A Watershed Algorithm GUI for Personalized fMRI-guided rTMS Target

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Abstract

The FDA approved personalized resting-state functional connectivity for precise target localization in rTMS. However, objective methods for pinpointing optimal connectivity clusters have remained limited. This study proposed a watershed-based approach with a graphical user interface, offering threshold-independent segmentation that outperformed traditional threshold-based methods. Demonstrated in the context of Alzheimer's disease, this approach enabled precise targeting within the default mode network, specifically the posterior cingulate cortex and inferior parietal lobule. By facilitating more accurate and individualized localization, this method holds promise for refining the precision of personalized rTMS treatment.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique increasingly used for the treatment of various neuropsychiatric disorders. One of the most crucial factors influencing the efficacy of rTMS is the selection of the stimulation target [1]. Precise localization of stimulation targets based on functional magnetic resonance imaging (fMRI) is emerging as a promising approach for individualized targeting [2]. Both functional connectivity (FC) [3-5] and effective connectivity [6] of resting-state fMRI (RS-fMRI) have shown effective therapeutic potential in enhancing rTMS outcomes. Additionally, task-based activation is being investigated for its ability to identify functionally relevant targets [7].

The process of identifying individualized, FC-guided superficial stimulation targets typically involves multiple steps. Previous studies have delineated the

superficial cortical target identified through FC analysis as the "stimulation target" and the deeper, associated region as the "effective region" [4, 8]. In the context of depression [8-10], the procedure begins by localizing a deep brain region, such as the subgenual anterior cingulate cortex (sgACC), using RS-fMRI data from a cohort of healthy individuals. Subsequently, FC analysis is employed to identify a group-level cluster in the superficial cortex. From this cluster, the peak FC is determined for each individual and selected as the cortical stimulation target. However, this conventional approach has several limitations. Firstly, threshold sensitivity can impact the size of the group-level target mask, resulting in increased spatial variability across individualized targets. Secondly, inter-individual heterogeneity can result in deviations of individualized clusters from the group-level mask, leading to poor alignment within predefined group-level boundaries. Lastly, the presence of multiple peaks in close proximity complicates individualized target identification, making it challenging to determine the most appropriate stimulation target.

To address these challenges, the watershed algorithm [11] offers a compelling alternative. This algorithm conceptualizes an image as a topographic surface, where pixel intensity represents height. By simulating the progressive flooding of this surface, the algorithm identifies watershed lines that delineate catchment basins, effectively segmenting the image into discrete functional regions. Unlike conventional threshold-dependent methods, the watershed approach is inherently robust, enabling more reliable boundary delineation and targeted region of interest (ROI) definition for subsequent analysis.

Moreover, RS-fMRI and positron emission tomography (PET) have revealed significant abnormalities in the default mode network (DMN), particularly spanning the posterior cingulate cortex (PCC) to the precuneus regions [12, 13]. In Alzheimer's disease, rTMS targeting the inferior parietal lobule (IPL) within the DMN has shown short-term cognitive benefits [14]. Given that DMN connectivity appears to play a crucial role in mediating rTMS effects, improved DMN-targeting methods could enhance therapeutic outcomes [15]. In this study, we propose a novel approach that leverages the watershed algorithm for fMRI-guided rTMS target selection, supported by a graphical user interface (GUI) pipeline designed to streamline clinical implementation. The primary objective of this approach is to enhance the accessibility of personalized rTMS treatments by providing a more robust and individualized method for target selection.

2. Materials and Methods

Exemplar Implementation Demonstration

In this study, we demonstrated a pipeline for selecting rTMS targets for Alzheimer's disease, guided by RS-fMRI FC Data from healthy participants served as an illustrative case, while the pipeline is currently being applied to Alzheimer’s patients in registered studies at Chictr.org.cn (ChiCTR2400086141 and ChiCTR2400087497). In our approach, the PCC was selected as the effective region and the IPL as the stimulation target, focusing on their roles as key nodes within the default mode network, as defined by Yeo et al. (2011) [16]. The workflow of the study is illustrated in Fig. 1.

