

PERSPECTIVE/ PERSPETIVA

## Training in Transcranial Magnetic Stimulation: Experience from a Clinical and Research Centre

## Formação em Estimulação Magnética Transcraniana: Experiência de um Centro Clínico e de Investigação

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**Keywords:** Education; Transcranial Magnetic Stimulation

**Palavras-chave:** Educação; Estimulação Magnética Transcraniana

### GUIDELINES AND CONSENSUS TO SET UP TRAINING IN TRANSCRANIAL MAGNETIC STIMULATION FOR CLINICAL AND RESEARCH SETTINGS

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation (NIBS) technique that has been proven to be safe and effective to treat several psychiatric disorders.<sup>1</sup> Currently, several TMS devices and protocols have been certified and/or cleared for clinical use by European and American regulatory agencies (*Conformité Européenne* Mark; Food and Drug Administration).<sup>1-8</sup> Moreover, evidence-based recommendations by clinical experts to support its clinical use have been published and periodically updated.<sup>1</sup> Such factors have allowed for the growth and expanded use of TMS as a clinical tool, consequently creating the need to standardize TMS practice according to best available evidence, irrespective of the provider.

The International Federation of Clinical Neurophysiology (IFCN) has published consensus guidelines for proper use of NIBS in investigational and clinical settings.<sup>8</sup> One

important step that should also be considered when designing a TMS clinic is providing adequate training for personnel. Consensus training guidelines endorsed by IFCN include three different classes of trainees – Technicians, Clinicians and Scientists.<sup>9</sup> Technicians apply TMS to patients or healthy subjects in clinical or research context, monitor potential side effects and assess clinical outcomes, including symptom severity. Clinicians are licensed physicians with complete residency training in Neuroscience specialties, such as Neurology, Psychiatry, Neurosurgery or Rehabilitation Medicine. They are responsible for establishing treatment indication and prescribing the appropriate protocol according to best available evidence, which will then be applied by themselves or TMS technicians. Clinicians should also supervise the treatment course, intervening when clinically necessary, for example upon moderate to severe side effects or treatment inefficacy. Scientists, often clinicians or individuals with a Ph.D. in neurosciences or related areas, are principal investigators (PI) or key co-investigators in research involving TMS.

Recebido/Received: 2023-04-19

Aceite/Accepted: 2023-07-26

Publicado Online/Published Online: 2023-08-22

Publicado/Published: 2023-09-30

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Scientists are responsible for designing the TMS protocol to be used in clinical trials or non-clinical research studies, applying the treatment themselves or supervising the work of TMS technicians. Studies with human subjects will typically require a clinician as PI or key co-investigator, to exert a clinical supervision role, namely in clinical trials, other clinical studies, studies involving vulnerable populations or studies with more intense or interventional protocols. The IFCN training method includes three core components: first, theoretical and didactic knowledge support; second, hands-on training experience should be provided; third, an observational period followed by supervised practice is recommended.<sup>9</sup>

Industry/company-dependent workshops and academic (industry-independent) training programs are proposed as adequate training settings. The former will typically instruct on proper use of specific TMS devices, while the latter will more frequently focus on broad application of TMS use, including different protocols, as well as safety and ethical issues.<sup>9</sup> In this context, the Clinical TMS Society has emphasized the importance of preferring industry-independent role of peer-to-peer and/or graduate medical education when securing appropriate TMS training of physicians and/or health-related staff, rather than relying solely on industry-sponsored training.<sup>10</sup>

Irrespective of the context, appropriate training for clinical purposes must be performed according to best TMS practice and well established and documented standard operating procedures.<sup>9</sup>

### **TMS AT THE CHAMPALIMAUD NEUROPSYCHIATRY UNIT**

The Champalimaud Foundation Neuropsychiatry Unit (CF-NPU) is an interface between the activities developed in the Champalimaud Clinical Center and Champalimaud Research, contributing towards both clinical care as well as basic, translational and clinical research. In 2018, the CF-NPU started a TMS Programme, including both research and clinical activities. The initial Scientists/Clinicians in this programme were trained in courses and internships at the Berenson-Allen Center in Beth Israel Deaconess Medical Centre, Boston, USA. Initial technicians were trained in the European Clinical TMS Certification Course (London, UK), the Neurosoft annual Utrecht TMS course (Utrecht, Netherlands) and the neuroCademy of neuroGroup workshop (Munich, Germany). Ongoing inhouse training has since been implemented for new members of the TMS Programme.

