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Title: Robotically Delivered fMRI-Guided Personalized Transcranial Magnetic Stimulation Therapy for Treatment-Resistant Depression

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Author Questionnaire

- 1. Microscopy:** Does your protocol require the use of a dissecting or stereomicroscope for performing a complex dissection, microinjection technique, or something similar? **No**
- 2. Software:** Does the part of your protocol being filmed include step-by-step descriptions of software usage? **Yes**
- 3. Filming location:** Will the filming need to take place in multiple locations? **No**
- 4. Testimonials (optional):** Would you be open to filming two short testimonial statements **live during your JoVE shoot**? These will **not appear in your JoVE video** but may be used in JoVE's promotional materials. **No**

Current Protocol Length

Number of Steps: 33

Number of Shots: 51

Introduction

Videographer: Obtain headshots for all authors available at the filming location.

Authors: Please note that **the questions will not appear on screen**. Please answer in **stand-alone full sentence with sufficient context**

INTRODUCTION:

~~REQUIRED: Summarize your research focus and the main questions it aims to answer.~~

- 1.1. **Bjorn Burgher**: This protocol demonstrates the workflow of fMRI-guided, robotically delivered, personalized TMS for depression.
 - 1.1.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera.

~~Describe the research gap or limitation in existing methods and how this protocol addresses them.~~

- 1.2. **Bjorn Burgher**: fMRI-guided TMS addresses the accuracy and precision problems associated with standard scalp-based targeting.
 - 1.2.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera.

CONCLUSION:

~~What does this protocol allow researchers to study or measure?~~

- 1.3. **Bjorn Burgher**: This protocol demonstrates the feasibility of using functional connectivity to personalize the treatment target in TMS for depression.
 - 1.3.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera.

~~Describe the most important consideration or challenge when performing this protocol.~~

- 1.4. **Bjorn Burgher**: The protocol requires substantial resources and specialized expertise, particularly for MRI, imaging analysis, and the use of neuronavigation and robotic systems.

- 1.4.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera.

~~How can future studies build on this work? Describe the questions or research directions that can be investigated next.~~

- 1.5. **Bjorn Burgher**: Future protocols will improve feasibility using technology that integrates neuronavigation, robotics, and imaging workflows.
 - 1.5.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera.

Videographer: Obtain headshots for all authors available at the filming location.

Ethics Title Card

This research has been approved by the local Human Research Ethics Committee

Protocol

Videographer: Please always record an audio slate while filming each shot mentioned in the shotlist.

- Screen patients for MRI safety exclusions (metal implants, claustrophobia, pregnancy)
- Assess baseline symptoms using MADRS, HAM-A, and HADS
- Acquire MRI scans (T1 + resting-state fMRI + field maps) using 3T scanner

Video editor: Please use a title card to show this information.

2. Resting-state Functional Connectivity Analysis

Demonstrators: Olivia Heppell, Bjorn Burgher

2.1. After converting the patient's MRI (*M-R-I*) DICOM (*Di-Com*) files into NIFTI (*Nifti*) format and performing RSFC (*R-S-F-C*) analysis [1], identify the standard space brain coordinates located at the center of gravity of the left dorsolateral prefrontal cortex or DLPFC (*D-L-P-F-C*) anti-correlated cluster in x, y, z format [2-TXT]. Then, obtain the standard space DLPFC-SGC (*D-L-P-F-C-S-G-C*) functional connectivity map produced in NIFTI format [3].

2.1.1. WIDE: Talent in front of the computer with patients file showing RFSC analysis.

2.1.2. SCREEN: 70318_screenshot_1.MOV: 00:00-00:20 **TXT: SGC: Subgenual cingulate cortex**

2.1.3. SCREEN: 70318_screenshot_2.MOV: 00:00-00:10. **TXT: NIFTI: Neuroimaging Informatics Technology Initiative**

2.2. Identify the standard space brain coordinate corresponding to the right abductor pollicis brevis motor area to approximate the target for resting motor threshold or RMT (*R-M-T*) testing [1].

2.2.1. SCREEN: 70318_screenshot_3.MOV: 00:00-00:06

2.3. Warp the DLPFC and M1 coordinates and DLPFC-SGC functional connectivity map from standard space to the patient's native space using transforms generated by the initial preprocessing pipeline prepared earlier [1].

