Title: Protocol for Repetitive Transcranial Magnetic Stimulation with Symptom Provocation to Treat Obsessive-Compulsive Disorder

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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? **No**

3. Filming location: Will the filming need to take place in multiple locations? **Yes**

    In the same building (3-5min walking).

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: 36
Number of Shots: 55

Introduction

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

INTRODUCTION:

1.1. **Nelson Descalco:** We developed a protocol to standardize the implementation of the only FDA-cleared treatment with transcranial magnetic stimulation for obsessive-compulsive disorder.

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

1.2. **Goncalo Cotovio:** Main challenges include translating protocols used in research for regulatory clearance into everyday clinical practice and ensuring reproducible and safe delivery across multiple centers.

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

CONCLUSION:

1.3. **Nelson Descalco:** This work fills the gap between regulation and daily clinical practice through a complete, step-by-step clinical protocol for delivering TMS for OCD.

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

1.4. **Silvia Almeida:** This protocol incorporates structured steps to develop and conduct individualized symptom provocation, as has been described in the research leading to clearance of TMS for OCD.

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

1.5. **Albino Oliveira-Maia:** Future research should focus on individualization of treatments, for example, through connectivity-based TMS targeting, expected to improve delivery precision and efficacy.

    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.

NOTE: Not filmed

~~Testimonial Questions (OPTIONAL):~~

~~*Videographer: Please capture all testimonial shots in a wide-angle format with sufficient headspace, as the final videos will be rendered in a 1:1 aspect ratio. Testimonial statements will be presented live by the authors, sharing their spontaneous perspectives.*~~

~~How do you think publishing with JoVE will enhance the visibility and impact of your research?~~

~~1.6.~~ **~~Nelson Descalco, Graduate student, Champalimaud Foundation and NOVA Medical School; Psychiatry resident, Unidade Local de Saúde Almada-Seixal~~**~~: (authors will present their testimonial statements live)~~

~~1.6.1.~~ ~~INTERVIEW: Named Talent says the statement above in an interview-style shot, looking slightly off-camera.~~

~~Can you share a specific success story or benefit you've experienced—or expect to experience—after using or publishing with JoVE? (This could include increased collaborations, citations, funding opportunities, streamlined lab procedures, reduced training time, cost savings in the lab, or improved lab productivity.)~~

~~1.7.~~ **~~Albino J. Oliveira-Maia, Director of Neuropsychiatry, Champalimaud Foundation; Professor of Psychiatry and Neuroscience, NOVA Medical School~~** ~~: (authors will present their testimonial statements live)~~

~~1.7.1.~~ ~~INTERVIEW: Named Talent says the statement above in an interview-style shot, looking slightly off-camera.~~

Ethics Title Card

This protocol is in accordance with the regulatory requirements of FDA clearance for treatment of OCD with rTMS, with procedures performed in compliance with institutional, national, and international guidelines for human welfare. Informed consent is obtained from all participants

Protocol

2. Baseline Psychological Appointment

Demonstrators: Sílvia Almeida and Sofia Marques

2.1. Before treatment, the psychologist assesses the patient to construct the symptom provocation list that will be used during TMS stimulation. When consulting the patient, first explain the rationale and procedure for symptom provocation and clarify any questions the patient may have **[1]**.

    2.1.1. Talent and patient talking and discussing symptom provocation procedure.

2.2. Administer the Yale-Brown Obsessive-Compulsive Scale Second or Y-BOCS-II *(Y-B-O-C-S-Second)* Edition symptom checklist to identify active obsessions and compulsions **[1-TXT]**.

    2.2.1. Talent shows the Y-BOCS-II checklist to the patient. **TXT: Ask for details and examples to understand the primary symptoms**

2.3. Next, create a draft list of primary symptoms, including obsessions, compulsions, and avoidance behaviors **[1]**. Ask the patient to rate each symptom using the visual analog scale and record the scores next to each item **[2]**. Collaboratively discuss and revise any ratings that appear inconsistent **[3]**.

    2.3.1. Talent writing down symptoms on a clipboard or laptop.

    2.3.2. Talent and patient reviewing and adjusting scores through discussion.

2.4. Complete the clinician-rated Y-BOCS-II severity scale based on the previous week using the symptom list and other relevant information regarding the patient's functioning **[1-TXT]**. ~~Use this as the baseline for future comparison following the repetitive transcranial magnetic stimulation cycle **[2]**.~~

    2.4.1. Talent filling in the severity scale while referring to notes and symptom list. **TXT: Use this as the baseline for future comparison**

    2.4.2. ~~Talent highlighting the final score and noting it as a baseline in the patient chart.~~ <mark>**NOTE**: Not filmed, VO moved as on-screen text</mark>

2.5. In collaboration with the patient, construct a symptom hierarchy from the primary symptoms list, selecting the most significant target symptoms for provocation that elicit

moderate distress **[1]**.

