Bayesian Optimization of Neurostimulation (BOONStim)

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Abstract

Background
Transcranial magnetic stimulation (TMS) treatment response is influenced by individual variability in brain structure and function. Sophisticated, user-friendly approaches, incorporating both established functional magnetic resonance imaging (fMRI) and TMS simulation tools, to identify TMS targets are needed.

Objective
The current study presents the development and validation of the Bayesian Optimization of Neuro-Stimulation (BOONStim) pipeline.

Methods
BOONStim uses Bayesian optimization for individualized TMS targeting, automating interoperability between surface-based fMRI analytic tools and TMS electric field modeling. BOONStim's Bayesian optimization performance was evaluated in a sample dataset (N=10) using standard circular and functional connectivity-defined targets, and compared to grid optimization.

Results
Bayesian optimization converged to similar levels of total electric field stimulation across targets in under 30 iterations, converging within a 5% error of the maxima detected by grid optimization, and requiring less time.

Conclusions
BOONStim is a scalable and configurable user-friendly pipeline for individualized TMS targeting with quick turnaround.

Keywords: Bayesian optimization, transcranial magnetic stimulation, functional connectivity, electric field modeling, individualized targeting

Introduction

Clinical and experimental application of transcranial magnetic stimulation (TMS) to brain regions is affected by large inter-individual variation in efficacy [1]. Individuals have unique functional connectivity and brain topography patterns [2–4] and individualized functional magnetic resonance imaging (fMRI) approaches and surface-based brain parcellations offer stronger brain-behavior links as compared to standard meta-analytic targets [2,5,6], which is highly relevant for neurostimulation. Recent work has highlighted that findings can also vary widely based on methodological variation in fMRI analyses [3]. A growing body of work also suggests that treatment response to rTMS may be influenced by individual differences in functional brain organization and that personalised targeting based on functional targets may improve outcomes [7–9].

TMS dose localization and intensity are also influenced by the structural variability and cortical geometry of the brain [10], which can be taken into account via TMS electric field simulations [11]. Several optimization approaches have been proposed for maximizing the electric field over regions of interest (ROIs) on an individual level [12–14]. As a result, there has been increasing interest in using individualized TMS targeting to increase treatment efficacy [8,15]. However, there is a need for more sophisticated approaches incorporating fMRI to identify TMS targets with electric field modeling to account for both functional and structural variability [16,17].

In this context, several limitations exist in the current state of fMRI and TMS tools to address individual variability. First, the current fast optimization tools only allow for a binarized, small circular ROIs, despite investigators increasingly using fMRI to define candidate TMS targets, which may manifest as anatomically meaningful non-circular parcels or weighted maps derived from functional connectivity. Second, the current tools present a barrier to entry for researchers, requiring in-house software to handle automation and data preprocessing, which also leads to reproducibility and scalability issues.

To address these issues, we have developed the **B**ayesian **O**ptimization **o**f **N**euro-**Stim**ulation (BOONStim) pipeline. BOONStim is an automated end-to-end pipeline for generating a TMS coil position from data organized as a Brain Imaging Dataset (BIDS), automating interoperability between surface-based fMRI analytic tools and TMS electric field modeling. BOONStim introduces a novel TMS Bayesian optimization algorithm that allows for more general ROI definitions and quick turnaround. Here, we present this pipeline and validation analyses.

Materials and Methods

Pipeline Overview

An overview of the BOONStim pipeline is shown in Figure 1. BOONStim is available as open-source code at: https://github.com/TIGRLab/BOONStim. BOONStim was built to support a modular, parallelizable, and customizable workflow scripted using Nextflow [18]. BOONStim leverages portable, isolated Singularity containers to encapsulate all its environments, including widely established fMRI software packages, reducing the burden of compute environment set-up for users. A small utility python library (Fieldopt) is packaged

with BOONStim that contains the optimization logic (https://github.com/TIGRLab/fieldopt). Use of separate Singularity containers for each of the major software packages allows for users to easily swap out container versions and reduce dependency conflicts between software.

