

Fast and Accurate Parameter Optimization of Transcranial Temporal Interference Stimulation by Selectively Employing Target-Specific Candidate Electrodes

Sangwoo Lee¹, Graduate Student Member, IEEE, Eun-Gyoung Yi¹,
Jaehoon Jeong, Graduate Student Member, IEEE, Hyungtaek Kim¹, Rak-Kyeun Hong, Donghyeon Kim,
and Chang-Hwan Im¹

Abstract—Transcranial temporal interference (TI) stimulation offers non-invasive modulation of deep brain regions with limited neocortical activation. Achieving focal TI stimulation requires individualized optimization of the stimulation parameters, including electrode configurations and injection currents. However, conventional exhaustive search (ES) approach is computationally expensive, hindering the clinical applicability of subject-specific parameter optimization. We propose a target-specific restricted exhaustive search (RES) strategy that substantially reduces the computational burden while preserving reliability of ES-based optimization. ES was conducted to identify the optimal two-pair TI stimulation parameters for three deep brain targets (the nucleus accumbens, hippocampal head, and caudate body) using 40 individual finite element head models. Target-specific restricted candidate electrode subsets were constructed based on the electrode selection patterns observed across multiple subjects. RES was then performed by constraining the search space only for these selected subsets. A 4-fold cross-validation approach was employed to quantify the average changes in the objective function and computational time, which were then compared with those of the conventional ES approach. A parametric analysis was also conducted to identify the size of the minimal subset that maintained a robust performance for each target. RES maintained an optimization accuracy comparable to that of conventional ES across all three

targets, while reducing the computation time approximately 30- to 100-fold, enabling optimization within minutes or seconds. Specifically, targeting the nucleus accumbens allowed for the most extensive search space reduction without compromising stimulation efficacy. This is the first study to identify target-specific electrode selection patterns across individuals to optimize TI stimulation. The RES strategy leverages these patterns to preserve the deterministic nature of ES while reducing the optimization time from hours to minutes, thereby facilitating the clinical application of personalized TI stimulation.

Index Terms—Temporal interference stimulation, individualized optimization, exhaustive search, target-specific electrode selection, computational modeling, non-invasive brain stimulation.

I. INTRODUCTION

TRANSCRANIAL electrical stimulation (tES) is a non-invasive neuromodulation technique used for delivering weak currents through scalp electrodes to modulate neuronal activity [1], [2], [3]. Conventional tES techniques have demonstrated clinical efficacy for various neurological and psychiatric conditions [4], [5], [6], [7]. Although these methods primarily modulate pyramidal neurons in neocortical regions, the pathophysiology of many brain disorders involves complex interactions between the cortical and subcortical structures [8], [9], [10]. However, achieving focal stimulation of subcortical targets with conventional tES remains challenging because the electric fields induced by the scalp electrodes attenuate rapidly with increasing depth [11]. To overcome this limitation, transcranial temporal interference (TI) stimulation has been proposed [12], [13]. In TI stimulation, two pairs of electrodes deliver high-frequency currents (e.g., ≥ 1 kHz) at slightly different frequencies. The intrinsic low-pass filtering properties of neuronal membranes prevent activation by these high-frequency carriers themselves [14], [15]. Instead, neurons preferentially respond to the low-frequency TI envelope with a frequency corresponding to the difference between the two carriers. This mechanism enables targeted modulation of deep brain regions with reduced neocortical activation. Early experimental studies focused on animal models such as rats and monkeys to validate the feasibility of TI stimulation for deep brain regions [12], [16], [17]. Recent human studies have

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Sangwoo Lee and Jaehoon Jeong are with the Department of Electronic Engineering, Hanyang University, Seoul 04763, Republic of Korea.

Eun-Gyoung Yi, Hyungtaek Kim, Rak-kyeun Hong, and Donghyeon Kim are with the Research Institute, Neurophet Inc., Seoul 06234, Republic of Korea (e-mail: donghyeon.kim@neurophet.com).

Chang-Hwan Im is with the Department of Electronic Engineering and the Department of Biomedical Engineering, Hanyang University, Seoul 04763, Republic of Korea (e-mail: ich@hanyang.ac.kr).

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further demonstrated the efficacy of TI stimulation for selectively targeting subcortical structures [18], [19], [20], [21]. For example, Violante et al. [18] showed that hippocampal TI stimulation enhanced the accuracy of episodic memories. Similarly, Wessel et al. [19] reported that striatal stimulation with theta-burst patterned TI stimulation improved motor skill learning.

Despite these promising results, the clinical translation of TI stimulation has been hindered by the difficulty in determining the optimal stimulation parameters. The identification of the electrode configurations and injection currents tailored to each individual presents a considerable computational bottleneck. Accordingly, many clinical studies have uniformly applied a stimulation parameter set optimized on a high-resolution template head model [22] to all participants [18], [19], [20]. However, this single-template-based approach does not account for the inter-individual variability in brain anatomy. von Conta et al. [23] showed that the distribution of the TI envelope varies considerably across individuals, even under identical stimulation parameters. This finding suggests that individualized optimization is essential to enhance the efficacy of TI stimulation. The most straightforward method for parameter optimization is the exhaustive search (ES), which evaluates all possible electrode configurations and injection currents to determine the optimal parameter set [24], [25], [26]. Although this method reliably finds the global optimum, it requires substantial computation time. For example, Lee et al. [25] reported that optimization required approximately 10 h when 61 candidate electrodes were placed according to the international 10–10 system. These extensive computational demands limit the practical applicability of personalized TI stimulation in clinical settings. To reduce this heavy computational burden, various optimization strategies utilizing evolutionary algorithms [27], [28], unsupervised learning [29], and reinforcement learning [30] have been proposed. However, these methods often fail to find the global optimum by converging to a local optimum. Convex optimization [31] also offers a fast and deterministic alternative; however, its solution relies on problem approximations that may deviate from the true global optimum. Therefore, achieving both computational efficiency and global optimality in parameter optimization of TI stimulation remains an unresolved challenge.

To overcome the trade-off between computational efficiency and optimization accuracy in TI stimulation, we focused on the number of candidate electrodes used for ES. Because the computation time scales with the candidate pool size, narrowing the search space is critical for computational efficiency. However, simply adopting a lower-resolution electrode configuration, such as the international 10–20 system, might decrease TI stimulation focality, which is a primary advantage of stimulation parameter optimization. Here, we hypothesized that the optimal electrode configuration for a specific target would exhibit similar spatial patterns across individuals. Based on this hypothesis, we propose a target-specific restricted exhaustive search (RES) strategy for two-pair transcranial TI stimulation. RES restricts the candidate pool to target-specific

electrodes identified based on their selection counts in the optimal electrode configurations derived from multiple head models.

