probes causing excess stimulation. It was hypothesized that TMS would induce unsafe levels of current in DBS circuitry due to prior research. Control was established of 0% TMS intensity and simulation was conducted using a constructed custom-made and highly accurate DBS circuit geometry implanted into a shoulder-head model of a human. It was found that TMS induces far higher amounts of current than the safety limit of 3.4 mA. These results were statistically significant from the control. It is suggested that TMS not be used on Parkinson's patients with DBS implants and that further research using physical shoulder-head model phantoms and real clinical DBS and TMS equipment be conducted due to conflicting research.

Introduction

Those suffering from Parkinson's Disease (PD) often face challenges including bradykinesia, slowness of movement; essential tremor, involuntary rhythmic shaking; hypophonic speech; and difficulties while swallowing and eating. In severe cases of PD, where other medications have not been effective, such symptoms are treated with the implantation of deep brain stimulation (DBS) probes into the brain. DBS functions by delivering a high-frequency electrical current to specific regions of the brain, most commonly the subthalamic nucleus or the globus pallidus internus, which has been shown to mitigate many debilitating symptoms of PD (Lozano and Lipsman, 2013). However, many symptoms still remain after DBS, including difficulties with swallowing and speaking, impeding patients' ability to live normally (Crary et al., 2012).

Repetitive transcranial magnetic stimulation (rTMS) is a potential treatment option for these remaining symptoms. The main principle that rTMS utilizes is Faraday's law of induction, as by creating time-varying magnetic fields outside of the head region through the use of an electric coil, an electrical field is induced in the brain stimulating the neurons in the region. This is a non-invasive technique, where the intensity can be changed by modifying the current in the coils (Kingman et al., 2002). rTMS at the primary motor cortex (M1) region of the brain has been shown to alleviate symptoms of Parkinson's Disease (Kobayashi and Pascual-Leone, 2003).

However, patients which have a DBS implant are susceptible to overstimulation during rTMS due to the fact that the highly conductive material implanted in the brain would have a strong electrical current induced when interacting with the magnetic field generated in rTMS (Magsood et al., 2020). Due to this fact, it is important to investigate the safety of rTMS and DBS combination therapy. While other studies have explored this concern, none are yet to use an in-vivo approach that takes into account the entire DBS circuit including the implantable pulse

generator (IPG) as well as accurate body geometry. This has led to overall inconclusive and largely varying results on whether rTMS can be used safely in combination with DBS. While some research has found that rTMS used in presence of deep brain stimulators does not cause excessive stimulation (Kumar et al., 1999; Kühn et al., 2002; Kühn and Huebl, 2011; Syeda et al., 2020), others have found an unsafe induced current (Shimojima et al., 2010; Deng et al., 2010; Magsood et al., 2020).

The purpose of the experiment is to create the most realistic model of a Parkinson's patient with deep brain stimulators to determine which intensity of rTMS is safe to be used, taking into consideration the impedance and electrical conductivities of the entire human body and DBS circuit including the IPG. It is important to consider the completion of the DBS circuit with IPG, as other studies haven't, because induced electric current cannot flow in an incomplete circuit (Chapman et al., 2015). Overall, this provides a more accurate prediction of the safety of the combination of rTMS and DBS, determining if it is appropriate for use in Parkinson's patients.

It was hypothesized that the maximum amplitude of rTMS would exceed the safety threshold of 3.4 mA induced current. This is due to prior research generally approaching this consensus (Magsood et al., 2020). The experiment was executed by conducting a Magneto Quasi-Static Simulation at 2500 Hz utilizing Sim4Life and Zurich MedTech's Duke model. The Duke model was embedded with a custom-made and highly accurate CAD geometry of a complex DBS probe. The independent variable being changed was the rTMS intensity, changing in intervals of 25% of the maximum 5000 amperes, and then the dependent variable measured was the induced current in the electric circuit of the probe. 25% intervals were used as induced current is affected very marginally at lower intervals, meaning 25% gives the most clarity with

the least extraneous experimentation. The control used was 0% rTMS intensity, to observe the base-induced current in the model.

Methods and Materials

For safety, computer-safety guidelines were used such as avoiding eye strain through frequent breaks and blue-light blocking glasses. A permission form was signed by a parent that indicated that they had read and understood the risks and possible dangers involved in the research and they consented to their child participating in this research.