BOONStim requires input T1-weighted and fMRI data to be organized according to the BIDS standard. MRI preprocessing is done using fMRIPrep and Ciftify, and SimNIBS and Freesurfer are used for head model reconstruction, after which this is registered to the fMRI cortical surface. These preprocessing pipelines can be configured to suit various MRI acquisition parameters using boutiques JSONs [19], enabling versioning and reproducibility.

Users may define their own fMRI target workflows to derive ROIs or use a MNI coordinate, which is resampled to the SimNIBS surface [20]. If the user is targeting a single coordinate, an ROI is drawn, whereas a surface-based target requires weighted optimization (see Figure 1). Once the target is represented on the FEM, our novel Bayesian optimization approach can be applied, or the current gold standard, grid optimization. Auxiliary dipole method (ADM) optimization can also be used for a single MNI coordinate [12].

BOONStim's Bayesian optimization process learns from a history of sampling points with basic assumptions about the smoothness of the underlying objective function, minimizing the number of samples to find a global maximum. It uses the information criterion called "multipoints expected improvement" or the q-EI, enabling parallel sampling for faster convergence [21]. The optimization objective is defined as follows:

$$p^*, \theta^* = \arg\max_{p,\theta} \sum_{t \in R} \|E_{p,\theta}(t)\|$$

Where p - a position vector specifying the centre of the TMS coil
θ - the orientation of the TMS coil handle
t - a tetrahedron from the head model
$E_{p,\theta}(t)$ - the electric field vector at a given tetrahedron t from a simulation of a coil at (p, t)
R - a region of interest

BOONStim produces output files which are ready to use with existing commercially available TMS neuronavigation software and hardware, including BrainSight and Localite inputs from the coordinates calculated during optimization, and the stokes correction factor based on an automated scalp-to-cortex distance assessment for both hemispheres [22]. It also provides a reference image, so the TMS operator can confirm that the coil position based on the inputted coordinates matches the optimization result, and the corrected T1 image to ensure the same coordinate system is used. Quality control pages are generated for each subject with results from sub-workflows (i.e., fMRIPrep, Ciftify, and SimNIBS) for data quality assurance.