The Champalimaud Clinical TMS programme serves mainly patients with treatment resistant episodes of major depression<sup>3,11</sup> as well as those with obsessive compulsive disorder (OCD) and needing adjunctive treatment,<sup>5</sup> in both cases with devices and according to therapeutic protocols with formal regulatory approval.<sup>12</sup> Since 2018, the CF-NPU has treated 114 patients for multiple indications,<sup>12</sup> with treatment prescribed by CF-NPU psychiatrists for their own patients or patients referred from external psychiatrists. Most patients were treated for major depressive

episodes, the majority with criteria for treatment resistant depression (TRD). Most treatments were performed using intermittent theta burst stimulation (iTBS), according to latest recommendations.<sup>1</sup> We have also offered off-label treatments for depression, namely low-frequency right dorsolateral prefrontal cortex (R-DLPFC) rTMS to patients with depressive episodes that did not tolerate Left-DLPFC protocols or had important comorbidities, such as severe anxiety or OCD. Recently, we initiated an rTMS program for OCD treatment, according to the most recent approved protocol.<sup>5</sup> Off-label treatments have also been offered for individual patients, for conditions such as chronic orofacial pain and post-traumatic stress disorder,<sup>13</sup> upon multidisciplinary discussion of each case and according to best available evidence and international guidelines,<sup>1</sup> for which the unit director has contributed. In addition to providing clinical care, the TMS programme and CF-NPU also conduct research on clinical use of TMS<sup>13-20</sup> or on using TMS as a research tool.<sup>21-33</sup>

### **CONSULTING AND SUPERVISION PROGRAMME**

In February 2021, once clinical and research practice at the CF-NPU TMS programme were well established, the Unit started a peer-to-peer consulting programme in TMS with the Central Jutland Region Hospitals in Denmark. Several of these hospitals, namely in Viborg, Gødstrup/Herning, Randers and Aarhus, either initiating or developing therapeutic TMS Centres, participated in this programme. The lead consultant was the head of the CF-NPU, a Psychiatrist and Researcher, with assistance from a more junior TMS physician and researcher. Other members of the unit, namely psychologists, nurses and researchers, with technician, research and/or development roles within the TMS programme, participated less regularly and upon request. The consulting programme was developed in online meetings, initially performed weekly progressing to fortnightly and, in the second year of consulting, monthly. Participants in the programme from Denmark were mostly physicians, already with experience or initial short-term training in TMS. The majority were initiating a new TMS programme at their local hospital, and required ongoing support and advice to organize their programme and with regards to problems raised by individual patients. Occasionally, TMS technicians also participated in the consulting sessions, either jointly with the respective physicians or in parallel sessions with their technician peers in Lisbon. The consulting programme lasted 2 years, with inclusion of new participants and hospitals from the Central Jutland Region Hospitals as it progressed. This required repetition of some components of the programme for these new members, but with reduced intensity and/or duration given the growing autonomy and empowerment of the local teams in Denmark.

Consulting included three main activities: an introductory course, regular question and answer sessions and ongoing email-based support. The Introductory Course on Therapeutic TMS was organized to review and consolidate prior

training. It was initially delivered fortnightly or monthly as an alternative to Q&A sessions and was then repeated with all training sessions in a single day on the second year of consulting. The following topics were covered in this training course: therapeutic rTMS for depression; setting a TMS clinic for TRD; finding TMS dose: determining motor

hotspot and resting motor threshold; finding the treatment target: locate left-dorsolateral prefrontal cortex; TMS for obsessive-compulsive disorder; Tinnitus and TMS. A more complete curriculum for each of these sessions is provided (Table 1).

Table 1. Complete curriculum of second edition of TMS training course.

Time	Activity/Theme
13:00-13:05	Welcoming & Intro
13:05-13:30	Basic principles of rTMS
13:30-14:00	rTMS for treatment resistant depression
14:00-14:15	Setting a rTMS Clinic to treat TRD: practical procedures
14:15-14:25	10 min Break
14:25-14:55	Finding TMS dose: determining motor hotspot and resting motor threshold
14:55-15:25	Finding the treatment target: locate left-dorsolateral prefrontal cortex
15:25-15:55	rTMS for obsessive-compulsive disorder
15:55-16:00	Wrap-up

rTMS – repetitive transcranial magnetic stimulation; TMS – transcranial magnetic stimulation; TRD – treatment resistant depression.