    2.5.1.   Talent and patient seated together discussing and organizing the hierarchy on a chart. ==**Author's NOTE:** For 2.5.1 and 2.6.1, reuse takes from A023_01140321_D005.mov-h265.MP4==

2.6.   Create a customized list of internal and external provocation stimuli based on the established hierarchy **[1]**.

    ==2.6.1.==   Talent showing the final provocation list and categorizing items into internal and external types.

3. Pre-treatment Team Briefing
Demonstrators: Sílvia Almeida and João Estrela

3.1.   Provide a concise summary of the patient's clinical history, highlighting the nature and severity of their obsessive-compulsive symptoms **[1]**.

    3.1.1.   Talent showing the patient's chart with emphasis on obsessive-compulsive disorder-related notes.

==**NOTE**: For steps 3.2 and 3.3, reuse footage from A023_01140228_D010.mov-h265.MP4==

3.2.   Review the individualized symptom provocation list, including the specific internal and external provocations that will be used **[1]**. Highlight annotations that indicate which items are especially effective and which should be avoided due to their potential to cause excessive distress **[2]**.

    3.2.1.   Talent reviewing the provocation list, pointing to various internal and external entries.

    3.2.2.   Talent marking or underlining annotations next to high-impact or high-distress items.

3.3.   Provide clinical notes or contextual strategies to facilitate the smooth and effective delivery of provocations **[1-TXT]**.

    3.3.1.   Talent adding side notes or sticky notes to the provocation list with tips and reminders. **TXT: Ensure staff are trained in communication with patients with OCD and anxiety management**

3.4.   Ensure that the psychologist maintains communication with the technician throughout the treatment course. Instruct the technician to thoroughly review and become familiar with the content of the symptom provocation list before starting the first treatment session **[1].**, and to to foster better engagement and adherence **[3]**.

~~3.4.1. Talent briefs the technician and hands over the symptom provocation list.~~

3.4.2. Talent reviewing the provocation list silently, taking notes. **TXT: Use natural, conversational language during provocations**

~~Talent practicing the delivery of provocation items in a natural tone, without reading verbatim from a script.~~ <mark>**NOTE**: Not filmed, VO moved as on-screen text</mark>

4. Initial Transcranial Magnetic Stimulation (TMS) Session

Demonstrators: João Estrela and Sofia Marques

4.1. Explain the treatment rationale for repetitive transcranial magnetic stimulation or rTMS *(R-T-M-S)*, expected sensations during stimulation, and possible side effects to ensure the patient feels comfortable and engaged **[1]**.

    4.1.1. WIDE: Talent seated beside the patient explaining the purpose of the treatment.

4.2. Using a single low-intensity pulse, demonstrate the tapping sensation on the forearm to help the patient anticipate the experience, if necessary **[1]**.

    4.2.1. Talent holding the stimulation coil and delivering a low-intensity pulse to their own forearm while explaining the sensation to the patient.

4.3. Then, place a lycra cap on the patient's head, aligning it with the patient's eyebrows and the apex of the helix on each ear to establish consistent reference points for future sessions **[1]**. Now, provide a pair of earplugs to the patient to reduce auditory discomfort during stimulation **[2]**.

    4.3.1. Talent gently placing the lycra cap on the patient's head and adjusting its position to align with facial and ear landmarks.

    4.3.2. Talent handing over earplugs to the patient.

4.4. To determine the motor hotspot, sit the patient comfortably with legs uncrossed and barefoot with both feet either resting on a cushioned leg support or hanging freely **[1-TXT]**.

    4.4.1. Talent positioning the patient's legs on a cushioned support. **TXT: Keep feet fully visible to observe movement**. <mark>**NOTE**: The author is not sure if this was shot. If not, then use any suitable footage where patient is seated</mark>

4.5. Then, using a measuring tape, trace the mid-sagittal line by measuring the distance from

the nasion at the bridge of the nose to the inion at the raised area on the lower back of the skull **[1]**.

4.5.1. Talent using a measuring tape to measure from the nasion to the inion along the center of the scalp.

4.6. To identify the intertragal line, measure the distance between the left and right tragus, which are the small cartilage nubs in front of each ear canal **[1]**. The intersection of this line with the mid-sagittal line defines the cranial vertex, Cz *(C-Z),* which will serve as the reference point **[2]**.