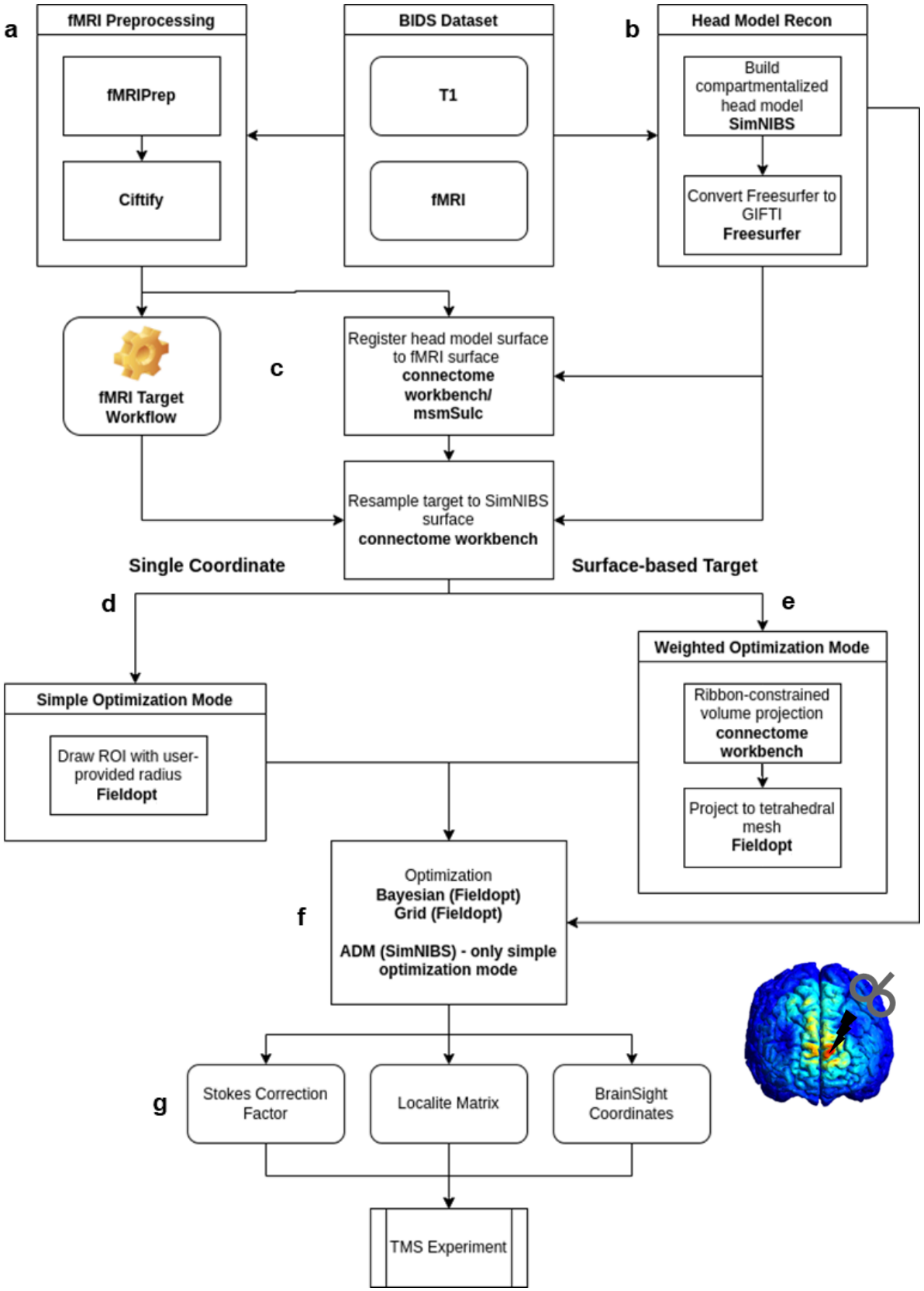

Figure 1. BOONStim pipeline overview

BOONStim utilizes Singularity container image files for widely established fMRI software packages including fMRIPrep [23], Ciftify [24], HCP (Human Connectome Project) Pipelines [25], SimNIBS (Simulation of Non-invasive Brain Stimulation) [13,14], Connectome Workbench [20], and Freesurfer [26], as well as Fieldopt. Input T1-weighted and fMRI data are required to be organized according to the Brain Imaging Data Structure (BIDS) standard, enabling flexible use of established preprocessing tools. **a)** MRI preprocessing is done using fMRIPrep [23], followed by Ciftify [24] to project the data to the cortical surface. **b)** T1-weighted head model reconstruction (recon) is achieved using SimNIBS [13,14] and Freesurfer [26] to generate a finite element method (FEM) model, which is also transformed to the surface (GIFTI format). **c)** Connectome Workbench/MSMSulc [27] is then used to register the head model to the fMRI surface. Users may define their own fMRI target workflows to derive ROIs using available parcellations or outputs from fMRIPrep and Ciftify, or a standard TMS target (i.e., MNI coordinate), after which the target ROI is resampled to the SimNIBS surface using Connectome Workbench [20]. **d)** If the user is targeting a single coordinate, simple optimization mode is used to draw an ROI with the provided parameters using Fieldopt. **e)** If a surface-based target is provided (e.g., functional connectivity maps), weighted optimization mode is used. BOONStim automates interoperation of the user-defined ROI with SimNIBS simulation software by mapping the user ROI directly into the FEM in which simulations are performed. This is achieved via ribbon-constrained volume projection using Connectome Workbench and a tetrahedral projection algorithm using monte carlo sampling to determine contributions of voxels to specific tetrahedra in Fieldopt. **f)** Once the target is represented on the FEM, the choice of optimization is flexible via a single configuration option, including Bayesian optimization or grid optimization. For a single MNI coordinate, there is also the option of using auxiliary dipole method (ADM) optimization [12]. **g)** BOONStim output files include coordinates calculated during optimization and the stokes correction factor, which are ready to use with TMS neuronavigation software and hardware.