The core of consulting was dedicated to discussion of clinical cases or challenges to application of TMS in each TMS centre. This was performed either during regular 1 hour-long Q&A sessions, or via email when there were pressing questions that required a more immediate response. Q&A sessions were performed jointly with the physicians from the several Danish TMS centres, and occasionally also with technicians from one or several of these centres, as per local decision. As mentioned above, some Q&A sessions were performed only among technicians with their peers in Portugal. In accordance with consultees' needs,

Q&A sessions were dedicated to review of practical aspects of the technique, providing clinical advice and supervision of TMS application, focusing mainly on questions arising from clinical practice, with discussion of specific clinical cases, as further detailed in Table 2. The consulting programme as described here was designed to be provided flexibly in accordance each TMS centre's needs and ended after 2 years when these centres decided it was no longer needed, since they were already autonomous both in the application of the technique and in the management of the TMS clinic.

Table 2. Examples of themes and topics.

Theme/Topic	Examples
Safety Concerns	Implication of tattoos in head or face
	Concomitant medication e.g.: Clozapine; Benzodiazepines
	Tinnitus and hearing loss
	Risk of seizures of iTBS
	Cardiac devices
Managing Side-effects	Possibility of changing stimulation side
	TMS induced-mania
	Within and between session stimulation intensity ramping up
	TMS intolerance due to pain and/or muscle contraction

Theme/Topic	Examples
Efficacy	Methodology for assessment of response to treatment
	Procedures for continuation and maintenance treatments
	Use of TMS in auditory hallucinations and negative symptoms in schizophrenia
	Use of TMS in depression with psychotic symptoms
	TMS versus ECT
	Efficacy of iTBS
	Left versus right DLPFC TMS efficacy
	Efficacy of accelerated TMS
Clinical Cases	Patient diagnosed with autism spectrum disorder and depression
	Patient diagnosed with multiple sclerosis and depression
	Patient diagnosed with obsessive-compulsive disorder and depression
	Patient diagnosed with bipolar depression
	Old-age patient diagnosed with depression
	Patient diagnosed with depression and substance use disorder
	Patient diagnosed with depression and Parkinson's disease
	Patient diagnosed with severe depression admitted in an inpatient unit
	Patient diagnosed with depression and concomitant coronary sent
Patients diagnosed with depression and concomitant mechanical aortic valve	

DLPFC – dorsolateral prefrontal cortex; ECT – electroconvulsive therapy; iTBS – intermittent theta burst stimulation; TMS – transcranial magnetic stimulation.

### INTERNSHIP TRAINING PROGRAMME

Also in 2021, the CF-NPU received its first Psychiatry trainees for TMS rotations. In Portugal, Psychiatry residency is distributed across 5 years of training, including several compulsory rotations covering core skills in Psychiatry. Additionally, the residency programme also includes a six-month period of elective rotations, allowing trainees to choose areas for complementary training. The CF-NPU provides training for Psychiatry residents who apply for an elective rotation, initially only in research and more recently also in TMS. Currently, we have provided training to five Portuguese psychiatry residents, several of whom have returned to their original training hospital and contributed to set up, or are leading, TMS clinics locally. The CF-NPU has several other TMS rotations planned for the future, including of an international psychiatry trainee.

The internship programme in TMS for Psychiatry residents has a duration of 3 to 6 months according to the objectives of each trainee. It was designed to include both clinical

and research activities, reflecting the conviction that both will contribute significantly for an enhanced understanding of the principles and practice of TMS in the clinical setting. Practical TMS training is the core aspect of this programme. Trainees are given the opportunity to observe daily TMS activities, with *in loco* training of both TMS theory and practice. They observe all steps of treatment for several patients, from the first TMS session, comprising motor hotspot and treatment target definition as well as resting motor threshold assessment, to the last session where treatment response is assessed, and a clinical report is produced. Since the CF-NPU provides TMS treatment mainly for major depressive episodes and OCD, training is available for both treatment modalities. In the case of OCD treatment, this includes a specific symptom provocation protocol.<sup>2,3,5,16</sup> Upon successful observation of treatment for several patients, trainees are also provided the opportunity to apply treatments under supervision from a trained technician. For example, observation of a minimum of 10 sessions of simple TMS and 10 sessions of TMS with psychometric