4.6.1. Talent using a measuring tape to measure across the head from one tragus to the other.

4.6.2. Talent pointing to the intersection point of both lines on the scalp.

4.7. Position the coil just posterior to the Cz, along the midline, with the handle oriented posteriorly and perpendicular to the sagittal plane **[1]**.

4.7.1. Talent positioning the coil on the patient's head just behind the Cz point, aligning the handle as instructed.

4.8. For motor threshold determination, change the stimulator settings to single-pulse mode **[1]**. Deliver initial stimulation pulses at lower intensity to help the patient get used to the tapping sensation and to assess tolerability **[2]**.

4.8.1. Show the stimulation device interface as the talent selects the Single-pulse option.

4.8.2. The low-intensity pulses are being delivered and patient is being observed.

4.9. Set the intensity to 50 percent of maximum stimulator output and deliver single pulses with an interstimulus interval of at least 3 seconds **[1-TXT]**.

4.9.1. Talent adjusting the intensity settings on the stimulator and delivering pulses while timing intervals of at least 3 seconds. **TXT: Increase stimulator output in 5% steps until lower limb response appears**

4.10. Once a motor response is detected, deliver another pulse at the same location to confirm visible dorsiflexion of the foot **[1]**.

4.10.1. Talent delivering a follow-up pulse and visually confirming upward movement of the patient's foot.

4.11. If foot dorsiflexion is confirmed, adjust the coil to identify the site that produces the strongest and most consistent visible contraction, defined as the leg motor hotspot **[1]**.

    4.11.1. Talent adjusting the coil to nearby locations and delivering pulses while monitoring for muscle contraction. **NOTE**: reuse footage from A023_01140034_D024.mov-h265.MP4

4.12. To determine the leg resting motor threshold, mark the anterior edge of the coil on the patient's cap without moving the coil from the identified location to ensure accurate coil placement in future sessions **[1]**.

    4.12.1. Talent carefully holding the coil in place and using a marker to draw along the anterior edge on the cap.

4.13. Gradually decrease the stimulation intensity in small steps to determine the lowest intensity that elicits visible muscle contraction in at least 3 out of 5 consecutive single pulses **[1]**. Record this value as the leg resting motor threshold in the patient's file **[2]**.

    4.13.1. Talent reducing the stimulator intensity in small increments and counting visible contractions.

    4.13.2. Talent documenting the determined threshold value in the patient's file. **NOTE:** reuse footage from A023_01140146_D054.mov-h265.MP4

4.14. To identify the treatment site, using a flexible ruler or measuring tape, locate the treatment site by measuring 4 centimeters anterior to the motor hotspot along the sagittal midline **[1]**. Mark the treatment site clearly on the patient's cap to serve as the coil placement reference for future sessions **[2-TXT]**.

    4.14.1. Talent using a measuring tape to mark a point 4 centimeters in front of the hotspot along the scalp midline.

    4.14.2. Talent marking the treatment site visibly on the lycra cap. **TXT: Treatment site corresponds to anterior cingulate/dorsomedial prefrontal cortex**

4.15. For symptom provocation, start the symptom provocation procedure. This should start with general questions about the patient's day to build rapport and gather contextual cues for guiding the provocations **[1]**.

    4.15.1. Talent conversing with the patient asking open-ended questions about their day.

4.16. Intentionally activate obsessive symptoms rTMS *(R-T-M-S)* to enhance treatment efficacy **[1]**. Aim to provoke a moderate anxiety level, rated between 4 and 7 on a 0 to

10 visual analog scale **[2]**.

4.16.1. WIDE: Talent explaining the concept of symptom provocation to the patient.

4.16.2. CLOSE-UP showing VAS: Talent showing the patient the visual analog scale.

4.17. Instruct patients to refrain from engaging in compulsions or anxiety-reducing behaviors until the session concludes, to maintain distress levels during the rTMS session **[1]**.

4.17.1. Talent briefing the patient to avoid performing any compulsions during the session.

4.18. Use the symptom provocation hierarchy flexibly, starting with less anxiogenic items and gradually progressing toward more distressing provocations **[1-TXT]**. As each provocation is delivered, ask the patient to rate their current anxiety on a visual analog scale from 0 to 10 **[2-TXT]**. If any, stop the patient's compulsive behavior **[3].**

4.18.1. Talent shows an example of an anxiogenic item (e.g., dirty cloth, printed image of a cluttered room). **TXT: Use psychologist's list as a guide, not a script**

4.18.2. Talent presenting the visual analog scale and the patient marking their anxiety level after each provocation. **TXT: Advance hierarchy if anxiety <4 to elicit moderate anxiety before stimulation**

Added shot: Patient performing a washing hands compulsion and talent stopping the compulsive behavior during its execution, following VAS rating.