Dataset

BOONStim was run on 10 subjects from the Dual Mechanisms of Cognitive Control dataset, intended for comparing preprocessing pipelines [28]. Data was acquired using a 3T Siemens Prisma Fit scanner, including an anatomical T1-weighted scan (isotropic resolution=0.8 mm, TR=2400 ms), two resting state fMRI scans with opposite phase encoding directions (isotropic resolution=2.4 mm, TR=1200 ms, duration=5.2 minutes per scan), and field map scans. See OpenNeuro for details (OpenNeuro Dataset: ds003452).

The performance of BOONStim's Bayesian optimization was evaluated using standard circular ROIs of the dorsolateral prefrontal cortex (DLPFC), the most common TMS target, and functional connectivity maps of the dorsomedial PFC (DMPFC) to verify the generalizability of the optimization algorithm, and compared to densely sampled grid optimization. We used the DMPFC as our functional connectivity-based target, which is a key node of the mentalizing network [29], as this pipeline was built in the context of a clinical trial targeting this network and social cognitive abilities.

Target Definitions

Standard circular ROI targets were produced by drawing a sphere (5, 10, and 20 mm radius) around the selected vertex (MNI coordinates:-46,45,38 [30]). Masked functional connectivity maps were used to generate functional connectivity-defined DMPFC targets. The DMPFC region was removed from a “mentalizing” map from Neurosynth [31], which was projected onto the cortical surface and used to compute mentalizing seed-based functional connectivity for each participant. A binarized DMPFC mask was applied to the seed-based functional connectivity map to produce a DMPFC-mentalizing connectivity map to optimize over for each participant.

Bayesian Optimization Validation

To verify the results of Bayesian optimization, we compared it to densely sampled grid optimization. For Bayesian optimization, we performed 30 optimizations for each participant given that it is stochastic. Grid optimization was performed for each participant using a 30x30 grid of locations with 36 orientations (5 degree increments), resulting in 32400 unique coil positions being evaluated. The coil position with a maximal dosage (i.e., simulated electric field stimulation) over the target was selected as the optimal position for a given participant and ROI.

For both the standard ROI targets and functional connectivity-defined targets, we computed the number of iterations required (up to a maximum of 30) for Bayesian optimization to converge onto the maxima detected by a densely sampled grid optimization, the percent difference between the simulated electric field stimulation over the target region using grid optimization and Bayesian optimization for each participant, and the number of iterations required to reach convergence.

Results

For both the standard circular ROI targets (Figure 2a) and the functional connectivity-based targets (Figure 2b), Bayesian optimization quickly converged to similar levels of total electric field stimulation over the target ROI compared to grid optimization across participants in under 30 iterations. Bayesian optimization also converged onto or within a 5% error of the maxima detected by densely sampled grid optimization for both standard ROI targets (Figure 2c) and functional connectivity-defined targets (Figure 2d). These properties appear to hold across standard ROI targets of different sizes and functional connectivity-defined targets being optimized over. Lastly, the total number of iterations required to achieve convergence ranged from 9 to 52 across participants for standard ROI targets (mean(SD)=22(6.9); Figure 2e) and from 9 to 53 for functional connectivity-defined targets (mean(SD)=22(8.0); Figure 2f), compared to 32400 iterations for densely sampled grid optimization.