In this study, we demonstrate the advantages of the proposed RES strategy using 40 finite element (FE) human head models. For the quantitative evaluation of the computational times and objective function values, a 4-fold cross-validation (CV) framework was employed, where 30 FE models were used to restrict the candidate electrodes, and the remaining 10 FE models were used to evaluate the performance of the proposed RES strategy for each CV iteration. Three deep brain regions frequently employed as target regions of interest (ROIs) in clinical neuromodulation studies were tested: the nucleus accumbens (NAc), hippocampal head, and caudate body [32], [33], [34]. The effectiveness of the RES strategy was compared with that of conventional ES using all candidate electrodes (hereafter referred to as Full ES) and with that of a cross-subject condition, where optimal parameter sets from other individuals were directly applied without any subject-specific optimization. The RES strategy addresses a critical barrier to the clinical translation of personalized TI stimulation by reducing the time for stimulation parameter optimization from hours to minutes. Unlike prior optimization studies that focused on algorithmic improvements, RES systematically reduces the search space using population-level electrode selection patterns. This retains the deterministic nature of ES within the reduced space, ensuring reliable identification of near-optimal solutions for practical treatment planning.

II. METHODS

A. Construction of Subject-Specific Head Models

1) *Data Acquisition*: T1-weighted magnetic resonance imaging (MRI) datasets were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI-3 and ADNI-4) database [35]. To reduce variability related to age and sex, the datasets were restricted to cognitively normal female subjects aged 63–80 years (mean $\pm$ SD = 71.6 $\pm$ 4.1 years). The dataset selection was performed using a multistep screening procedure. First, all candidate MRI scans were visually inspected to exclude data with imaging artifacts (e.g., vitamin E markers) or severe head inclination. Next, subject-specific head models were generated through the automated segmentation and subsequent mesh generation pipeline described in Section II-A.2. Datasets were further excluded if the projected electrode positions resulted in anatomically implausible placements, such as electrodes extending into the orbital cavity or those positioned markedly below the eyes. Additionally, scans with visible head coil imprints or significant geometric distortions on the scalp surface were excluded. After applying these criteria, a total of 40 datasets with the most reliable anatomical quality and electrode placement feasibility were selected for subsequent analyses.

2) *Computational Modeling*: MRI segmentation was performed using a deep learning-based segmentation framework (Neurophet Inc., Seoul, Korea) built on the Split-Attention U-Net (SAU-Net) architecture [36]. The framework has been

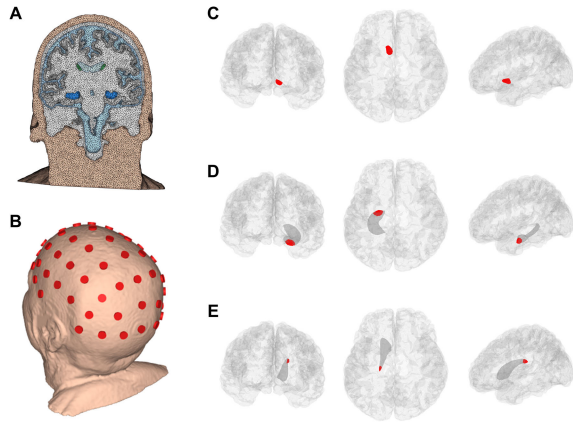


Fig. 1. Subject-specific finite element head model, scalp electrode configuration and target ROIs. (A) Coronal cross-sectional view of the tetrahedral head model generated from the representative subject. The head model was segmented into 14 tissue layers, including major tissues such as the gray matter, white matter, CSF, skull, and skin. (B) Three-dimensional rendering of the scalp surface of the same subject with 57 active electrodes placed according to the international 10–10 system. (C–E) Locations of the three target ROIs: the left NAc (C), left hippocampal head (D), and left caudate body (E). The gray regions illustrate the NAc, hippocampus, and caudate nucleus. The red regions highlight the specific target ROIs.

validated on multicenter, multivendor datasets, demonstrating segmentation performance comparable to that of FreeSurfer [37]. Using this framework, the brain was initially segmented into eight primary anatomical classes: cerebral gray matter (GM), cerebral white matter (WM), cerebellar GM, cerebellar WM, ventricles, cerebrospinal fluid (CSF), skull, and skin. To facilitate the precise modeling of subcortical stimulation targets, the bilateral NAc, hippocampus, and caudate nucleus were additionally delineated as distinct anatomical labels within the cerebral GM. Consequently, a total of 14 anatomical tissue compartments were generated, providing a high-resolution structural basis for subsequent tetrahedral mesh generation and finite element method (FEM)-based electric field simulations. Tetrahedral mesh generation was performed using the Computational Geometry Algorithms Library (CGAL, version 6.1) [38]. The segmented MRI volumes were converted into tetrahedral meshes using a Delaunay triangulation-based meshing algorithm. The mesh generation parameters were tuned to achieve a balance between geometric fidelity and computational efficiency. Specifically, a facet size of 1.3 mm, a facet distance of 2.35 mm, and a maximum tetrahedral element volume of 2.0 mm³ were adopted. These values ensured stable mesh quality with smooth boundary representations while maintaining tractable computational costs for subsequent FEM simulations. On average, the generated head models consisted of approximately 3.02 million elements, providing sufficient spatial resolution for the reliable estimation of subcortical electric fields. A representative tetrahedral head model is shown in Fig. 1A.

3) Target ROIs: Three target ROIs in the left hemisphere were defined: the NAc, hippocampal head, and caudate body. The left hemisphere was selected for demonstration purposes. The proposed strategy is equally applicable to targets in the right hemisphere. Because of its relatively small volume, the entire NAc was designated as the target ROI. For the

hippocampal head, the target ROI was defined as the subset of nodes within a 1 cm radius from the most anterior node of the hippocampal region. Similarly, for the caudate body, the target ROI was defined as the subset of nodes within a 1 cm radius from the most posterior node of the caudate nucleus. The three target ROIs are shown in Fig. 1C–E.

B. Framework for Optimization of TI Stimulation Parameters

1) Electric Field Calculations: A leadfield matrix was constructed using FEM to facilitate the efficient computation of electric field distributions under multi-electrode configurations and to support the subsequent optimization of the TI stimulation parameters. The leadfield matrix characterizes the linear relationship between the electrode current inputs and the resulting electric field responses under a quasistatic approximation, which can be expressed as

$$\mathbf{L}\mathbf{x} = \mathbf{E}, \quad (1)$$

where $\mathbf{L}$ denotes the leadfield matrix, $\mathbf{x}$ represents the vector of electrode currents, and $\mathbf{E}$ corresponds to the nodewise electric field vector [39]. Electrode positions on the scalp surface were defined according to the international 10–10 electrode system, yielding an initial set of 69 electrodes. To ensure reliable electrode-skin contact, 12 electrodes located near the ears or orbital regions (F9, FT9, TP9, P9, F10, FT10, TP10, P10, T7, T8, TP7, and TP8) were excluded, resulting in 57 candidate electrode contact locations for leadfield construction (Fig. 1B). Each nominal electrode location was represented by a finite contact patch on the external scalp boundary, with a consistent circular geometry and an effective contact area of 1 cm². Neither the electrode material nor a conductive gel layer was explicitly meshed as a separate conductive domain.