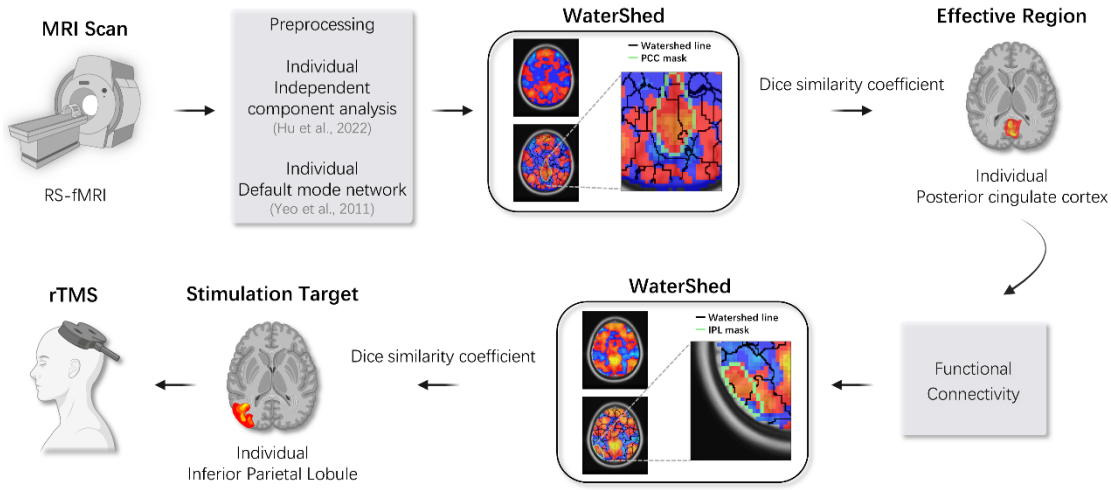

Fig. 1 Workflow for Personalized rTMS Target Identification Based on RS-fMRI.

Following data acquisition and preprocessing, independent component analysis (ICA) identifies each individual's default mode network (DMN). Watershed segmentation is then applied to define both the effective region and stimulation target. The effective region is determined as the peak within the cluster showing the highest Dice similarity between the PCC and individual watershed clusters within the DMN. PCC seed-based functional connectivity analysis is subsequently conducted to locate a stimulation target within the inferior parietal lobule (IPL). The final individualized stimulation target for rTMS is defined by the peak within the IPL cluster that shows the highest Dice similarity to individual watershed clusters within the DMN.

Datasets

This study utilized datasets from previous research [17], which are freely accessible via NITRC (https://www.nitrc.org/projects/reliability). These datasets were collected with approval from the Ethics Committee of the Center for Cognition and Brain Disorders (CCBD) at Hangzhou Normal University (HZNU). RS-fMRI and 3D-T1 data were obtained from 21 healthy participants (mean age: 21.8 ± 1.8 years; 11 females), all of whom had no history of neurological, psychiatric, or neuropsychological disorders. Written informed consent was obtained from each participant prior to their

inclusion in the study.

Preprocessing of RS-fMRI

The preprocessing pipeline for RS-fMRI data included the following steps: slice timing correction, motion correction, spatial normalization to the standard Montreal Neurological Institute (MNI) space, and spatial smoothing. For identifying the stimulation target, additional preprocessing steps were performed after spatial normalization, including the regression of head motion, white matter (WM), and cerebrospinal fluid (CSF) signals, as well as the removal of linear trends.

Identification of the Effective Region

Individual independent component analysis

Individual independent component analysis (ICA) identifies functional networks by analyzing the temporal synchronization of spontaneous brain activity across various regions. This individualized ICA approach facilitates a more personalized mapping of brain function [18]. The peak coordinates identified by ICA have demonstrated robust test-retest reliability [18]. In this study, ICA was applied to extract subject-specific components associated with the DMN to determine the effective region.