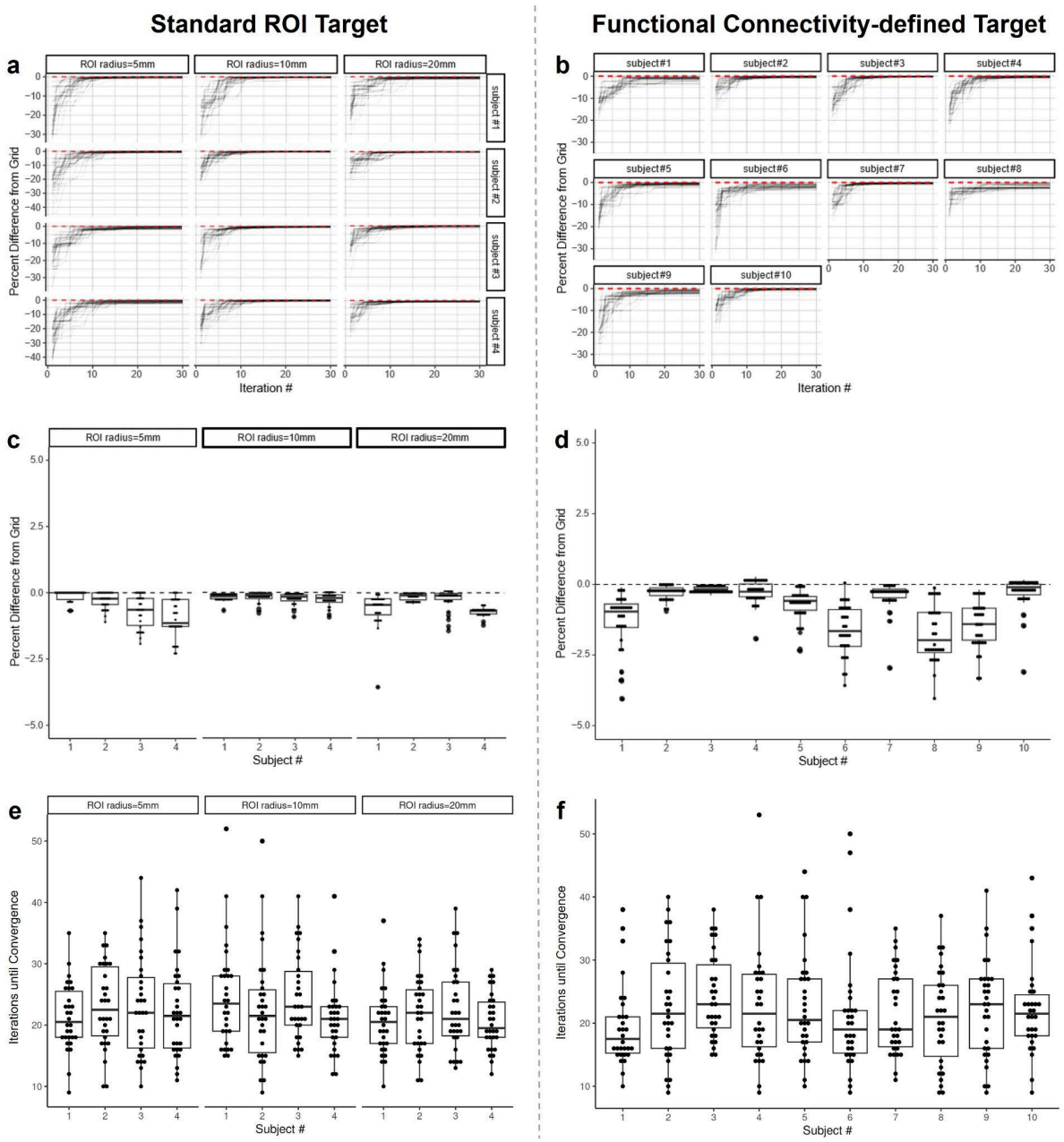

Figure 2. Bayesian Optimization Validation

Left panels display results for optimizing over the standard ROI target with a radius of 5 mm, 10 mm, and 20 mm for four representative subjects, and **right** panels for optimizing over the functional connectivity-defined target for all 10 subjects. **a-b** display the percent difference of Bayesian optimization from grid-based optimization maxima as the number of iterations increases. Percent differences are plotted because the objective value achieved by the optimization varies across subjects based on the size of the ROI, scalp-to-cortex distance, and functional connectivity. Each line represents one of 30 optimizations performed for each participant, and the red dotted line at 0 represents the maxima detected by densely sampled grid optimization. **c-d** show the percent difference of Bayesian optimization from grid-based optimization maxima, where each data point represents one of 30 optimizations performed for each participant. **e-f** display the number of iterations required for Bayesian optimization to

reach convergence, where each data point represents one of 30 optimizations performed for each participant.

Discussion

BOONStim represents a scalable end-to-end pipeline that facilitates fMRI-guided, individualized TMS targeting. BOONStim pairs established fMRI methodology with a novel Bayesian optimization algorithm that solves TMS optimization over generalized ROIs within a reasonable time-frame and percentage error. Our results show that Bayesian optimization performs similarly to grid-based optimization with fewer iterations. Three key advantages that BOONStim has over other methods include:

1. Speed
Bayesian optimization reached convergence in far fewer iterations than grid-based optimization for both standard and functional connectivity-defined ROIs, requiring less time. This is critical in the context of clinical trials where turnaround times between acquiring fMRI data and delivering TMS treatment can be restrictive.

2. Generality across target ROIs