Modeling

To simulate the presence of a DBS probe within a patient, precise and accurate geometry of the probe needed to be modeled. This was done using Autodesk Inventor to create a Computer-Aided Design of the Medtronic DBS Lead Model 3389. The schematics for the created model can be seen in *Figure 1*.

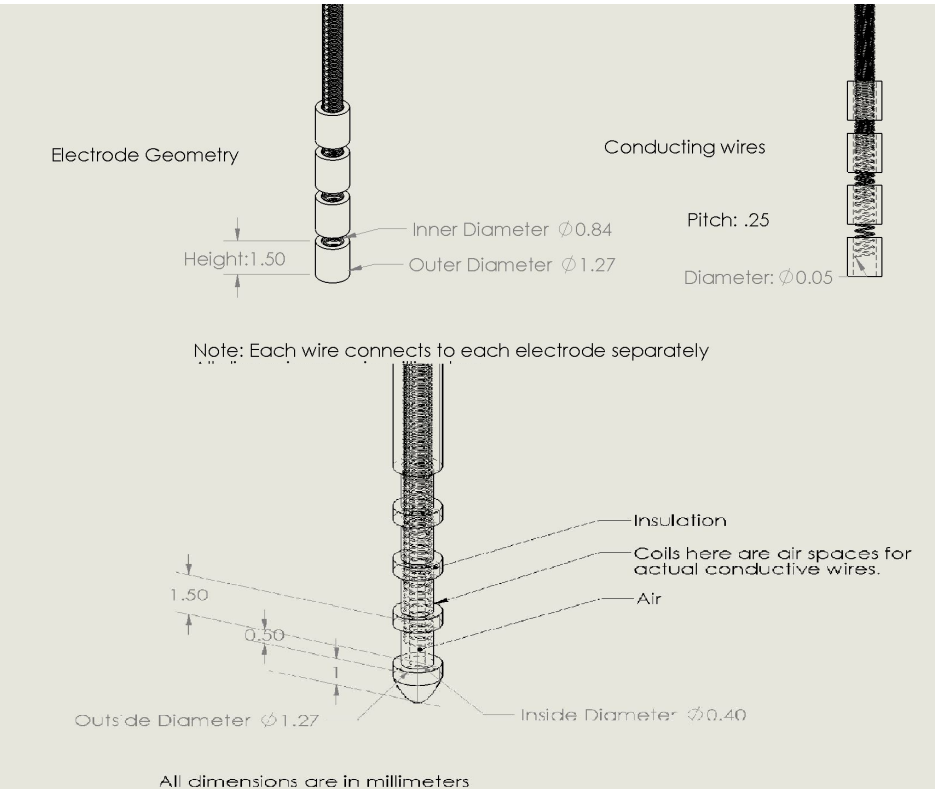


Figure 1. Electrode Schematics

To include the IPG, the circuit was extended and contoured to fit the Zurich MedTech's anatomical Duke model, such that the IPG is implanted near the clavicle and the electrode is implanted in the subthalamic nucleus. A complete version of the model implanted into the anatomical Duke model is represented in *Figure 2.* Previous models created were too large in data size for simulation, leading to discontinuities in the calculation, and large simulation times. Using discretization techniques, the model was made lower in file size while preserving full geometry.

Simulation

The program Sim4Life was used to simulate rTMS being used in a patient with implanted DBS probes. In Sim4Life, the Duke model, an anatomical model of an adult human male with extreme detail created by Zurich MedTech, was imported. Within it, the created DBS geometry was implanted such that the stimulation site is the subthalamic nucleus and the IPG is in the clavicle. Then, a TMS coil was positioned above the M1 region of the brain at a 45-degree angle 1 mm away from the skin's surface in accordance with standard operating procedures. This setup is visualized in *Figure 2* with all components of the Duke model transparent excluding skin tissue and gray matter.