Watershed Algorithm for the Posterior Cingulate Cortex

We employed the Fernand Meyer watershed algorithm for the functional image segmentation [11]. In this approach, voxel values are interpreted as terrain elevations, with lower values corresponding to valleys and higher values corresponding to peaks. The algorithm simulates a flooding process where water floods from the valleys until it encounters adjacent regions. The points at which different waters meet form "watershed

line," which effectively delineate boundaries between distinct regions, even in the presence of noise [19].

The Dice similarity coefficient (DSC) was employed to quantify the overlap between watershed-derived clusters and the target templates across participants. By selecting the cluster with the highest DSC value, we identified personalized targets that best aligned with the desired reference region. The detailed The DSC equation is given as follows [20]:

$$\mathrm{DSC} = \frac{2|\mathrm{A} \cap \mathrm{B}|}{|\mathrm{A}| + |\mathrm{B}|}$$

Where A is the set of voxels in the watershed cluster, and B is the set of voxels in the reference region.

Identification of the Stimulation Target

To identify the stimulation target, functional connectivity analysis was conducted using seed-based correlation. The peak coordinate of the individualized effective region was designated as the seed center. A spherical ROI with a radius of 5 mm was defined around the seed to generate functional connectivity maps. Watershed segmentation was subsequently applied to the resulting functional connectivity map, and DSC was calculated to evaluate the spatial overlap between clusters and the predefined stimulation target region. The cluster with the highest DSC was selected, and its peak coordinate was designated as the stimulation target.

3. Results

Multi-Peak Distribution in Target Selection

Fig. 2 illustrates the comparison between watershed-based and threshold-based

methods for selecting the effective region and stimulation target in two participants, specifically addressing challenges associated with multi-peak distributions. Watershed segmentation was applied to individual DMN maps to delineate relevant clusters. In the upper panel of Fig. 2, the first row shows the effective region identified by the watershed-based method, while the second row displays the cluster containing the peak point identified by the traditional threshold-based approach. The watershed segmentation method demonstrated a stronger alignment with our predefined PCC template, achieving a higher Dice Similarity Coefficient (DSC = 0.50) compared to the threshold-based method (DSC = 0.15).

For the stimulation target, watershed segmentation was similarly applied to individual FC maps to delineate relevant clusters. In the lower panel of Fig. 2, the first row represents the results from the watershed-based approach, while the second row displays the cluster containing the peak point identified by the traditional threshold-based method. The watershed-based method achieved a closer match with our predefined IPL boundaries, with a DSC of 0.45, compared to the threshold-based method, which yielded a DSC of 0.16.

Individualized Target Shift from Predefined Boundaries in Target Selection

The watershed segmentation method enables the identification of optimal targets even when individual clusters do not perfectly align with predefined boundaries. Fig. 3 illustrates a case in which the peak connectivity of one participant was offset from the predefined IPL boundaries by a single voxel. Despite this slight shift, the cluster containing this peak demonstrated a high degree of overlap with the predefined IPL

region, achieving a Dice Similarity Coefficient (DSC) of 0.29.