2.3.1. SCREEN: 70318_screenshot_4.MOV: 00:00-00:10

2.4. Provide the psychiatrist performing the TMS targeting with the native space brain coordinates for DLPFC and M1 and DLPFC-SGC functional connectivity map [1].

2.4.1. Talent shows the native space brain coordinates and connectivity map to the

psychiatrist.

3. Preparation for Neuronavigation

3.1. To navigate to the storage location of the patient's native T1w (*T-One-W*) images, click **File** and select **New Session** in the neuronavigation [1]. Create a session folder and select either **DICOM (.dcm)** or **nifti (.nii)** (*Di-Com-D-C-M or NIFTI-N-I-I*), depending on the storage format of the T1w images [3].

3.1.1. SCREEN: 70318_screenshot_5.mp4: 00:04-00:10

3.1.2. SCREEN: 70318_screenshot_6.mp4: 00:00-00:10, 00:13-00:15

3.2. Adjust the surface threshold on the scalp on the T1w image using the Adjust Surface Threshold option located in the menu bar in the neuronavigation software [1].

3.2.1. SCREEN: 70318_screenshot_7.mp4: 00:04-00:17

3.3. Using the Adjust Scalp Threshold option, adjust the scalp surface threshold to inflate or deflate [1]. Ensure minimization of epidural space or scalp overinflation from the scalp surface definition [2].

3.3.1. SCREEN: 70318_screenshot_8.mp4: 00:03-00:18

3.3.2. SCREEN: 70318_screenshot_9.mp4: 00:17-00:30

3.4. To segment brain tissues from non-brain tissues, using the brain segmentation option, select a **large white matter tract** and click **Calculate** so the software determines relative contrast values of brain and non-brain tissue [1]. Then, check that the defined brain surface adequately aligns with the grey matter surface [2].

3.4.1. SCREEN: 70318_screenshot_10.mp4: 00:04-00:23.

3.4.2. SCREEN: 70318_screenshot_11.mp4: 00:05-00:20

3.5. Now, using the Patient Registration option, predefine anatomical landmarks [1]. Mark the nasion, right tragus, and left tragus onto the patient's native-space T1w image in preparation for coregistration with the patient's actual scalp landmarks [2].

3.5.1. SCREEN: 70318_screenshot_12.mp4: 00:03-00:10

3.5.2. SCREEN: 70318_screenshot_13.mp4: 00:10-00:46

3.6. Next, enter the native-space DLPFC target and the M1 coordinates in x, y, z format using right-anterior-superior orientation with the planning option in the menu bar [1].

3.6.1. SCREEN: 70318_screenshot_14.mp4: 00:03-00:25, 00:33-00:52 *Video editor: Please speed it up*

3.7. Reposition the DLPFC target to the nearest gyrus if it falls within a sulcus [1]. To verify that the repositioned brain coordinate remains within the selected anti-correlated cluster, overlay the native space DLPFC-SGC functional connectivity map onto the patient's native space T1w image [2] and enter the coordinates of the repositioned

brain target in the MRI visualization software [3].

3.7.1. SCREEN: 70318_screenshot_15.mp4: 00:24-00:33

3.7.2. SCREEN: 70318_screenshot_16.MOV: 00:07-00:30

3.7.3. SCREEN: 70318_screenshot_17.MOV: 00:07-00:23

3.8. Reposition the M1 coordinate to the precentral gyrus if necessary [1].

3.8.1. SCREEN: 70318_screenshot_18.mp4: 00:13-00:25

3.9. Calculate the perpendicular entry points of the TMS coil on the scalp for the DLPFC and M1 coordinates [1]. Ensure the approach angle of the TMS coil relative to the left side of the head is set to 45 degrees during calculation of the entry point [2].

3.9.1. SCREEN: 70318_screenshot_19.mp4: 00:03-00:20

3.9.2. SCREEN: 70318_screenshot_20.mp4: 00:05-00:28

3.10. Overlay a 6 by 4 entry or target grid spaced at 5 by 5 millimeter intervals in the entry or target option in the control area to create additional targets for RMT testing [1].