To construct the leadfield matrix, the potential at a single internal node at the centroid of each subject-specific head mesh was fixed at 0 V to remove the gauge freedom of the Neumann problem. This node carried no injected current and did not act as a physical reference or return electrode. Each leadfield basis field was generated from an auxiliary configuration in which a unit current was injected at one active scalp contact patch and returned through a common auxiliary return region on the external scalp boundary (hereafter the return region). The electric potential induced by the activation of each electrode was computed by solving the Laplace equation under quasi-static conditions:

$$\nabla \cdot (\sigma \nabla V) = 0 \text{ in } \Omega, \quad (2)$$

where σ denotes tissue-specific isotropic conductivity and Ω represents the computational domain [40]. For a prescribed signed total current I , a spatially uniform normal current density $q = I/A$ was imposed over the corresponding area on the scalp boundary, where A denotes its area. The same treatment was applied at each active electrode patch and at the return region. The finite-element boundary load was assembled by area-weighted surface integration. This formulation corresponds to a gap-type reduced boundary electrode model [41], rather than an equipotential Dirichlet-electrode model, a

complete electrode model, or an explicit electrode/gel-domain model. Zero normal current density was imposed on the portion of the external scalp boundary outside the current-carrying areas, corresponding to a homogeneous Neumann boundary condition. Internal tissue interfaces were coupled through continuity of electric potential and normal current density. The resulting partial differential equation was solved using the conjugate gradient (CG) method, and the electric potential was computed at each mesh node.

Isotropic conductivities were assigned to each segmented compartment based on commonly used literature values: 0.276 S/m for the cerebral and cerebellar GM and the subcortical structures, 0.126 S/m for WM, 1.65 S/m for CSF and ventricles, 0.01 S/m for skull, and 0.465 S/m for skin [42]. These values were consistently applied across all simulations.

The electric field was computed as the negative gradient of the electric potential:

$$\mathbf{E}_i = -\nabla V = (E_x, E_y, E_z). \quad (3)$$

The element-wise electric fields were converted to node-wise representations by averaging the electric fields of the neighboring tetrahedral elements. The resulting node-wise electric field vectors were assembled into a precomputed leadfield matrix, where each column represents the field response to a unit current injected at a specific electrode and returned through the return region. Owing to the linearity of the quasi-static formulation, the electric fields generated by arbitrary electrode current combinations were efficiently obtained via linear superposition, obviating the need for repeated FEM simulations. For each subject, the leadfield matrix was stored as an $n \times 57 \times 3$ array, where n denotes the number of nodes, 57 corresponds to the number of active electrodes, and 3 is the number of electric-field vector components (E_x, E_y, E_z). The 57-channel leadfield matrix provided a precomputed basis for the subsequent optimization of the TI stimulation parameters.

2) Exhaustive Search Optimization: An optimization problem was formulated based on the precomputed leadfield matrix described in the previous section. The resulting electric field generated by a specific electrode pair was calculated by linearly combining the corresponding columns of the leadfield matrix: one corresponding to 1 mA injection current at the first active electrode and -1 mA at the return region, and the other corresponding to -1 mA injection current at the second active electrode and 1 mA at the return region. This linear combination yielded a direct current flow between the two active electrodes with zero net current at the return region. By modulating this spatial field with a sinusoidal time function, the time-varying electric field during alternating current stimulation was obtained. This process was identically applied to the other electrode pair, resulting in two independent electric field distributions, denoted as $\mathbf{E}_1$ and $\mathbf{E}_2$. The TI electric field was modeled via the superposition of two independent sinusoidal fields generated by distinct electrode pairs with slightly different frequencies, f_1 and f_2 . The resultant electric field $\mathbf{E}(\mathbf{r}, t)$ at node $\mathbf{r}$ and time t was evaluated as a linear combination of these two time-varying fields, expressed as

$$\mathbf{E}(\mathbf{r}, t) = \alpha \mathbf{E}_1(\mathbf{r}) \sin(2\pi f_1 t) + \beta \mathbf{E}_2(\mathbf{r}) \sin(2\pi f_2 t), \quad (4)$$

where α and β are scalar constants determining the amplitudes of the injection currents. Consistent with a previous study [12], the carrier frequencies f_1 and f_2 were set to 2.00 and 2.01 kHz, respectively, yielding the resulting TI envelope frequency ($f_{TI} = |f_1 - f_2|$) of 10 Hz. The maximal envelope amplitude $A(\mathbf{r})$, representing the modulation depth at each spatial location, was calculated as described in a previous study [43]:

$$A(\mathbf{r}) = 2\min(|\alpha \mathbf{E}_1(\mathbf{r}) \cos \theta|, |\beta \mathbf{E}_2(\mathbf{r}) \cos(\theta - \varphi(\mathbf{r}))|), \quad (5)$$

where φ represents the angle spanned by the two electric field vectors and θ ($0 \leq \theta < 2\pi$) denotes the angle between $\mathbf{E}_1$ and a unit vector lying on the plane spanned by these two vectors. The maximal envelope amplitude is achieved along the direction defined by the unit vector at the specific angle θ where the magnitudes of the two terms in (5) become equal.

Based on the modulation depth $A(\mathbf{r})$, an exhaustive search optimization was conducted. To maximize the modulation depth in the target while minimizing the modulation depth in the neocortical regions, we employed the peak ratio (PR) as the objective function [25]. This metric is defined as the ratio of the peak modulation depth in the target ROI to the peak modulation depth in the neocortical regions, expressed as

$$\text{PR} = \frac{T}{C}, \quad (6)$$

where T and C denote the maximal modulation depths in the target ROI and the neocortical regions, respectively. A constraint of $T \geq 0.2$ V/m was imposed, consistent with previous findings that electric fields above this intensity are sufficient to induce phase-entrainment resonance [44], [45]. All possible two-pair electrode configurations derived from a pool of N candidate electrodes ($N = 57$ for Full ES) were evaluated. For each configuration, the amplitudes of the injection currents α and β were set to a fixed total (summed) intensity of 2 mA, with α varying from 0.5 to 1.5 mA with a step size of 0.05 mA [25]. This total current intensity has been confirmed to be safe in a human TI stimulation study [46]. Consequently, considering three possible pairing configurations for any four selected electrodes, the total number of combinations M in the exhaustive search was calculated as follows:

$$M = \left(\frac{N}{4}\right) \times 3 \times 21, \quad (7)$$

where N is the number of candidate electrodes. The constant 3 denotes the number of ways to pair four electrodes into two channels, and 21 denotes the number of injection current combinations. In the case of Full ES ($N = 57$), this resulted in a total of 24,885,630 combinations. Among the feasible solutions satisfying this constraint, the combination of the electrode configuration and injection currents that maximized the objective function was selected as the optimal stimulation parameter set.