4.19. Once the patient reports a subjective anxiety level between 4 and 7, proceed immediately with coil placement and initiate the transcranial magnetic stimulation session **[1]**. Record the item from the provocation hierarchy that triggered the desired distress level **[2-TXT]**.

4.19.1. Talent placing the coil on the marked treatment site and preparing the stimulator for activation.

4.19.2. Talent entering into a file the specific provoking item that caused the 4–7 anxiety rating. **TXT: Keep focusing on this item throughout stimulation**

4.20. Start the TMS treatment by setting the treatment protocol on the stimulator to high-frequency stimulation and 100 percent of the leg motor threshold, with 50 trains, totalling 2000 pulses over approximately 18 minutes **[1]**.

4.20.1. Show the stimulator settings interface as the talent selects Frequency: 20 Hz, Intensity: 100% leg motor threshold, and inputs 50 trains, 2 seconds on, 20 seconds off, totaling 2000 pulses and 18-minute duration. **NOTE**: Use footage from A023_01140140_D052.mov-h265.MP4

4.21. Ensure the coil orientation aligns with the previously marked positioning and hold the coil in place using either the mechanical arm of the TMS system or by manual positioning **[1]**.

4.21.1. Talent securing the coil using the mechanical arm or holding it steadily and verifying alignment with the marked orientation on the cap.

4.22. Confirm with the patient that they are comfortable and that the earplugs are properly placed before beginning the session **[1]**. Also, verify that all technicians and individuals present in the room are also wearing hearing protection **[2]**.

4.22.1. Talent checking the patient's posture and comfort level, then inspecting the earplugs to ensure correct placement.

4.22.2. Shot of the individuals in the room wearing hearing protection.

4.23. Inform the patient that the session is about to start. If the patient is unfamiliar with TMS or sensitive to stimulation, use ramping to reduce discomfort during the initial sessions **[1]**.

4.23.1. Talent speaking to the patient with reassurance and notifying them that the session will begin momentarily. **NOTE**: can use A023_01140101_D033.mov-h265.MP4

4.23.2. ~~Talent activating the ramping feature on the stimulator~~.

4.24. After confirming the coil's precise alignment over the treatment site, initiate the treatment protocol in the stimulator **[1-TXT]** while ensuring accurate coil placement throughout the procedure **[2]**.

4.24.1. ~~Talent adjusting and inspecting the coil placement~~.

4.24.2. Show the stimulator interface as the talent initiates the programmed treatment protocol. **TXT: If discomfort is reported, reassure and adjust coil or intensity as needed** **NOTE**: can use A023+01140141_D053.mov-h265.MP4

Added shot: Starting treatment in the TMS stimulator

4.25. Remind the patient to continue thinking about the provoking item to maintain an adequate level of obsessive-compulsive distress during stimulation **[1]**.

4.25.1. Talent gently prompting the patient to stay focused on the distressing thought throughout the session.

4.26. Once stimulation concludes, carefully remove the coil followed by the cap, and instruct the patient to take out their earplugs **[1]**. Instruct the patient to stand up slowly and observe them for any signs of dizziness or imbalance **[2-TXT]**.

4.26.1. Talent removing the coil, then lifting off the cap, and guiding the patient to remove their earplugs.

4.26.2. Talent helping the patient rise from the chair and watching closely for any unsteadiness. **TXT: Ask if any discomfort or side effects occurred during/after session**

Results

5. Results

5.1. This protocol is based on the results of the pivotal randomized clinical trial published by Carmi et al, American Journal of Psychiatry, 2019 that led to regulatory clearance of TMS for OCD. In this clinical trial, at week 6 of treatment, 38.1% of patients in the active treatment group achieved a full response, compared to 11.8% in the sham group **[1],** and 55% of patients in the active group showed a partial response, compared to 28% in the sham group **[2].**

    5.1.1. LAB MEDIA: Figure 1. *Video editor: Highlight the green bar labeled "Full Response" for "Active treatment" and the orange bar labeled "Full Response" for "Sham treatment"*

    5.1.2. LAB MEDIA: Figure 1. *Video editor: Highlight the green bar labeled "Partial Response" for "Active treatment" and the orange bar labeled "Partial Response" for "Sham treatment"*

- **psychologist**
Pronunciation link: https://www.merriam-webster.com/dictionary/psychologist
IPA: /saɪˈkɑ·lə·dʒɪst/
Phonetic Spelling: sy-KAL-uh-jist

- **provocation** (as in "symptom provocation")
Pronunciation link: https://www.merriam-webster.com/dictionary/provocation
IPA: /ˌproʊ·vəˈkeɪ·ʃən/
Phonetic Spelling: pro-voh-KAY-shun