3.10.1. SCREEN: 70318_screenshot_21.mp4: 00:04-00:20

4. Preparation of the Robotic Arm Workflow

4.1. Once the patient is seated in a motorized treatment chair with a neck rest, recline the patient and raise the legs to a comfortable position [1-TXT].

4.1.1. Talent reclining the chair and raising the patient's legs to a comfortable position.
TXT: Ensure the neck rest adequately supports the head and neck

4.2. Using a headband or double-sided tape, fix the patient reference tracker to the patient's right forehead [1]. Position the patient's head using the motorized chair so that it is within the visual field of the neuronavigation camera [2].

4.2.1. Talent attaching the patient reference tracker to the patient's right forehead using a headband or double-sided tape.

4.2.2. Talent adjusting the motorized chair to position the patient's head within the visual field of the neuronavigation camera.

4.3. Then, return to the patient registration option in the menu bar to coregister the patient's anatomical landmarks and scalp surface to the predefined anatomical landmarks and scalp surface on the T1w image [1]. Touch the pointer to the patient's actual scalp landmarks and acquire each landmark by pressing the **Green** button on the foot or hand switch [2].

4.3.1. SCREEN: 70318_screenshot_22.mp4: 00:05-00:20

- 4.3.2. Talent touching the pointer to the patient's scalp landmarks and pressing the green button on the foot or hand switch to acquire each landmark.
- 4.4. Touch the pointer to the scalp and gently run it across the patient's scalp to acquire 300 scalp landmarks while pressing the green button on the foot or hand switch [1].
 - 4.4.1. Talent moving the pointer across the patient's scalp while pressing the green button to acquire multiple scalp landmarks.
- 4.5. Check the spatial alignment accuracy between the actual and predefined anatomical landmarks and scalp surface at the end of the patient registration procedure, reported as root mean square deviation in millimeters [1-TXT].
 - 4.5.1. SCREEN: 70318_screenshot_23.mp4: 00:00-end **TXT: Ensure RMS < 3 mm; Repeat steps if needed**
- 4.6. Reposition the cobot so the patient reference tracker is at an optimal distance and angle within the visual field of the neuronavigation camera [1]. Ensure the visual field of the neuronavigation camera can also detect one of the cobot reference points [2]. Check the visual field by selecting **Check Tracking System** in the menu bar [3].
 - 4.6.1. WIDE: Talent adjusting the cobot to reposition for optimal tracking by the neuronavigation camera. **NOTE: 4.6.1 and 4.6.2 are filmed in a single shot**
 - 4.6.2. Shot showing the neuronavigation camera view including both the patient reference tracker and a cobot reference point.
 - 4.6.3. SCREEN: 70318_screenshot_24.mp4: 00:04-00:15 **TXT: Purple crosshairs indicate visible reference points**
- 4.7. Enable manual mode in the cobot option in the control area to manually move the coil-mounted robotic arm into the workspace. Click **Move to Park position** in the cobot option panel [1] to move the coil into the neutral position [2].
 - 4.7.1. SCREEN: 70318_screenshot_25.mp4: 00:03-00:25
 - 4.7.2. Show the coil moving to the neutral position.
- 4.8. Manually position the cobot or adjust the motorized chair so the coil is directly above the patient's head with a separation of several centimeters [1].
 - 4.8.1. Talent adjusting the cobot or motorized chair to position the coil above the patient's head with a small gap.
- 4.9. Now, calibrate the coil force sensor function in the cobot option within the control area of the neuronavigation software to trigger a sensor pop-up window with four pressure lights [1-TXT]. Place a finger on the coil and gradually increase and then decrease pressure so all four pressure lights turn on and then off in sequence [2].
 - 4.9.1. SCREEN: 70318_screenshot_26.mp4: 00:11-00:43. **TXT: Activate lights left-to-right, then off right-to-left to enable "OK"**

- 4.9.2. Talent pressing on the coil with a finger to sequentially activate and deactivate all four pressure lights.