C. Assessment of Cross-Subject Parameter Transferability

To investigate the necessity of individualized parameter optimization of TI stimulation, we evaluated the stimulation

efficacy by cross-applying the optimal TI parameters across different head models. The optimal stimulation parameter sets obtained from Full ES for all 40 head models were used for this analysis (see Fig. S1 – 3 for the individual electrode configurations and injection currents determined by Full ES optimization). For each head model, the spatial distribution of the modulation depth $A(\mathbf{r})$ was calculated by applying the optimized electrode configurations and injection currents derived from each of the other 39 models. The PR value was computed for each cross-application instance. This process was repeated for all 40 head models.

We calculated the normalized PR (nPR) values as the ratio of the cross-applied PR to the individual benchmark PR, which corresponded to the value obtained with the subject-specific optimized parameters. This normalization scaled the individual benchmark to 1, thereby removing inter-individual differences in the absolute PR values. This enabled a relative assessment of the performance degradation due to cross-subject parameter transfer. The nPR values were visualized using a heatmap to illustrate the impact of anatomical variability on TI stimulation efficacy. A filtered heatmap was generated to identify the cross-subject applications that maintained acceptable performance. Two performance maintenance criteria were applied: (i) the maximum modulation depth in the target ROI was at least 0.2 V/m, and (ii) the nPR was at least 0.9. Criterion (i) corresponded to the minimum threshold for phase-entrainment resonance [44], [45], whereas criterion (ii) filtered out cases with markedly degraded stimulation focality relative to the subject-specific optimization.

D. Restricted Exhaustive Search Strategy

The key principle of the RES strategy is to identify and retain only the electrodes that consistently contribute to optimal configurations across individuals. For this purpose, the head models were divided into derivation and validation groups (details are provided in Section II-E). Based on the optimal configurations identified from the Full ES results of the derivation group models, the selection count of each electrode was aggregated for each of the three target regions. Using these selection counts, we established the restricted subsets (RSs) of candidate electrodes: the subset selected at least once was defined as RS1, whereas the subset selected at least twice was designated as RS2. More generally, RS_n included only electrodes selected at least n times, resulting in progressively smaller candidate pools as the threshold n increased. To evaluate the trade-off between search space reduction and optimization performance, subsets RS1 through RS6 were generated for each target region. Because two-pair TI stimulation requires at least four electrodes to form two current channels, a candidate pool of exactly four electrodes forces all of them to be used. In this case, the spatial selection of electrodes is fully determined, leaving only the pairing among the four electrodes and the injection current ratio adjustable. As a result, the electrode positions can no longer be optimized, which is the primary objective of the search. While all target regions and cross-validation folds retained more than four candidate electrodes up to RS6, cases with only

four candidate electrodes first appeared at a threshold of seven. Thresholds above six were therefore not considered. RES was performed on the validation group by applying an optimization procedure identical to that described in Section II-B.2, utilizing only the electrodes within the corresponding RS as candidates.

E. Validation Framework and Comparative Analysis

To evaluate the proposed strategy, we employed a 4-fold cross-validation framework using the 40 head models. The dataset was divided into four subsets with equal number of head models. In each fold, three subsets formed the derivation group ($N_{model} = 30$) to establish the RSs described in Section II-D. The remaining subset served as the validation group ($N_{model} = 10$). This procedure ensured that the derivation and validation data remained independent in every fold. Optimization was initially performed on the validation group models using three methods: (i) Full ES, (ii) RES using RS1 (RES-RS1), and (iii) RES using RS2 (RES-RS2). The performance of these methods was then compared with a cross-subject condition, in which the optimal parameters from the derivation group were directly applied to the validation models. To account for inter-individual differences in the absolute magnitude of PR values, the nPR was employed as the comparative performance metric. Full ES, RES-RS1, and RES-RS2 conditions each yielded 40 outcome measures (one per validation model across the four folds). The cross-subject condition generated 1,200 outcomes by applying 30 optimal parameter sets from the derivation models to 10 validation models within each fold. Computation time was also evaluated and compared for the three optimization conditions.

We extended the comparative analysis to investigate the trade-off between search space reduction and optimization performance. The impact of reducing the number of candidate electrodes (N) on the nPR values was quantified across RES utilizing subsets RS1–RS6. A non-inferiority test was conducted to statistically determine whether the optimization performance of RES remained within an acceptable range compared with that of Full ES (details provided in Section II-F). The optimization procedures were implemented using in-house scripts written in Fortran 90 that were originally developed in our previous studies [25], [26]. To ensure a consistent experimental environment, all computations were executed on a computer with an Intel i9-13900F CPU.

F. Statistical Analysis

A non-inferiority test was conducted for each target ROI to identify the most compact candidate subset that maintained acceptable optimization performance compared with Full ES. Because the nPR values did not follow a normal distribution for most conditions (Shapiro–Wilk test, $p < 0.05$), the Wilcoxon signed-rank test was employed [47]. The null hypothesis (H_0) was that the median nPR of a given RES condition was lower than $1 - \delta$, and the alternative hypothesis (H_1) was that it was not lower than this limit ($\alpha = 0.025$, one-sided) [48]. The non-inferiority margin was set to $\delta = 0.03$ (3%). In the absence of a standardized criterion for optimizing TI stimulation, we adopted the rigorous quality

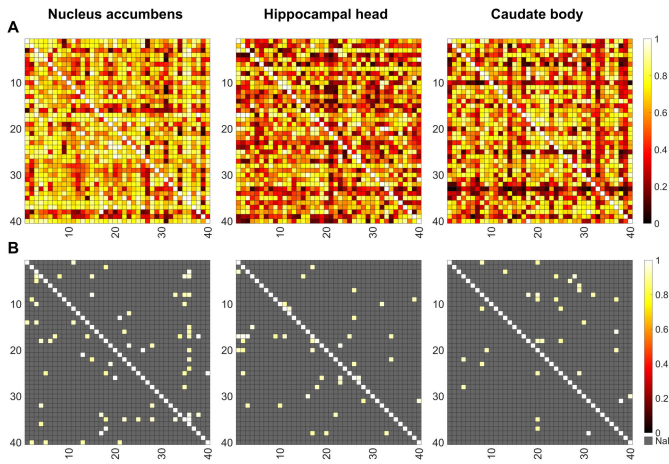


Fig. 2. Heatmaps illustrating the nPR obtained by cross-applying the optimal T1 parameters to different head models. (A) 40×40 heatmaps showing the nPR values for all combinations of the 40 head models. (B) Filtered heatmaps presenting only the cross-application cases that satisfy specific performance criteria: $\text{nPR} \geq 0.9$ and maximum modulation depth within the target ROI ≥ 0.2 V/m. Cases not satisfying these criteria are masked in gray.

assurance tolerances used in dosimetric comparisons (e.g., the 3% dose criterion in radiotherapy) [49]. The tests were conducted from RES-RS1 to RES-RS6 using a fixed-sequence gatekeeping procedure [50], terminating at the first instance where non-inferiority was not established. The statistical tests were performed using MATLAB R2023b (The MathWorks, Inc., Natick, MA, USA).