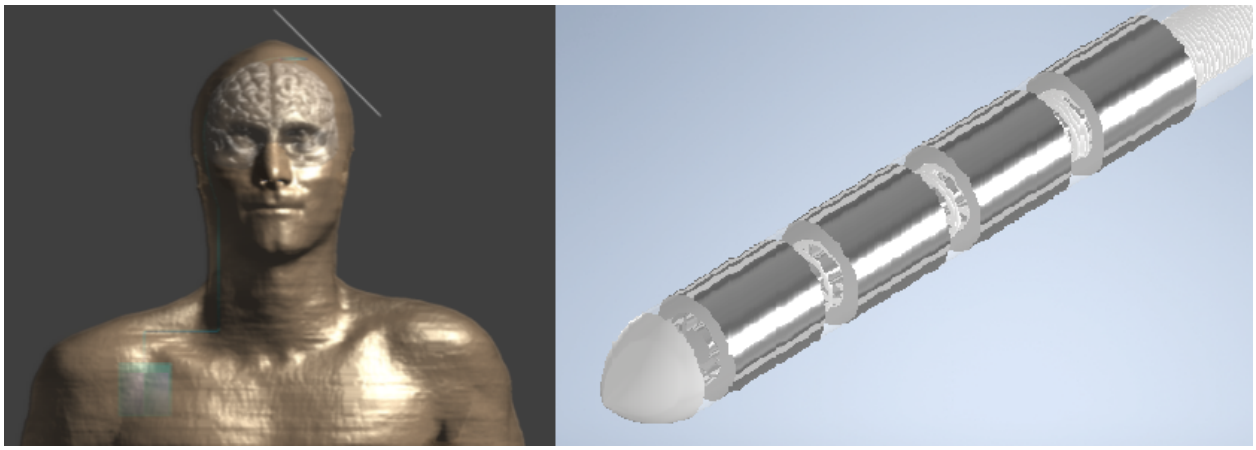


Figure 2. Experimental Setup with Transparency

The current sources of the TMS coil were established at 5000A (100% maximum amplitude), and a Magneto Quasi-Static Simulation was conducted at 2500 Hz with a maximum of 10,000 iterations. This means that each calculation was repeated 10,000 times by the software to ensure accuracy. This process was repeated for 0%, 25%, 50%, and 75% maximum amplitude. Additionally, each intensity was repeated once with a slightly different TMS coil position to replicate natural inconsistencies in clinical application, leading to a total of 20,000 trials for each rTMS intensity level.

Analysis

After the simulation was completed, a coronal slice of the model at the location of the probe was examined. The highest point of the induced electric field in the DBS circuit was observed and recorded. To view the distribution of the electric field, a surface view was interpolated for both gray matter in the brain and the DBS circuit and visualized. Examples of a coronal slice view and the interpolated surface views can be seen in Figure 3.