5. Resting Motor Threshold Testing

- 5.1. Place three electromyograph electrodes connected to the MEP monitor along the ventral length of the right abductor pollicis brevis [1]. Select the **MEP** protocol on the TMS machine and set the sensitivity to 200 microvolts per division [2]. Select **Recall** and then select **Timing** to display the MEP interface [3].
 - 5.1.1. WIDE: Talent placing three electromyograph electrodes along the ventral length of the right abductor pollicis brevis.
 - 5.1.2. Show selection of the motor evoked potential protocol and adjustment of sensitivity to 200 microvolt per division on the transcranial magnetic stimulation machine. **NOTE: 5.1.2 and 5.1.3 were combined into a single filming shot, 5.1.2**
 - 5.1.3. Show selection of Recall and then Timing to display the motor evoked potential interface.
- 5.2. To instruct the coil-mounted robotic arm to move to the first M1 target in the grid, select the target in the entry and target option panel in the control area [1]. Select **Coil Alignment** in the cobot option panel to position the coil on the patient's scalp [2].
 - 5.2.1. SCREEN: 70318_screenshot_27.mp4: 00:04-00:07
 - 5.2.2. SCREEN: 70318_screenshot_27.mp4: 00:07-00:17
- 5.3. Select the stimulator option in the control area of the neuronavigation software and set the initial stimulation intensity to 40 percent in the amplitude option [1]. Click **Single Pulse** to deliver a pulse while moving sequentially to each of the targets in the M1 grid [2-TXT].
 - 5.3.1. SCREEN: 70318_screenshot_28.mp4: 00:08-00:22
 - 5.3.2. SCREEN: 70318_screenshot_29.mp4: 00:39-00:49, 01:59-02:05, 02:18-02:25
TXT: Precise positioning of the TMS coil is not required for motor targets
- 5.4. Increase the stimulation intensity as needed to observe a MEP or visible thumb flexion [1]. Identify the target that produces the strongest MEP along with the largest amplitude flexion of the right thumb, fingers, or wrist [2].
 - 5.4.1. Show increasing stimulation intensity and observing motor evoked potential responses on the electromyography display.
 - 5.4.2. Split view showing motor evoked potential signals on the screen and visible flexion of the patient's right thumb or fingers indicating the optimal target.
- 5.5. Select the **Optimal M1 target** in the entry and target panel and click **Coil Alignment** in the cobot option panel to position the coil on the patient's scalp [1]. Adjust the

stimulation intensity of single pulses at this target at set intervals until the RMT is determined [2]. Identify the RMT as the minimum stimulation intensity required to evoke 5 out of 10 movements with a MEP greater than 50 millivolt on electromyography [3].

- 5.5.1. SCREEN: 70318_screenshot_30.mp4: 00:08-00:24. **TXT: In the Stimulation panel, MEP max [uV] values above 50 indicate a MEP**
- 5.5.2. SCREEN: 70318_screenshot_30.mp4: 00:52-01:07.
- 5.5.3. Show identification of the resting motor threshold based on motor evoked potential responses on electromyography.

6. Delivering Stimulation to the Personalized DLPFC Target

- 6.1. Instruct the patient to close the eyes, relax, and avoid focusing on any specific thought to maintain consistent brain states across fMRI and TMS [1].
 - 6.1.1. Talent instructing the patient to close the eyes and relax in the treatment chair.
- 6.2. Instruct the coil-mounted robotic arm to move to the DLPFC target by selecting the target in the entry and target option panel in the control area [1]. Select **Coil Alignment** in the cobot option panel to position the coil on the patient's scalp [2].
 - 6.2.1. SCREEN: 70318_screenshot_31.mp4: 007-00:11
 - 6.2.2. SCREEN: 70318_screenshot_31.mp4: 00:12-02:23
- 6.3. Select the **Programmed 3 Minute Intermittent Theta Burst Stimulation** protocol in the menu option on the TMS machine [1]. Select **Recall** and then **Timing** to prepare the machine to deliver the 3-minute intermittent theta burst stimulation protocol [2].
 - 6.3.1. Show selection of the programmed 3 minute intermittent theta burst stimulation protocol in the menu. **NOTE: 6.3.1. and 6.3.2 are filmed in a single shots, 6.3.1**
 - 6.3.2. Show selection of Recall and Timing to prepare the stimulation protocol.
- 6.4. Select the **Stimulator** option in the control area and set the stimulation intensity to 80 percent of RMT for the first session, 100 percent for the second session, and 120 percent for subsequent sessions [1]. Click **Start/Stop Trains** (*Start-Or-Stop-Trains*) to deliver the full train of repetitive TMS pulses [2].
 - 6.4.1. SCREEN: 70318_screenshot_32.mp4: 00:14-00:20.
 - 6.4.2. SCREEN: 70318_screenshot_32.mp4: 03:49-04:04 **TXT: Each pulse is indicated in the Stimulation panel.**
- 6.5. Perform left dorsolateral prefrontal cortex stimulation daily for up to 20 to 30 weekday sessions [1].
 - 6.5.1. Talent administering repeated daily transcranial magnetic stimulation sessions to the patient.

