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Reliability of targeting methods in TMS for depression: Beam F3 vs. 5.5 cm

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A B S T R A C T

Background: No consensus exists in the clinical transcranial magnetic stimulation (TMS) field as to the best method for targeting the left dorsolateral prefrontal cortex (DLPFC) for depression treatment. Two common targeting methods are the Beam F3 method and the 5.5 cm rule.

Objective: Evaluate the anatomical reliability of technician-identified DLPFC targets and obtain consensus average brain and scalp MNI152 coordinates**.**

Methods: Three trained TMS technicians performed repeated targeting using both the Beam F3 method and 5.5 cm rule in ten healthy subjects ($n = 162$). Average target locations were plotted on 7T structural MRIs to compare inter- and intra-rater reliability, respectively.

Results: **(1)** Beam F3 inter- and intra-rater reliability was superior to 5.5 cm targeting ($p = 0.0005$ and 0.0035). **(2)** The average Beam F3 location was 2.6±1.0 cm anterolateral to the 5.5 cm method.

Conclusions: Beam F3 targeting demonstrates greater precision and reliability than the 5.5 cm method and identifies a different anatomical target.

Dear editor

Repetitive transcranial magnetic stimulation (TMS) is an effective treatment for major depressive disorder when targeted at the left prefrontal cortex [1]. The optimal cortical target within the left prefrontal cortex is controversial and, to date, lacks standardization ([1–3]). Two targeting methods have become mainstream options for clinicians - the 5.5 cm rule and the Beam F3 method ([4,5]). Beam F3 targeting accounts for head size and shape, whereas most of the early clinical trials were conducted with the 5.5 cm rule ([4–6]). Neither targeting method requires neuroimaging for target localization, but both potentially sacrifice precision and reproducibility due to some degree of error inherent in using scalp targeting methods ([7,8]).

Minimizing spurious variability in identifying the treatment target is important for consistency. To our knowledge, this study is the first to compare the reproducibility of identifying the Beam F3 and the 5.5 cm target, evaluating both differences between technicians and the consistency of individual technicians with repeated measures. We establish data-driven average brain and scalp coordinates for these targets based on our results and relate these to other coordinates proposed in the literature.

Ten healthy subjects, ages 20 to 44 (average age 31.0, six male and four female), participated in the study. Subjects obtained T1-weighted 7T MRI brain scans within 30 days of participation. Images were loaded into Brainsight (Rogue Research, Montreal, Quebec) for neuronavigation-based measurements.

Three trained TMS technicians performed repeated scalp measurements on each subject at three time points over the course of 1 month, with at least 24 hours separating measurement sessions ($n = 162$ total measurements, 81 at each scalp target). The Beam F3 and 5.5 cm rule target were measured using standard measurement procedures ([1,4]). The Beam F3 method incorporated the adjustments recommended by Mir-Moghtadaei et al. ([2]). Points were then registered on each subject's MRI using Brainsight.

Distances between the targets as identified by the two methods were measured both on the scalp directly and using Brainsight tools. The anatomical images and associated target coordinates were warped into a common anatomical space (MNI152) and analyzed with Freesurfer. We first evaluated reliability between the Beam F3 method and the 5.5 cm rule. We separately evaluated inter-rater reliability relative to a group-averaged target coordinate and intra-rater reliability relative to a technician-specific average target coordinate. Generalized linear mixed models were used to test for differences in distance between targeting methods with random effects for subject and technician. We also calculated the average MNI152 coordinates from each method, with cortical targets represented by the coordinate on the pial surface closest to the scalp, identified using Freesurfer. Additional details of the targeting methods, imaging processing, and statistical analysis are available in Supplemental Appendix A.

Fig. 1A shows the spatial distribution of all Beam F3 (red) and 5.5 cm (green) measurements as well as group mean centroids (black) displayed on an MNI152 composite scalp; Beam F3 targets were on average more anterolateral than 5.5 cm rule targets. The gross