III. RESULTS

A. Inter-Individual Anatomical Variability in Optimization Performance

Cross-application of optimal stimulation parameters across different head models revealed substantial inter-individual variability in stimulation efficacy (Fig. 2A). While subject-specific optimization (diagonal elements) yielded an nPR of 1.0, the cross-application of optimal stimulation parameters resulted in a marked performance degradation across all three regions. Among the cross-application cases, targeting the NAc yielded the highest mean nPR (0.646), followed by the caudate body (0.569) and the hippocampal head (0.546). Figure 2B presents filtered heatmaps with two performance maintenance criteria: a maximum target modulation depth of at least 0.2 V/m and an nPR of at least 0.9. The proportion of cross-application cases that satisfied both criteria was consistently low, with 4.10% for the NAc, 2.56% for the hippocampal head, and 2.12% for the caudate body, suggesting that subject-specific optimization is necessary to increase stimulation efficacy.

B. Target-Specific Patterns of Electrode Selection

Figure 3 shows the spatial distribution of the electrode selection counts obtained from a representative derivation group, along with the configuration of the RSs established based on these patterns. When targeting the NAc, the selected electrodes were predominantly concentrated in the lateral frontal regions

owing to its anterior location (Fig. 3A). For the hippocampal head, the distribution was concentrated in the lower regions owing to its inferior anatomical position (Fig. 3B). In contrast, the selection patterns for the caudate body exhibited less distinct spatial characteristics than those for the other regions (Fig. 3C). Based on these patterns, the defined RSs were visualized in 3D space. RS1 (Fig. 3D–F) served as a conservative subset, retaining a relatively broad search space. For RS2 (Fig. 3G–I), the selection count threshold was increased to further shorten the optimization time, yielding a smaller number of candidate electrodes. Figure 3D–I also shows that the number of electrodes in RS1 and RS2 increased in the following order: NAc, hippocampal head, and caudate body.

C. Performance and Efficiency of RES

To evaluate optimization accuracy, we compared the nPR distributions of RES-RS1, RES-RS2, and the cross-subject condition against the Full ES baseline (Fig. 4A). Notably, for the NAc, both RES-RS1 and RES-RS2 achieved a median nPR of 1.0, indicating that these methods successfully identified the same optimal parameter sets as Full ES in more than half of the subjects. Furthermore, RES-RS1 and RES-RS2 yielded highly concentrated nPR distributions with similar 25th percentiles (0.989 and 0.985, respectively). This result demonstrates that the optimal electrodes selected by Full ES were predominantly contained in the refined RS2. Nevertheless, the lowest nPR among all targets was observed in the NAc. Even in this case, the nPR (0.864 under RES-RS2) remained higher than the 75th percentile of the cross-subject condition (0.797). Consistent with the high performance observed in the NAc, RES-RS1 maintained a median nPR of 1.0 for both the hippocampal head and caudate body. Targeting the caudate body using RES-RS2 yielded the lowest median value (0.976) across all targets, but the performance drop remained marginal, being less than a 2.5% reduction compared with Full ES. The cross-subject condition showed substantially lower nPR values and higher variability than RES-RS1 and RES-RS2 across all three target regions. Although rare instances where the nPR values exceeded 1.0 were observed (one case each for the NAc and the hippocampal head), these did not reflect effective stimulation. Instead, these values resulted from the application of parameter sets that were discarded during optimization owing to insufficient target modulation depth (<0.2 V/m), despite their high PR values.

Figure 4B shows the computation times for each optimization strategy. Given the logarithmic scale shown in Fig. 4B, a substantial reduction in computation time was evident across all targets when RES-RS1 and RES-RS2 were used. This reduction was most prominent in the NAc, which utilized the smallest number of candidate electrodes in both RS1 and RS2. The average computation time dropped from 1.6 h for Full ES to 5.5 min for RES-RS1, and further to 53.0 s for RES-RS2, representing a reduction of more than 100-fold relative to Full ES. Although the time reduction was the least pronounced in the caudate body, RES-RS2 still achieved an average computation time of 3.2 min, reflecting a nearly 30-fold decrease. In summary, the RES strategy