Results

7. Results

- 7.1. The study demonstrated an overall response rate of 52% [1] and remission rate of 33% [2].
 - 7.1.1. LAB MEDIA: Figure 1A. *Video editor: Highlight the bar labelled “All” with the number 52 in the response section*
 - 7.1.2. LAB MEDIA: Figure 1A. *Video editor: Highlight the bar labelled “All” with the number 33 in the remission section*
- 7.2. The a priori subgroups showed distinct response [1] and remission rate profiles, indicating lower treatment responsiveness in the subgroups associated with comorbidity and bipolar depression [2].
 - 7.2.1. LAB MEDIA: Figure 1A,B. *Video editor: Show the subgroup response bars for G1, G2, and G3 so the different heights can be compared*
 - 7.2.2. LAB MEDIA: Figure 1A,B. *Video editor: Show the subgroup remission bars for G1, G2, and G3 so the different heights can be compared*
- 7.3. Pre-treatment, the group average functional connectivity of the SGC-DLPFC was minus 0.25 [1].
 - 7.3.1. LAB MEDIA: Figure 2B. *Video editor: Highlight the “Pre” point in the left graph at about -0.25*
- 7.4. In the subset of patients who underwent pre- and post-TMS fMRI, a specific reduction in anti-correlated RSFC was observed from pre-treatment to post-treatment [1], with the negative resting-state functional connectivity approaching 0 [2].
 - 7.4.1. LAB MEDIA: Figure 2B. *Video editor: Highlight the left graph labelled “DLPFC - SGC” and show the line moving upward from “Pre” to “Post”*
 - 7.4.2. LAB MEDIA: Figure 2B. *Video editor: Emphasize that the “Post” point in the left graph is closer to the dashed 0 line than the “Pre” point*

1. DICOM

Pronunciation link: <https://www.merriam-webster.com/dictionary/DICOM>

IPA: /ˈdaɪ,kɑ:m/

Phonetic Spelling: dye·kaam

2. NIFTI
Pronunciation link: <https://www.merriam-webster.com/dictionary/NIFTI>
IPA: /'nɪfti/
Phonetic Spelling: nif·tee
3. RSFC
Pronunciation link: No confirmed link found
IPA: /,ɑːr ɛs ɛf 'siː/
Phonetic Spelling: ar-es-ef·see
4. dorsolateral
Pronunciation link: <https://www.merriam-webster.com/dictionary/dorsolateral>
IPA: /,dɔːr,soʊ'lətərəl/
Phonetic Spelling: dor·soh·lat·uh·ruhl
5. prefrontal
Pronunciation link: <https://www.merriam-webster.com/dictionary/prefrontal>
IPA: /pri:'frʌntəl/
Phonetic Spelling: pree·frun·tuhl
6. cortex
Pronunciation link: <https://www.merriam-webster.com/dictionary/cortex>
IPA: /'kɔːr,tɛks/
Phonetic Spelling: kor·teks
7. anti-correlated
Pronunciation link: <https://www.merriam-webster.com/dictionary/anticorrelated>
IPA: /,æn.taɪ'kɔːrə,lertɪd/
Phonetic Spelling: an·tie·kor·uh·lay·tuhd
8. subgenual
Pronunciation link: <https://www.merriam-webster.com/dictionary/subgenual>
IPA: /sʌb'dʒɛnjuəl/
Phonetic Spelling: sub·jen·yoo·uhl
9. cingulate
Pronunciation link: <https://www.merriam-webster.com/dictionary/cingulate>
IPA: /'sɪŋɡjələt/
Phonetic Spelling: sing·gyuh·luht
10. abductor
Pronunciation link: <https://www.merriam-webster.com/dictionary/abductor>
IPA: /æb'dʌktər/
Phonetic Spelling: ab·duk·ter
11. pollicis
Pronunciation link: <https://www.merriam-webster.com/dictionary/pollicis>
IPA: /'pɔːlɪ,sɪs/