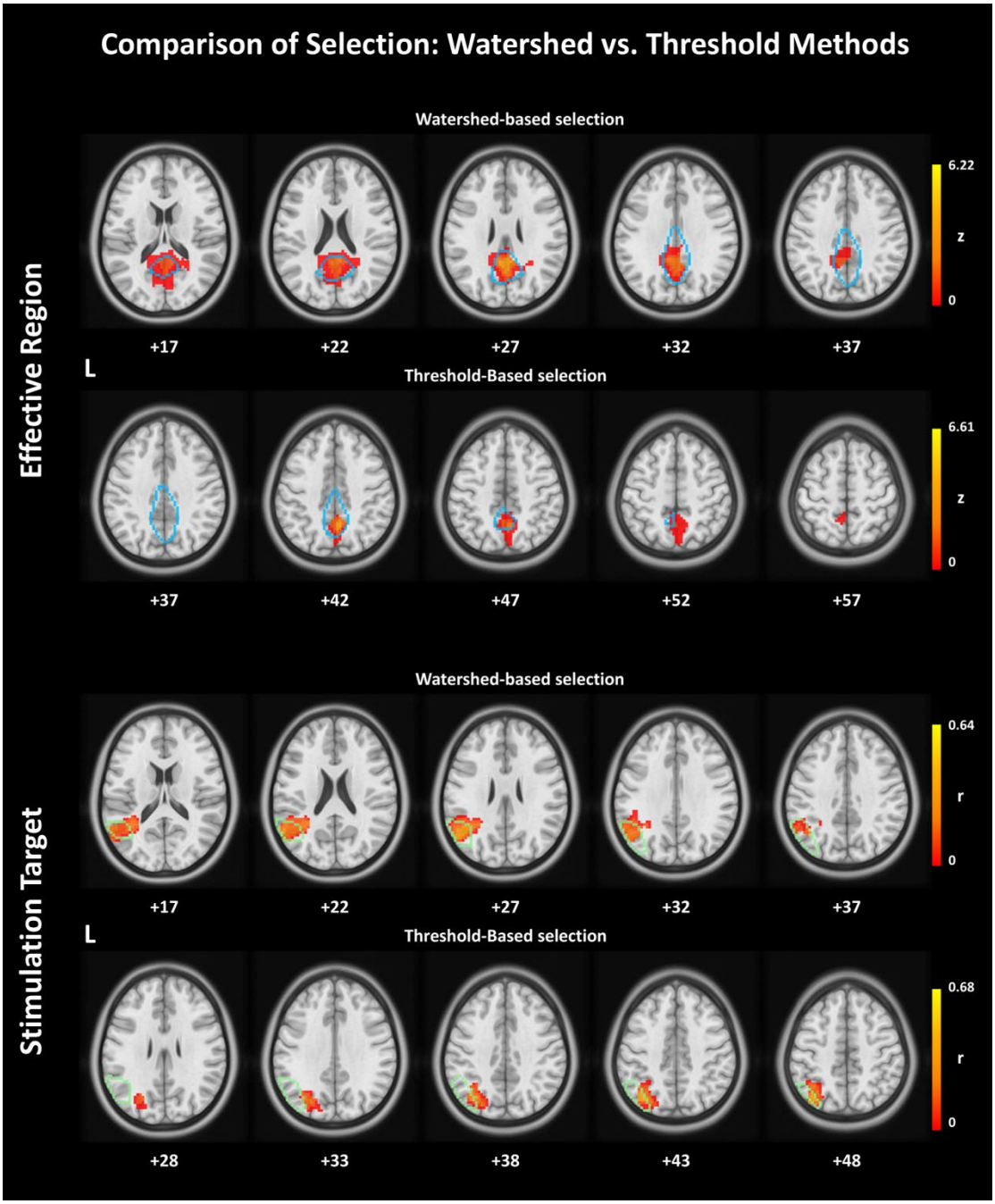

Fig. 2 Comparison of Watershed-Based and Threshold-Based Methods for Effective Region and Stimulation Target Selection.

The upper panel compares the effective regions identified by watershed-based and threshold-based selection methods. The lower panel illustrates the differences in stimulation target selection between these two methods. Blue regions denote the boundaries of the posterior cingulate cortex (PCC), while green regions indicate the boundaries of the inferior parietal lobule (IPL). The watershed-based approach, especially in the presence of closely spaced peaks, allows for precise individualized selection, thereby reducing the risk of including neighboring clusters that marginally extend into the target region, ultimately improving targeting accuracy. L: left.