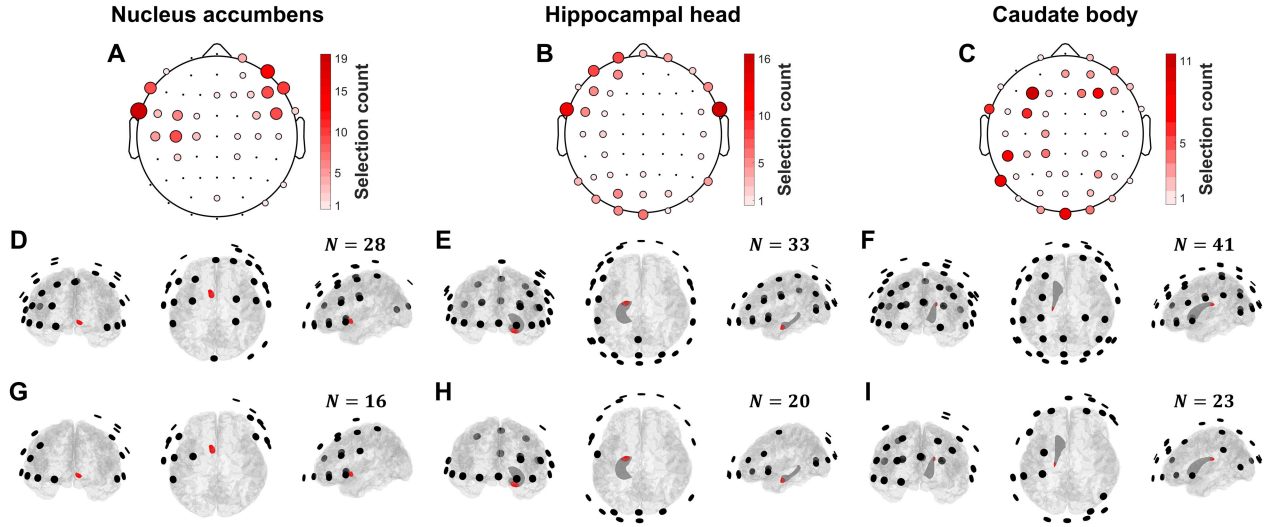


Fig. 3. Spatial distribution of electrode selection counts and configuration of restricted subsets. (A-C) 2D topographic plots illustrating the selection count of each electrode within the derivation group ($N_{\text{model}} = 30$). The color intensity and marker size indicate the number of selections in the optimal electrode pairs (see Table S1 for detailed information). (D-F) 3D visualizations of restricted subset 1 (RS1), comprising candidate electrodes selected at least once. (G-I) 3D visualizations of restricted subset 2 (RS2), comprising candidate electrodes selected at least twice. The black markers represent the electrodes included in each subset, while the red regions indicate the target regions. For each panel, the subplots display the anterior, superior, and left lateral views. N denotes the number of electrodes included in each RS. The results displayed correspond to a representative derivation fold, selected independently for each target region, to best approximate the average distribution.

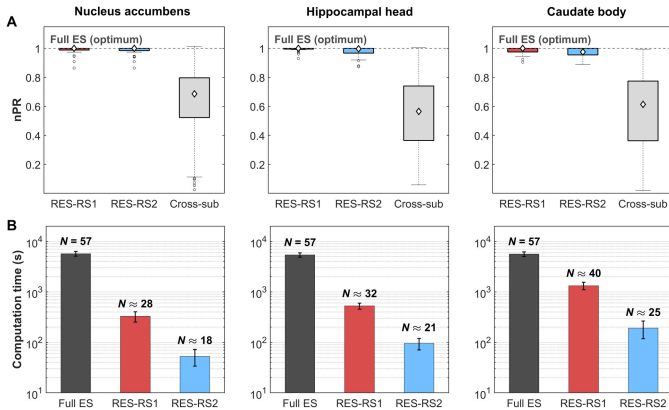


Fig. 4. Evaluation of the RES strategy based on optimization performance and computation time. (A) Boxplots displaying the distribution of nPR values for RES (RES-RS1 and RES-RS2) and the cross-subject condition (Cross-sub) relative to Full ES baseline (dashed line at 1.0). The diamond markers indicate the median values, and the boxes span the interquartile range (IQR). The whiskers extend to the most extreme data points that are not considered outliers. Outliers are depicted as individual circles. (B) Average computation time required for Full ES, RES-RS1, and RES-RS2, presented on a logarithmic scale. The error bars represent the standard deviation. The values annotated above the bars (N) denote the average number of candidate electrodes for each condition, averaged across the four cross-validation folds. The standard deviations of N across folds were 1.3 (RS1) and 1.7 (RS2) for the NAc, 0.8 (RS1) and 1.3 (RS2) for the hippocampal head, and 1.8 (RS1) and 2.2 (RS2) for the caudate body. Full ES used all 57 electrodes in every fold.

consistently maintained optimization accuracy comparable to Full ES across all three target regions, while considerably reducing the computational burden. Among these targets, RES demonstrated the highest optimization accuracy and computational efficiency when targeting the NAc, followed by the hippocampal head and caudate body.

Next, the spatial distributions of the TI modulation depth were compared for a single representative subject across five experimental conditions: Full ES, RES-RS1, RES-RS2,

and two cross-subject conditions (Fig. 5). For the cross-subject conditions, field distributions reflecting the median performance were presented to depict typical outcomes. To illustrate spatial differences, a subject whose RES-RS2 results differed from Full ES across all three targets was selected for visualization. As shown in the field distributions, Full ES, RES-RS1, and RES-RS2 conditions successfully achieved focal stimulation across all targets, with the TI modulation concentrated in the target ROI rather than in the neocortex. The similarity among the three conditions extended beyond the quantitative PR values to the spatial patterns of the generated fields. In contrast, the cross-subject conditions exhibited inferior performance, characterized by either insufficient target modulation or excessive neocortical exposure. For the NAc, both Cross 1 and Cross 2 resulted in insufficient target modulation ($T < 0.2$ V/m). For both the hippocampal head and caudate body, the Cross 1 condition failed to reach the target threshold of the maximum modulation depth (T : 0.159 and 0.136 V/m, respectively). While the Cross 2 condition met the target requirement in both regions, it generated substantial off-target modulation in the neocortex exceeding 0.2 V/m (C : 0.327 and 0.288 V/m, respectively).

Figure 6 illustrates the changes in nPR corresponding to the reduction in the number of electrodes used for optimization. According to the results of the non-inferiority test with a 3% margin, targeting the NAc allowed for the largest search space reduction. Notably, non-inferiority was established even when RS3 was used, which reduced the average number of electrodes to 15. For the hippocampal head, the non-inferiority criterion was met up to RS2. In the case of the caudate body, the criterion was met only up to RS1.

IV. DISCUSSION

In this study, we propose a novel optimization strategy for two-pair TI stimulation to eliminate the primary computational