and motor threshold assessment is required. Subsequently, the trainee performs a minimum of 10 supervised sessions in each modality previously described and, finally, a minimum of 10 sessions of each in autonomous practice. The TMS training programme for Psychiatry trainees also includes exposure to clinical decision-making processes and physician follow-up. Trainees participate in several weekly meetings that include team decision-making about TMS, and multidisciplinary meetings (Table 3). These meetings will also provide opportunities to interact with the team of TMS clinicians and thus facilitate access to psychiatry and/or psychiatry appointments with patients in the TMS programme. Finally, access to Champalimaud Clinical Centre Seminars is provided. Trainees are also stimulated to take part in TMS research at the CF-NPU, including discussion

of research methods and theoretical framework, while receiving training according to each specific project's needs. Additionally, in research meetings, namely at lab meeting, proposals or ongoing research projects are discussed. A clinical and translational neuroscience meeting with other Champalimaud laboratories also takes place, and opportunities to participate in Champalimaud Research (CR) meetings, conferences and symposia are provided. These more general CF-NPU and CR activities include sessions dedicated to TMS. Nevertheless, most internship training is provided in a peer-to-peer environment, aiming to include trainees as learners but also as active participants in their own training, inviting them to discuss and participate in daily TMS activities under supervision by expert technicians, clinicians, and researchers.

Table 3. Available weekly meetings.

Time	Monday	Tuesday	Wednesday	Thursday	Friday
08:00-09:00					
09:00-10:00		Lab Meeting			
10:00-11:00		Clinical TMS <sup>1</sup>			
11:00-12:00		Challenging Cases			
12:00-13:00	CISS/CoPS	New Referrals			
13:00-14:00					Clinical Seminar
14:00-15:00	Administrative			Clinical Neuroscience	
15:00-16:00					
16:00-17:00					
17:00-18:00			TMS Group		
18:00-19:00					

Meetings for all clinical and/or scientific Community are in orange. In green are represented the NPU clinical meetings, while in yellow are represented the NPU scientific meetings. In blue are the meetings specifically associated to TMS.

<sup>1</sup> This meeting occurs fortnightly.

CISS – Champalimaud Internal Seminar Series; CoPS – Champalimaud OPen Seminar; TMS – transcranial magnetic stimulation.

## FUTURE PERSPECTIVES AND CONCLUSIONS

Transcranial magnetic stimulation use in Psychiatry has been increasing as a new treatment option with proved efficacy in several psychiatric disorders. Moreover, TMS has also been used as a tool to study potential neurophysiologic mechanisms associated to those conditions. TMS is thus a promising specialized treatment alternative in several mental health settings and should not be overlooked when planning and designing mental health services, at local, national and international levels. However, the introduction of TMS in clinical practice settings must be supported by

expert recommendation and/or guidelines, including proper training of staff with updated documentation to support practice and safeguard ethical and professional obligations. We thus propose that NIBS training should be flexibly provided in clinical training programs, namely for psychiatry trainees, through organized curricular programs, internships or other peer-to-peer supervised training. We believe the training experience of the TMS programme at the CF-NPU, as described here, provides interesting frameworks for development in other TMS centres.