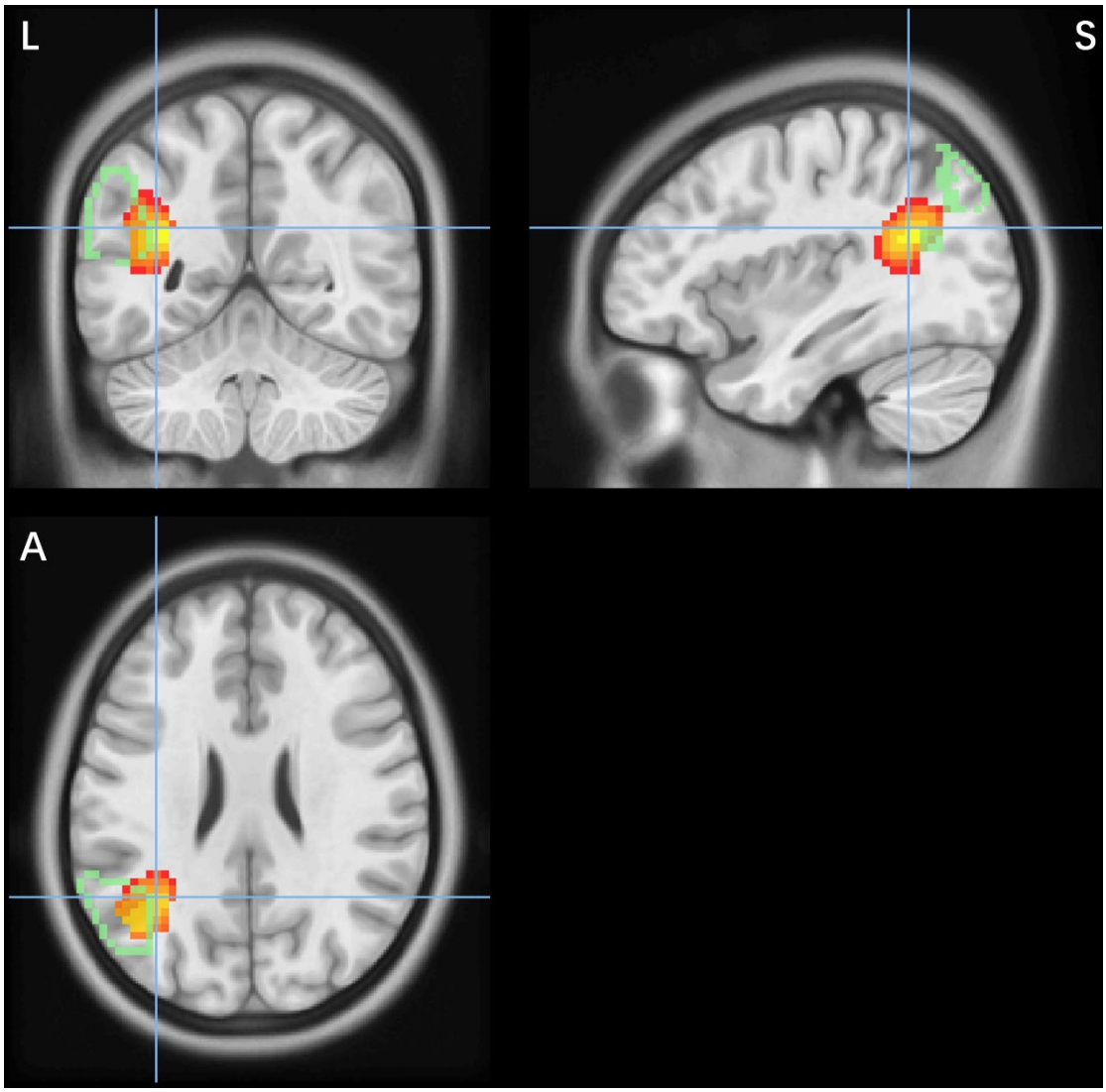

Fig. 3 Individualized Target Shift Relative to Predefined Boundaries

Coronal, sagittal, and axial views illustrating the individualized displacement of stimulation targets from predefined boundaries within the inferior parietal lobule (IPL) for a representative subject. Red regions represent the stimulation target cluster identified via the watershed method, with the crosshair indicating the peak value as the designated stimulation target. Green denotes the predefined IPL boundaries. A: anterior, S: superior, L: left.