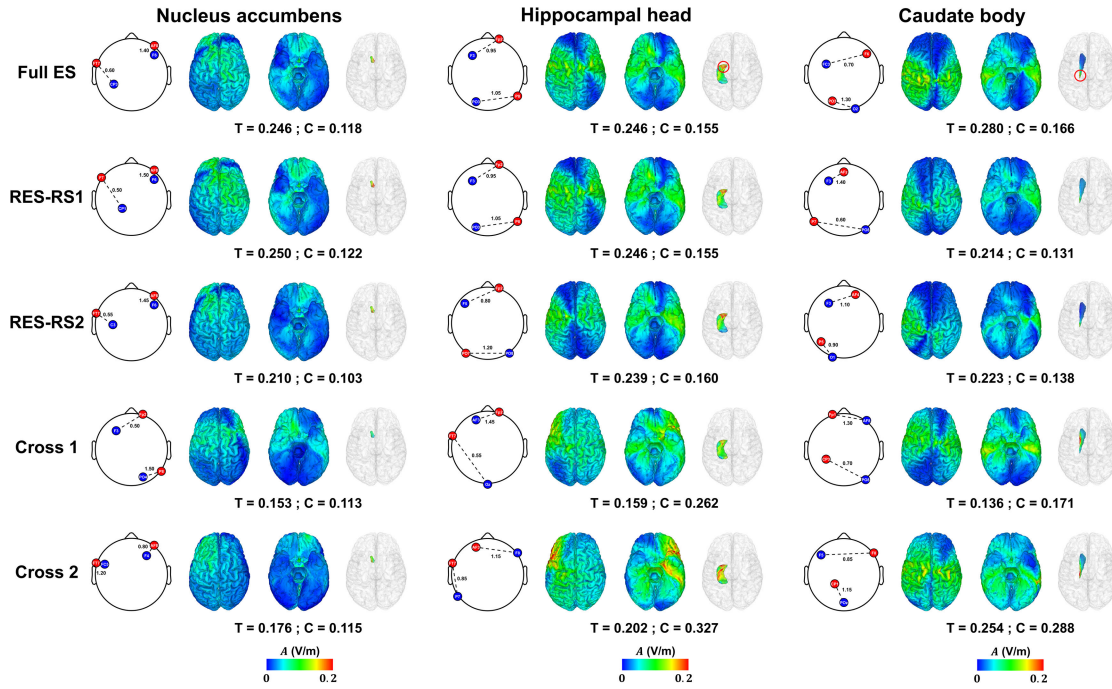


Fig. 5. Distributions of the TI modulation depth in the neocortical and deep target regions for a single subject. Comparisons are presented across five experimental conditions: Full ES, RES-RS1, RES-RS2, and two cross-subject applications (Cross 1 and Cross 2). Cross 1 and Cross 2 display the distributions obtained using parameter sets representing the median performance (ranked 15th and 16th out of 30 derivation models) when applied to this validation subject. For each target region, the first column displays the electrode configuration and injection currents (mA). The two middle columns illustrate the distribution of TI modulation depth in the neocortical regions from the superior and inferior views. The last column visualizes the distribution in the deep target region. The quantitative metrics are listed below each panel. T and C denote the maximum modulation depths in the target ROI and the neocortex, respectively, in units of V/m. The red circles indicate the anatomical location of the target ROIs (the hippocampal head and the caudate body). The nucleus accumbens (NAc) is not circled as the entire structure serves as the target ROI.

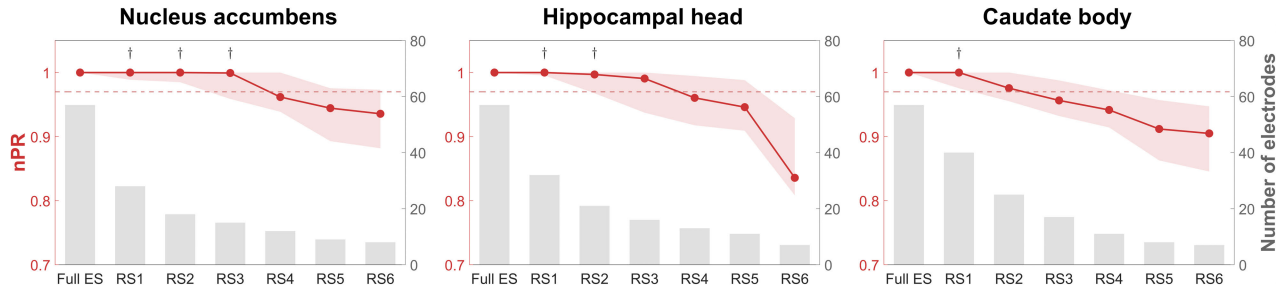


Fig. 6. Parametric analysis of the trade-off between search space reduction and optimization performance. The solid red line with markers represents the median optimization performance (nPR, left axis) for Full ES and RES with sequential RSs, while the shaded region indicates the interquartile range (IQR). The gray bars denote the average search space size (number of candidate electrodes, right axis) across the four folds. The horizontal dashed line represents the pre-defined non-inferiority margin ($\delta = 3\%$). The dagger symbols (†) indicate the conditions under which non-inferiority to Full ES was achieved (one-sided Wilcoxon signed-rank test, $p < 0.025$).

bottleneck in personalized treatment planning. To the best of our knowledge, this is the first study to identify target-specific electrode selection patterns across individuals during ES optimization. By leveraging these patterns to restrict the candidate electrode pool, the RES strategy substantially improves the balance between computational efficiency and optimization accuracy. Since the total number of combinations scales with the fourth power of the number of candidate electrodes (Eq. 7), even a moderate reduction in the candidate pool leads to a considerable decrease in computation time. Specifically, by employing the RS2 subset comprising electrodes selected at least twice across 30 derivation group models, the RES strategy reduced the computation time by a factor of 30–100 depending on the stimulation target. Note that this acceleration was achieved with marginal performance loss. Even for the

caudate body, which showed the largest deviation, the median nPR reduction remained less than 3% relative to Full ES. Our results suggest that the RES strategy serves as a flexible and practical optimization framework applicable to various deep brain targets.

The necessity of such subject-specific optimization is underscored by our analysis of inter-individual variability. Previous computational studies have addressed the influence of individual anatomical characteristics on TI stimulation. Lee et al. [25] first demonstrated that optimal TI parameter sets vary across individuals. Subsequent studies assessed the inter-individual variability in electric field distribution and stimulation efficacy using fixed parameters on a larger cohort [23]. Most recently, Brahma et al. [51] highlighted the need for subject-specific optimization by demonstrating that individually optimized

parameters yielded superior stimulation focality compared with fixed parameter sets. Here, we extended these findings by examining the cross-subject transferability of individually optimized parameters. We derived optimal parameter sets for 40 head models using Full ES and observed a marked reduction in the nPR values when these parameters were applied to different subjects. Under the two performance maintenance criteria, fewer than 5% of the cross-application cases satisfied the conditions across all three targets. We also observed that no single parameter set satisfied the criteria for all head models in any of the three targets. These results demonstrate that the template-based approach commonly adopted in clinical studies of TI stimulation [18], [19], [20] cannot reliably maintain stimulation efficacy, necessitating individualized parameter optimization. In addition, the degree of transferability varied across targets. The proportion of cross-application cases maintaining performance was the highest in the NAc, followed by the hippocampal head and caudate body. This indicates that the impact of inter-individual variability on stimulation efficacy is target-dependent.