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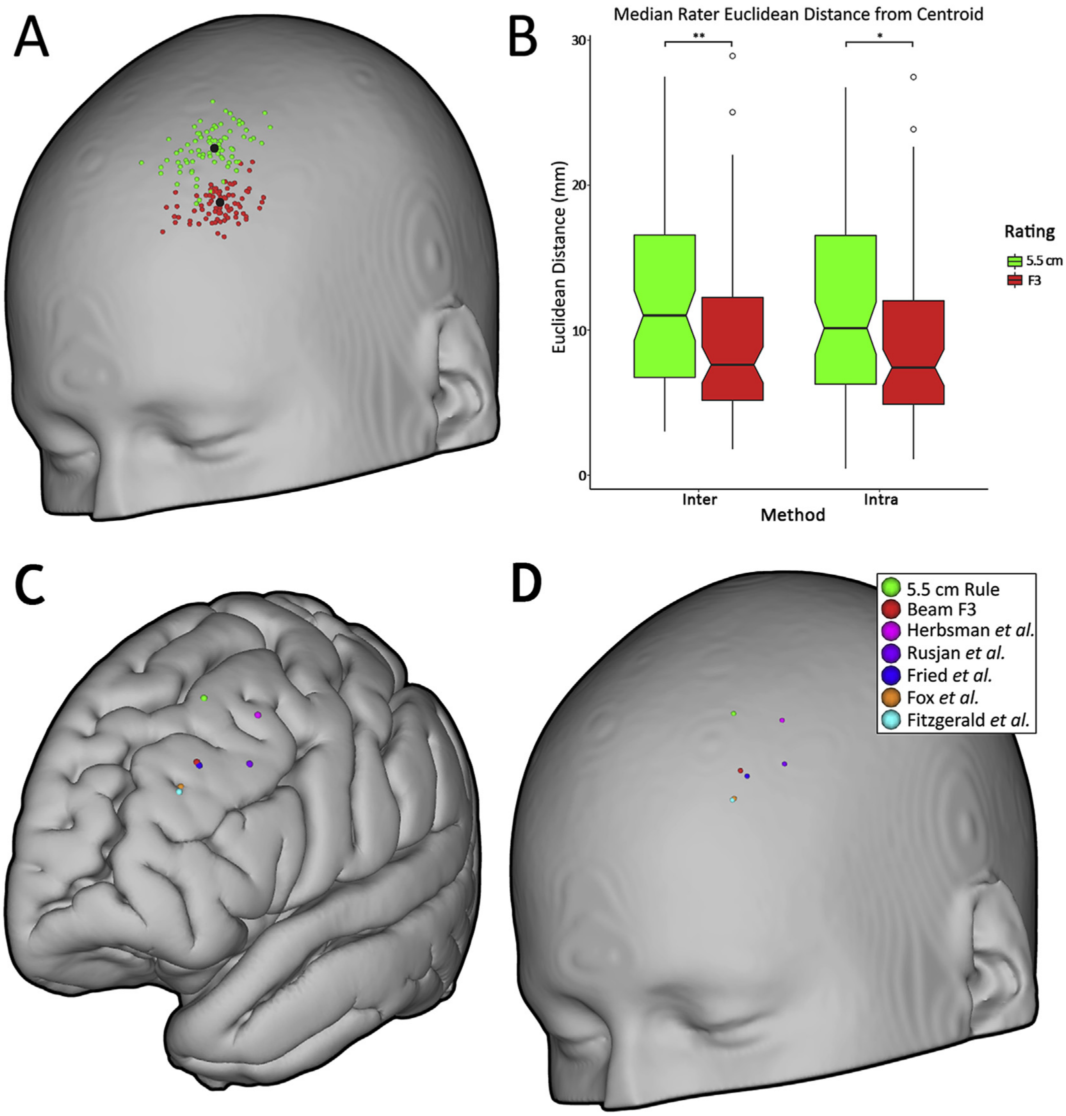

Fig. 1. Comparing targeting reliability between Beam F3 method and 5.5 cm rule techniques (A,B) and comparing the group mean centroids to other published transcranial magnetic stimulation targets (C,D). (A) Scatter plot of all 162 technician measurements plotted on an MNI composite scalp for Beam F3 (red) and 5.5 cm rule (green). The black circles demonstrate the group average centroids for each targeting method. (B) Box and whisker plot showing the inter-rater and intra-rater reliability between methods, represented by the median distance from each individual measure to the group average centroid. The horizontal black lines on each plot represent the median Euclidean distance for each measurement method, and the colored boxes represent the interquartile range. The whiskers represent the maximum and minimum values as defined by the extension of the upper or lower quartile value by 1.5 times the interquartile range. Outliers denoted as open circles. The Beam F3 technique demonstrated less variability both within and across technicians (*p = 0.0035, **p = 0.0005). (C,D) Variability in DLPFC coordinates depicted on the cortical surface (C) and the scalp surface (D). In addition to the 5.5 cm rule (green) and Beam F3 (red) group centroids derived from this study, we also show a dorsolateral prefrontal cortex target associated with antidepressant response as published in Herbsman et al. ([11], magenta)^; a prefrontal cortex target proposed based on Brodmann areas and working memory task activation in Rusjan et al. ([12], purple)^; a target activated by working memory tasks on functional MRI in Fried et al. ([13], blue)^; a prefrontal target anti-correlated with the subgenual cingulate cortex based on group average resting-state functional connectivity MRI in Fox et al. ([14], orange)^; and a stimulation target proposed for neuronavigated TMS in Fitzgerald et al. ([15], cyan)^. All targets are plotted on MNI152 atlas cortical and scalp surfaces. Our Beam F3 target most closely approximates with the Fried et al. [13] dorsolateral prefrontal cortex target. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