4. Discussion

This study introduces a novel method for personalized target localization in rTMS, utilizing watershed segmentation of fMRI data. By applying the watershed algorithm to functional images and leveraging the Dice similarity coefficient, our method accurately identifies regions that optimally align with the desired target area, representing a significant advancement in precision targeting.

Our approach offers several key advantages over traditional threshold-dependent techniques:

1) Multi-Peak Distribution in Target Selection. The watershed algorithm effectively segments functional images into distinct regions by treating image intensity as the altitude of a terrain, thereby clearly delineating boundaries between different functional clusters. This methodology allows for a more nuanced identification of optimal clusters without relying on subjective threshold settings. This is particularly advantageous in scenarios where clusters are challenging to differentiate or exhibit sub-peak values (Fig. 2).

2) Individualized Target Shift from Predefined Boundaries. Our method identifies optimal targets even when individual clusters do not completely align with predefined

boundaries (Fig. 3). This adaptability is essential for accounting for individual variability, particularly when group-level boundaries derived from healthy populations may not be directly applicable to specific clinical populations. By considering these individual differences, our method provides a more tailored approach to target selection, thereby enhancing precision.

To enhance clinical accessibility, all watershed computation steps were integrated into the GUI of the RESTplus toolkit [21]. We developed a GUI pipeline that enables users without specialized coding or neuroimaging expertise to apply this method. The GUI facilitates one-click watershed segmentation by allowing users to input preprocessed individual fMRI data and specify the target region template (Fig. S1). Additionally, It could provide the watershed cluster with the highest Dice coefficient and a complete list of Dice coefficients for all clusters. This streamlined, user-friendly interface significantly reduces the complexity of personalized target identification for rTMS, promoting broader adoption in clinical settings.

Individual variability remains a critical challenge in TMS target localization [2, 22], particularly among clinical populations [1, 2]. For example, in post-stroke patients, motor activation during tasks such as finger tapping often shifts due to compensatory neuroplasticity, resulting in peak activation that may not correspond to traditional motor areas [23]. Consequently, multiple peak clusters may arise within a target region, or clusters may extend beyond expected boundaries. To address these challenges, the watershed algorithm can be used to segment functional activation maps, thereby accurately preserving functional regions even when clusters extend beyond expected

boundaries. Unlike conventional threshold-based methods that are unable to objectively identify sub-peak cluster boundaries or ignore clusters extending beyond predefined regions, the watershed algorithm offers a clear advantage by precisely delineating functional clusters, ensuring both accuracy in target identification and adaptability to individual variability. Although the demonstration of our method primarily utilized RS-fMRI, the approach and GUI are equally applicable to task fMRI data.

The inherent limitations of TMS, including its shallow stimulation depth [24] and the potential for side effects [25, 26] such as headaches, discomfort, or muscle twitching, complicate the determination of optimal stimulation targets. Direct stimulation of peak activation or peak functional connectivity regions is often impractical due to these side effects, and selecting sub-peak regions, which often belong to the same cluster or are located nearby, may not effectively mitigate the side effects mentioned above.

Our approach mitigates these issues by providing a ranked list of clusters based on Dice coefficients, thereby offering clinicians a range of potential targets that can be balanced for both efficacy and tolerability. This flexibility enhances clinical decision-making, allowing for more individualized, safer, and more effective target localization that maximizes patient comfort and improves therapeutic outcomes.

In summary, we have developed a watershed-based approach for guiding personalized rTMS target localization and designed a corresponding GUI toolbox. This GUI-driven pipeline lowers the barrier for clinical implementation by enabling clinicians without specialized neuroimaging expertise to effectively apply individualized neuromodulation strategies. Our method sets the stage for broader

adoption of personalized rTMS interventions, enhancing accessibility and allowing for more tailored treatment approaches.

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7. Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

8. **Data availability**

The dataset analyzed in the current study had been shared on https://www.nitrc.org/projects/reliability/.

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