**Declaração de Contribuição**

**FV, GC e PF:** Elaboração do manuscrito.

**AOM:** Conceptualização e planeamento do trabalho; revisão e edição do manuscrito.

**Contributorship Statement**

**FV, GC and PF:** Drafting of the article.

**AOM:** Conceptualization and planning of the work; revision and editing of the manuscript.

**Responsabilidades Éticas**

**Conflitos de Interesse:** AJO-M foi coordenador nacional para Portugal de um estudo não interventivo (EDMS-ERI-143085581, 4. 0) para caraterizar uma Coorte de Depressão Resistente ao Tratamento na Europa, patrocinado pela Janssen-Cilag, Ltd (2019-2020), de um ensaio de terapia com psilocibina para depressão resistente ao tratamento, patrocinado pela Compass Pathways, Ltd (EudraCT número 2017-003288-36), e de um ensaio de esketamina para depressão resistente ao tratamento, patrocinado pela Janssen-Cilag, Ltd (EudraCT NUMBER: 2019-002992-33). Recebeu também uma subvenção da Schuhfried GmbH para a normalização e validação de testes cognitivos, recebeu pagamentos ou honorários da MSD, Neurolite AG, Janssen e do Observatório Europeu da Droga e da Toxicodependência, e participou em conselhos consultivos da Janssen e da Angelini. Nenhuma das agências acima mencionadas teve qualquer papel na preparação, revisão ou aprovação do manuscrito, nem na decisão de o submeter a publicação. Os restantes autores declararam não ter quaisquer potenciais conflitos de interesse que envolvam este trabalho, incluindo actividades financeiras relevantes fora do trabalho submetido e quaisquer outras relações ou actividades que os leitores possam considerar como tendo influenciado, ou que dêem a impressão de influenciar potencialmente o que está escrito.

**Suporte Financeiro:** GC foi financiado pela Fundação para a Ciência e Tecnologia (FCT; Portugal) através de uma Bolsa de Doutoramento (SFRH/BD/130210/2017. GC e AJO-M foram apoiados pela bolsa PTDC/MED-NEU/31331/2017 da FCT. AJO-M foi apoiada pela bolsa PTDC/MEC-PSQ/30302/2017-IC&DT-LISBOA-01-0145-FEDER, financiada por fundos nacionais da FCT e cofinanciada pelo FEDER, no âmbito do Acordo de Parceria Lisboa 2020 - Programa Operacional Regional de Lisboa, e por uma Starting Grant do Conselho Europeu de Investigação no âmbito do programa de investigação e inovação Horizonte 2020 da União Europeia (acordo de subvenção n.º 950357). AJO-M foi também apoiada pelo projeto BOUNCE (contrato de subvenção n.º 777167), e pelo projeto FAITH (contrato de subvenção n.º 875358), ambos financiados pelo Programa de Investigação e Inovação Horizonte 2020 da União Europeia. O conteúdo deste estudo é da exclusiva responsabilidade dos autores e não representa necessariamente a posição oficial da Fundação para a Ciência e Tecnologia ou do Conselho Europeu de Investigação.

**Proveniência e Revisão por Pares:** Não comissionado; revisão externa por pares.

**Ethical Disclosures**

**Conflicts of Interest:** AJO-M was national coordinator for Portugal of a non-interventional study (EDMS-ERI-143085581, 4.0) to characterize a Treatment-Resistant Depression Cohort in Europe, sponsored by Janssen-Cilag, Ltd (2019-2020), of a trial of psilocybin therapy for treatment-resistant depression, sponsored by Compass Pathways, Ltd (EudraCT number 2017-003288-36), and of a trial of esketamine for treatment-resistant depression, sponsored by Janssen-Cilag, Ltd (EudraCT NUMBER: 2019-002992-33). He is also recipient of a grant from Schuhfried GmbH for norming and validation of cognitive tests, has received payment or honoraria from MSD, Neurolite AG, Janssen, and the European Monitoring Centre for Drugs and Drug Addiction, and participated in advisory boards for Janssen and Angelini. None of the aforementioned agencies had a role in the preparation, review, or approval of the manuscript, nor in the decision to submit the manuscript for publication. The remaining authors have declared that they have no potential conflicts of interest involving this work, including relevant financial activities outside the submitted work and any other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing what is written.

**Financial Support:** GC was funded by Fundação para a Ciência e Tecnologia (FCT; Portugal) through a PhD Scholarship (SFRH/BD/130210/2017. GC and AJO-M were supported by grant PTDC/MED-NEU/31331/2017 from FCT. AJO-M was supported by grant PTDC/MEC-PSQ/30302/2017-IC&DT-LISBOA-01-0145-FEDER, funded by national funds from FCT and co-funded by FEDER, under the Partnership Agreement Lisboa 2020 - Programa Operacional Regional de Lisboa, and by a Starting Grant from the European Research Council under the European Union's Horizon 2020 research and innovation programme (grant agreement no. 950357). AJO-M was also supported by the BOUNCE project (grant agreement no. 777167), and by the FAITH project (grant agreement no. 875358), both funded by the European Union's Horizon 2020 Research and Innovation Programme. The content of this study is solely the responsibility of the authors and does not necessarily represent the official views of the Fundação para a Ciência e Tecnologia or the European Research Council.

**Provenance and Peer Review:** Not commissioned; externally peer reviewed.

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