Phonetic Spelling: paal·uh·sis

12. brevis

Pronunciation link: <https://www.merriam-webster.com/dictionary/brevis>

IPA: /'brɛvɪs/

Phonetic Spelling: brev·iss

13. neuronavigation

Pronunciation link: <https://www.merriam-webster.com/dictionary/neuronavigation>

IPA: /,nʊrəˌnævə'geɪʃən/

Phonetic Spelling: nyoo·roh·nav·uh·gay·shuhn

14. epidural

Pronunciation link: <https://www.merriam-webster.com/dictionary/epidural>

IPA: /,ɛpɪ'dʊrəl/

Phonetic Spelling: eh·puh·door·uhl

15. segmentation

Pronunciation link: <https://www.merriam-webster.com/dictionary/segmentation>

IPA: /,sɛgmən'teɪʃən/

Phonetic Spelling: seg·men·tay·shuhn

16. nasion

Pronunciation link: <https://www.merriam-webster.com/dictionary/nasion>

IPA: /'neɪʒiən/

Phonetic Spelling: nay·zee·uhn

17. tragus

Pronunciation link: <https://www.merriam-webster.com/dictionary/tragus>

IPA: /'treɪɡəs/

Phonetic Spelling: tray·guhs

18. coregistration

Pronunciation link: <https://www.merriam-webster.com/dictionary/coregistration>

IPA: /,koʊˌrɛdʒɪ'streɪʃən/

Phonetic Spelling: koh·rej·uh·stray·shuhn

19. sulcus

Pronunciation link: <https://www.merriam-webster.com/dictionary/sulcus>

IPA: /'sʌlkəs/

Phonetic Spelling: sul·kuhs

20. gyrus

Pronunciation link: <https://www.merriam-webster.com/dictionary/gyrus>

IPA: /'dʒaɪrəs/

Phonetic Spelling: jy·ruhs

21. electromyograph

Pronunciation link: <https://www.merriam-webster.com/dictionary/electromyograph>

IPA: /ɪˌlɛktroʊˈmaɪəˌɡræf/

Phonetic Spelling: ih·lek·troh·my·uh·graf

22. evoked

Pronunciation link: <https://www.merriam-webster.com/dictionary/evoked>

IPA: /ɪˈvɒkt/

Phonetic Spelling: ih·vohkt

23. amplitude

Pronunciation link: <https://www.merriam-webster.com/dictionary/amplitude>

IPA: /ˈæmpləˌtuːd/

Phonetic Spelling: am·pluh·tood

24. intermittent

Pronunciation link: <https://www.merriam-webster.com/dictionary/intermittent>

IPA: /ˌɪntərˈmɪtənt/

Phonetic Spelling: in·ter·mit·uhnt

25. theta

Pronunciation link: <https://www.merriam-webster.com/dictionary/theta>

IPA: /ˈθeɪtə/

Phonetic Spelling: thay·tuh

26. remission

Pronunciation link: <https://www.merriam-webster.com/dictionary/remission>

IPA: /rɪˈmɪʃən/

Phonetic Spelling: rih·mish·uhn

27. comorbidity

Pronunciation link: <https://www.merriam-webster.com/dictionary/comorbidity>

IPA: /ˌkoʊmɔːrˈbɪdəti/

Phonetic Spelling: koh·mor·bid·uh·tee

28. bipolar

Pronunciation link: <https://www.merriam-webster.com/dictionary/bipolar>

IPA: /ˌbaɪˈpoʊlər/

Phonetic Spelling: by·poh·ler

29. connectivity

Pronunciation link: <https://www.merriam-webster.com/dictionary/connectivity>

IPA: /kəˌnɛkˈtɪvɪti/

Phonetic Spelling: kuh·nek·tiv·uh·tee