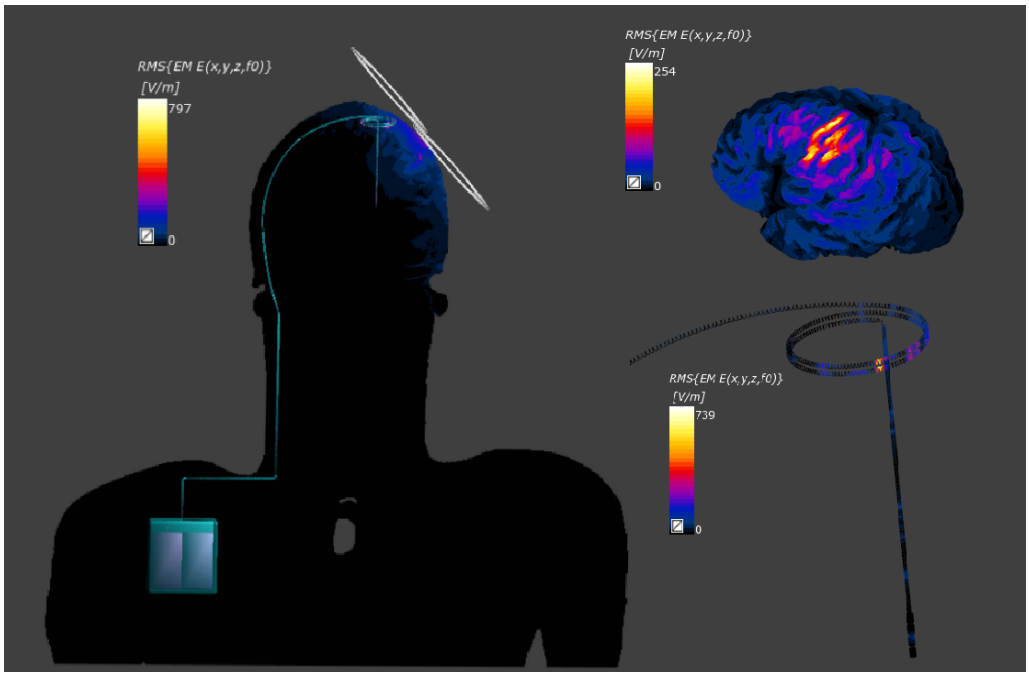


Figure 3. 5000A slice view (left), gray matter surface (top-right), surface DBS (bottom-right)

From the determined maximum induced electric field, the induced current was calculated by multiplying the cross-sectional surface area of the probe's conductive wiring by the volts per meter measurement to get a current value, which was then recorded. Each calculated current value was then determined to be safe or unsafe through comparison to the safety threshold of 3.4 mA.

Results

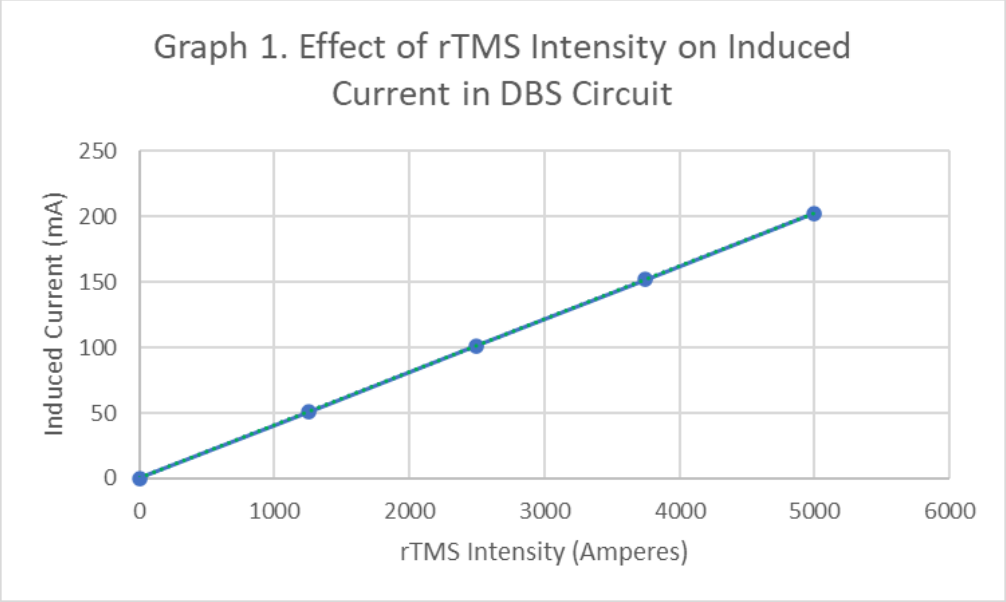
Table 1 demonstrates the statistical analysis for the different coil configurations used to simulate slight inconsistencies used in the clinical practice of rTMS. From the resulting t-test, it can be determined that each level of rTMS intensity is, to a 99.9% certainty, significantly different from the control of 0 amperes. An a-posteriori determination of the nodal gradient average error and equilibrated fluxes was done, but not included for statistical significance testing as it does not reflect clinical practice, however, verifies simulation accuracy.

Table 1. Effect of rTMS Intensity on Induced Current in DBS Circuit

Descriptive Information	rTMS Intensity (Amperes)				
	0	1250	2500	3750	5000
Mean (mA)	0	52.919	101.253	151.872	202.497
Range (mA)	0	4.59	9.19	13.768	18.359
Maximum (mA)	0	52.919	105.848	158.756	211.676
Minimum (mA)	0	48.329	96.658	144.988	193.317
Variance	0	10.534	42.228	94.779	168.526
Standard Deviation	0	3.246	6.498	9.735	12.982
1 SD	0	49.673-56.165	94.755-107.751	142.137-161.607	189.515-215.479
2 SD	0	46.427-59.411	88.256-114.250	132.401-171.343	176.533-228.461
3 SD	0	43.181-62.657	81.758-120.748	122.666-181.078	163.552-241.442
Number (1000s)	20	20	20	20	20