This target dependency was consistently observed in the RES optimization results. Although the RES strategy generally demonstrated stable performance across all three targets, the degrees of optimization accuracy and efficiency varied. As shown in Fig. 6, optimizations for the NAc and hippocampal head were not inferior to that for Full ES, even with substantially reduced candidate subsets (RS3 and RS2, respectively). In contrast, the caudate body was less tolerant of search space reduction. Optimization for this target required the most conservative threshold (RS1) and longer computation times, along with a slight reduction in nPR values. We attribute these target-dependent performance variations primarily to the spatial distribution of the optimal electrodes, as detailed in Section III-B (Fig. 3). The distinctive anatomical locations of the NAc and hippocampal head resulted in electrode selection concentrated in the lateral frontal and lower regions, respectively (Fig. 3A–B). These selection patterns formed compact RSs that efficiently covered the optimal solutions for most individuals. However, the caudate body is located in the deep central region, at a similar distance from many scalp electrodes. This position allows diverse electrode configurations to achieve comparable stimulation focality. As a result, even minor inter-individual anatomical variations can alter the optimal electrode pairs in Full ES. This variability led to less spatially concentrated selection patterns (Fig. 3C) with an increased number of electrodes in the RSs. Despite the larger candidate pool, the RSs for the caudate body were less likely to encompass subject-specific optimal electrodes, which account for the lower nPR compared with the other two targets. We further examined whether this target dependency was driven by inter-individual spatial variability across targets. To investigate this hypothesis, we registered the cortical surfaces to the fsaverage template in FreeSurfer [52] and quantified the spatial variability of each target. As shown in Fig. S4 in the Supplementary Materials, the spatial variability was comparable across all three targets with no statistically significant differences. This finding confirms that the observed target dependency is driven by the inherent spatial characteristics

of the targets themselves, rather than by the inter-individual variations in their anatomical coordinates. Consequently, we propose a target-adaptive approach by employing aggressive search space reduction for targets with distinct spatial characteristics, while adopting more conservative thresholds for deep central structures.

Compared with existing optimization approaches, the RES strategy offers a practical advantage by combining computational efficiency with the reliability of ES. For instance, a previous study employing a hybrid approach combining genetic algorithms and multi-objective particle swarm optimization [28] reported a computation time of 16.7 min using 27 particles. In such stochastic frameworks, a trade-off exists where increasing the number of particles reduces the risk of becoming trapped in local optima but inevitably prolongs the computation time. Moreover, these methods do not ensure consistent reproducibility in repeated trials. By contrast, RES retains the deterministic nature of an exhaustive search within a reduced search space. This enables the reproducible identification of solutions near the global optimum within a substantially shorter optimization time (approximately 1–3 min using RES-RS2). Other learning-based approaches [29], [30] achieve rapid optimization but also do not guarantee the global optimum, exhibiting sensitivity to initialization and hyperparameter settings. These methods have predominantly been investigated in the optimization of multi-channel TI stimulation, where ES is computationally infeasible. For two-pair TI stimulation, we propose that the target-specific RES strategy serves as a highly effective solution. In practice, this framework enables a straightforward clinical workflow. Target-specific RSs are first derived offline from a large set of head models for each ROI. For a new patient, RES is then performed using only the subset matched to the target ROI, achieving optimization substantially faster than Full ES.

The RES strategy can also be combined with other emerging optimization approaches. Recently, leadfield-free optimization has been proposed [53], which searches for optimal electrode placements by continuously adjusting their positions on the scalp surface. This approach has the potential to identify more optimal electrode positions than methods constrained by a predefined electrode system. However, it is prone to convergence at local minima, depending on the initial electrode positions. A multi-start approach is employed to mitigate this issue at the cost of increased computation time. Because the RES strategy can rapidly identify near-optimal electrode configurations, it may provide suitable initial positions for such leadfield-free approaches, potentially reducing the need for multi-start procedures.

Although the RES strategy provides an effective approach for optimizing two-pair TI stimulation, some limitations remain that outline important directions for future studies. First, the validation in this study relied on head models derived from a homogeneous cohort of elderly female subjects. This cohort selection was appropriate to validate the feasibility of the proposed strategy. However, a previous study has demonstrated distinct modulation depth distributions across different ages and sexes even under identical TI stimulation conditions [54]. The same study also revealed that specific anatomical

features, such as WM-to-head volume ratio, exert a more direct influence on stimulation outcomes than demographic labels alone. Therefore, extending the validation to diverse demographic groups characterized by these anatomical features is necessary to establish the generalizability of the framework. Specifically, future studies will aim to classify a larger cohort of head models based on these anatomical features, thereby deriving specialized RSs for each subgroup. We anticipate that employing an RS matched to the specific anatomical characteristics of each subject will further refine optimization accuracy. In addition, patients with atypical head anatomy could be screened in advance and assigned a more conservative subset with a lower selection count threshold. Such patients are more likely to have optimal electrodes outside a compact subset. The conservative subset therefore helps maintain optimization accuracy. Although computation time would increase for these cases, it would remain substantially lower than that of Full ES, as even the most conservative subset in our study (RS1) achieved a marked reduction relative to Full ES. Second, the anisotropic electrical conductivity of brain tissues was not considered in our simulation. Previous studies have indicated that WM anisotropy can alter the current flow reaching deep brain structures, despite having negligible effects in neocortical regions [55], [56]. Accordingly, a study utilizing anisotropic head models for parameter optimization in TI stimulation has emerged [30]. Future research should investigate how the RSs generated from anisotropic models differ from those derived from isotropic models. Moreover, validating whether anisotropic optimization leads to improvements in the stimulation efficacy through in vivo human experiments would be a promising research direction. Finally, this study was limited to three target ROIs. Applying the RES strategy to a broader range of deep brain targets and determining the optimal candidate subset size for each target remain important next steps. To ensure clinical viability, deep brain structures should be subdivided into detailed anatomical subregions (e.g., the hippocampal head, body, and tail) with pre-computed RSs generated for each subregion. Our future work will focus on constructing a comprehensive RS dictionary corresponding to these detailed subregions to enable the rapid selection of target-specific candidate electrodes. Addressing these limitations would enable the application of the RES framework across a wider range of clinical conditions with improved optimization accuracy.

Beyond addressing these limitations, future work may also incorporate artificial intelligence techniques to further enhance the proposed framework. In the current approach, a fixed RS is predefined for each target and applied uniformly across subjects. A learning-based model could instead analyze an individual's MRI to recommend a subject- and target-specific candidate subset, including its size and constituent electrodes. Such individualized subsets could improve optimization accuracy beyond that of a fixed subset. As a more ambitious direction, learning-based models might predict optimal stimulation parameters directly from MRI data, reducing the reliance on exhaustive search. The feasibility of such generalized models is supported by the present finding that optimal electrode selection patterns are largely consistent across individuals. At

the same time, the target-dependent nature of this consistency would need to be taken into account in their development. Collectively, these data-driven extensions could provide a practical path toward fully automated and personalized treatment planning for TI stimulation.

V. CONCLUSION

In conclusion, this study proposed a target-specific RES strategy that enables rapid and reliable optimization of two-pair transcranial TI stimulation parameters. By constraining the search space based on empirically derived electrode selection patterns, RES substantially reduces the computational burden while ensuring reproducible and near-optimal solutions. The degree of this search space reduction can be adaptively adjusted based on the spatial characteristics of each stimulation target, thereby providing flexibility across diverse clinical applications. This framework represents a meaningful step toward bridging the gap between computational optimization and clinical practice in personalized TI stimulation.

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