Unlike other pipelines which work on a single MNI coordinate or require small ROIs for accurate estimation, BOONStim can use weighted scalar-valued functional connectivity maps as inputs, and its Bayesian optimization was not significantly impacted in its ability to converge to a maxima across various sizes, shapes, and types of ROIs across participants. This approach is successfully being used in ongoing clinical trials targeting both the DMPFC (NCT06118268) and the DLPFC (NCT05583747).

3. User-friendly interoperability of established fMRI and TMS simulation software
BOONstim integrates the current best fMRI data processing practices and automates operability with TMS simulation software to optimize TMS targeting. The scalability of BOONStim allows researchers to run high-throughput TMS experiments without worrying about many of the pipeline implementation details.

Conclusions

BOONStim enables researchers to perform automated individualized coil optimization in TMS trials with minimal setup and define rich targets with variable shapes and weights, such as functional connectivity maps. BOONStim is a tool built on reproducible fMRI analytic approaches that serves as a scalable and configurable end-to-end solution for TMS practitioners to reduce the burden of performing sophisticated fMRI-based targeting with electric field modeling. This pipeline is also extensible to newer optimization techniques and fMRI methodology.

CRediT authorship contribution statement:
Lindsay D. Oliver: Writing - Original Draft, Review & Editing, Formal Analysis, Visualization. **Jerrold Jeyachandra**: Conceptualization, Methodology, Software, Formal Analysis, Visualization, Writing - Original Draft Preparation, Review & Editing. **Erin W. Dickie**: Conceptualization, Methodology, Writing - Review & Editing. **Colin Hawco**: Conceptualization, Methodology, Writing - Review & Editing. **Salim Mansour**: Software, Writing - Review & Editing. **Robert W. Buchanan**: Funding Acquisition, Writing - Review & Editing. **Anil K. Malhotra**: Funding Acquisition, Writing - Review & Editing. **Daniel M. Blumberger**: Funding Acquisition, Methodology, Writing - Review & Editing. **Zhi-De Deng**: Methodology, Software, Supervision, Writing - Review & Editing. **Aristotle N. Voineskos**: Conceptualization, Supervision, Funding Acquisition, Writing - Original Draft, Review & Editing.

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