Results of t-test: at df=19999, α=0.001, t=3.090 for significance
0A vs 1250A: 22.058; $p < 0.001$
0A vs 2500A: 22.035; $p < 0.001$
0A vs 3750A: 22.0615; $p < 0.001$
0A vs 5000A: 22.059; $p < 0.001$
All remaining differences significant with $p < 0.001$

This significant difference is important as the induced current in the DBS circuit for each rTMS intensity far exceeds the safety threshold of 3.4 mA, as can be seen in *Graph 1*. This is in support of the initial research hypothesis that the rTMS at maximum amplitude would exceed the safety threshold. Additionally, the null hypothesis that rTMS does not generate a significant increase in induced current from no rTMS is rejected.



Discussions and Conclusions

This study suggests that rTMS therapy for the treatment of Parkinson's Disease is not safe for patients who already have DBS probes implanted into the brain. This is due to the fact that the induced current in the DBS probe when a TMS coil is active is significantly above the safety threshold of 3.4 mA. It was recommended that rTMS should not be used on patients with DBS implants in clinical practice until any ways to mitigate interaction with the DBS circuitry is found or other research suggests differently.

These results align with a few previously conducted studies (Shimojima et al., 2010; Deng et al., 2010; Magsood et al., 2020). However, it is important to note that the observed results in this experiment show a much higher induced current than some of the other studies (Shimojima et al., 2010; Magsood et al., 2020) where the induced current remained less than 1 mA above the safety threshold. This is likely due to the fact that these studies did not account for the completion of the IPG circuit. The one study which did, showed similar levels of induced current, 83 mA, to the current work (Deng et al., 2010). *This indicates that the inclusion of the IPG is highly important to the current flow.* Additionally, it is noted that the current experiment still achieves more than double the induced current as the study produced an 83 mA result, and this can be due to several factors. The most important of which is that the current work uses two loops at the top of the DBS circuitry, as is common with surgical procedure, this increases the concentration of conductive material within the magnetic field of rTMS, which can cause a higher induced current.

Several studies found opposing results to the current work (Kumar et al., 1999; Kühn et al., 2002; Kühn and Huebl, 2011; Syeda et al., 2020). The main reason for this is likely due to the fact that the created models either did not use in-vivo conditions, taking into account the anatomical body and the resulting contour and concentration of the conductive material such that it can fit in a body through surgery. The concentration of conductive material, the completion of the circuit with the IPG, and the presence of loops can likely explain the differences in observed induced current.

However, due to still conflicting overall research on the subject, it is important that further research be conducted on this subject to form a consensus. One way to explore this could be by creating a physical phantom model which replicates the electrical properties of a person from the clavicle up. This has previously been done for just the head to a high level of detail and

can be amended to include the shoulder such that the IPG is included. This would allow for use of actual DBS leads implanted in patients and true clinical rTMS coils for testing, vastly decreasing the chances of errors due to modeling inconsistencies or incorrect simulation parameters (Magsood et al., 2020).

Potential sources of error include unseen discontinuities or inaccuracies created when creating the 3D model of the DBS circuit, which is unlikely but possible due to human error. Additionally, the simulation detail may have been too low, causing the software to expand concentrations of conductive material to be larger than the reality, which may have exacerbated the observed induced current.

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Appendix A- Experimental Design Diagram

Title: The Effect of Transcranial Magnetic Stimulation on Induced Current of Deep Brain Stimulation Circuit of Parkinson's Patients

Hypothesis: If the TMS intensity is maximum (5000A), then the induced current will exceed the safety limit of 3.4 mA.

TMS Intensity (A)				
0	1250	2500	3750	5000
20000 iterations	200000 iterations	20000 iterations	200000 iterations	20000 iterations

Dependent Variable: Induced Current in mA

Constants: TM Stimulator Model (Magstim 200), anatomical model (Sim4Life Duke), temperature (22 degrees Celsius), 3D model for DBS circuit, Defined electrical properties for all components, IPG configuration, Stimulation site (anterior commissure).