- **Obsessive-Compulsive** (from "Obsessive-Compulsive Disorder / Scale")

  - **Obsessive**: https://www.merriam-webster.com/dictionary/obsessive
  IPA: /əbˈsɛs·ɪv/ → uh-SESS-iv
  - **Compulsive**: https://www.merriam-webster.com/dictionary/compulsive
  IPA: /kəmˈpʌl·sɪv/ → kuhm-PUL-siv

- **checklist**
Pronunciation link: https://www.merriam-webster.com/dictionary/checklist
IPA: /ˈtʃɛkˌlɪst/
Phonetic Spelling: CHECK-list

- **baseline**
Pronunciation link: https://www.merriam-webster.com/dictionary/baseline
IPA: /ˈbeɪsˌlaɪn/
Phonetic Spelling: BAYSE-lyn

- **hierarchy**
Pronunciation link: https://www.merriam-webster.com/dictionary/hierarchy
IPA: /ˈhaɪ·əˌrɑr·ki/
Phonetic Spelling: HY-uh-RAR-kee

- **transcranial** (as in "transcranial magnetic stimulation")
Pronunciation link: https://www.merriam-webster.com/medical/transcranial merriam-webster.com+1
IPA: /ˌtræn·zkrəˈni·əl/
Phonetic Spelling: tran-skruh-NEE-uhl

- **magnetic** (as in "magnetic stimulation")
Pronunciation link: https://www.merriam-webster.com/dictionary/magnetic
IPA: /mægˈnɛt·ɪk/
Phonetic Spelling: mag-NET-ik

- **stimulation**
Pronunciation link: https://www.merriam-webster.com/dictionary/stimulation
IPA: /ˌstɪm·yəˈleɪ·ʃən/
Phonetic Spelling: stim-yoo-LAY-shun

- **nasion** *(anatomical landmark on skull)*
Pronunciation link: No confirmed link found on Merriam-Webster.
IPA (approximate): /ˈneɪ·zi·ən/
Phonetic Spelling: NAY-zee-uhn

- **inion** *(anatomical skull landmark)*
Pronunciation link: No confirmed link found on Merriam-Webster.
IPA (approximate): /ˈɪn·i·ən/ or /ˈɪn·jən/
Phonetic Spelling: IN-ee-uhn

- **tragus** *(ear cartilage in front of ear canal)*
Pronunciation link: https://dictionary.cambridge.org/pronunciation/english/tragus Cambridge Dictionary+1
IPA: /ˈtreɪ·gəs/
Phonetic Spelling: TRAY-guhs

- **cranial** (as in "cranial vertex / skull")
Pronunciation link: https://www.merriam-webster.com/dictionary/cranial

IPA: /ˈkreɪ·ni·əl/
Phonetic Spelling: KRAY-nee-uhl

- **vertex** (as in "cranial vertex, Cz")
Pronunciation link: https://www.merriam-webster.com/dictionary/vertex
IPA: /ˈvɜr·tɛks/
Phonetic Spelling: VUR-teks

- **coil** (as in TMS coil)
Pronunciation link: https://www.merriam-webster.com/dictionary/coil
IPA: /kɔɪl/ or /kɔɪl/
Phonetic Spelling: KOYL

- **dorsiflexion** (as in foot dorsiflexion during motor-threshold testing)
Pronunciation link: https://dictionary.cambridge.org/us/dictionary/english/dorsiflexion
Cambridge Dictionary+1
IPA: /ˌdɔːr·sə'flek·ʃən/
Phonetic Spelling: dor-suh-FLEK-shun

- **threshold** (as in "motor threshold")
Pronunciation link: https://www.merriam-webster.com/dictionary/threshold
IPA: /ˈθrɛʃˌhoʊld/
Phonetic Spelling: THRESH-hold

- **Hertz** (Hz — frequency unit)
Pronunciation link: https://www.merriam-webster.com/dictionary/Hertz
IPA: /hɜrts/
Phonetic Spelling: HURTS

- **anxiogenic** *(as in "anxiogenic items") — "anxiety-producing"*
Pronunciation link: No confirmed link found on Merriam-Webster.
IPA (approximate): /ˌæŋ·zi·oʊˈdʒɛn·ɪk/
Phonetic Spelling: ang-zee-oh-JEN-ik

- **compulsion** (as in "compulsive behaviors / compulsions")
Pronunciation link: https://www.merriam-webster.com/dictionary/compulsion
IPA: /kəmˈpʌl·ʃən/
Phonetic Spelling: kuhm-PUL-shun