mean distance between an F3 target and a 5.5 cm rule target was 2.60 cm (s d. = 1.01 cm) (Fig. 1B).

The average Euclidean distance from each individual target to the group average centroid on the scalp was 28.3% smaller for Beam F3 targeting as compared to 5.5 cm rule targeting (0.95±0.61 vs. 1.22±0.66 cm, p = 0.0005), suggesting greater precision targeting the Beam F3 site. When looking at results within each individual technician's personally determined centroid (thus measuring how reliably a technician could return to their personally-determined average target session to session), the increased precision with Beam F3 targeting held true – average distance from target to technician-specific centroid was 25.8% smaller for Beam F3 targeting (0.93±0.62 vs. 1.17±0.68 cm, p = 0.0035). A similar analysis using median instead of mean values demonstrates the same findings (Fig. 1B).

Average coordinates are displayed in Fig. 1. The Beam F3 brain MNI152 coordinate was [-40.6, 41.7, 34.3] and scalp coordinate was [-49.3, 48.7, 41.0]. The 5.5 cm rule average brain coordinate was [-33.6, 30.8, 51.1] and scalp coordinate was [-42.0, 38.5, 60.0]. For comparison, Fig. 1C and 1D show our targets compared to previously published DLPFC targets. Some published coordinates required adjustment to a pial or scalp surface coordinate for visualization purposes – original coordinates, coordinates transformed into MNI space (as shown in Fig. 1C and 1D) and references are listed in Supplemental Tables 1 & 2

The first major finding in this study is that Beam F3 targeting enhances precision and reproducible stimulation site identification, both for an individual technician across time and across technicians trying to reliably navigate to the same point.

The second finding is that the Beam F3 and 5.5 cm rule techniques lead to significantly different brain targets, with Beam F3 usually lying more anterolateral than the 5.5 cm rule target. On the Yeo et al. (2011) 17-network cortical parcellation atlas derived from functional connectivity measures, the Beam F3 coordinate lands on a node of the salience or ventral attention network, whereas the 5.5 cm coordinate lands on a node of the frontoparietal control network ([9,10]).

An important contribution from this study is the generation of standardized average Beam F3 and 5.5 cm rule coordinates in MNI152 space, both on the cortical and scalp surfaces. These coordinates can serve as reference points for future research.

Taken together, our findings suggest that the Beam F3 method allows for improved inter- and intra-rater reliability and precision compared to the 5.5 cm rule and identifies a target more than 2 cm anterolateral to the 5.5 cm target. While the Beam F3 method has a higher level of precision and reproducibility compared to the 5.5 cm rule, evidence tying the Beam F3 method to greater treatment efficacy is limited. Comparative efficacy trials of the different targeting methods are needed to guide clinical recommendations.

Declaration of competing interest

There are no conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

CRediT authorship contribution statement

Nicholas T. Trapp: Writing - original draft, Conceptualization, Investigation, Formal analysis, Visualization. **Joel Bruss:** Visualization, Formal analysis, Software, Writing - review & editing, Data curation. **Marcie King Johnson:** Writing - review & editing, Investigation. **Brandt D. Uitermarkt:** Writing - review & editing, Investigation, Conceptualization, Visualization. **Laren Garrett:** Writing - review & editing, Validation, Data curation. **Amanda Heinzerling:** Writing - review & editing, Validation, Data curation. **Chaorong Wu:** Formal analysis, Methodology. **Timothy R. Koscik:** Software, Data curation, Writing - review & editing. **Patrick Ten Eyck:** Formal analysis, Methodology, Writing - review & editing. **Aaron D. Boes:** Conceptualization, Writing - review & editing, Supervision, Resources.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.01.010.

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