Nexstim

SmartFocus® nTMS

SmartFocus® nTMS: A Drug-Free, Personalized Treatment for Depression

Nexstim's world-leading SmartFocus® nTMS technology is solidly grounded in scientific and clinical research. We closely collaborate with key opinion leaders who, like us, believe TMS can harness the brain's own healing power—neuroplasticity. Our unique SmartFocus® nTMS technology features 3D-neuronavigation, which allows for accurate and personalized stimulation based on a patient's MRI scan.

"Visualization of the therapy in the brain inspires confidence in both the patient and the physician."

Marja-Liisa Kemppainen, MD.,
Department of Psychiatry, Oulu University Hospital, Finland

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Indications for Use:

FDA (K171902, K182700): Nexstim Navigated Brain Therapy (NBT®) System 2 is indicated for the treatment of major depressive disorder (MDD) in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode. Nexstim NBT® System 2 is intended to be used by trained clinical professionals.

CE: Nexstim NBT® System for depression is intended to be used for treatment of major depressive disorder (MDD) by targeting and delivering non-invasive repetitive TMS stimulation to the patient's dorsolateral prefrontal cortex.

What is TMS?

Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique whereby pulses of electromagnetic fields target and interact with specific brain regions from outside the head.

As a non-invasive method, TMS is not associated with the side effects commonly caused by anti-depressants.

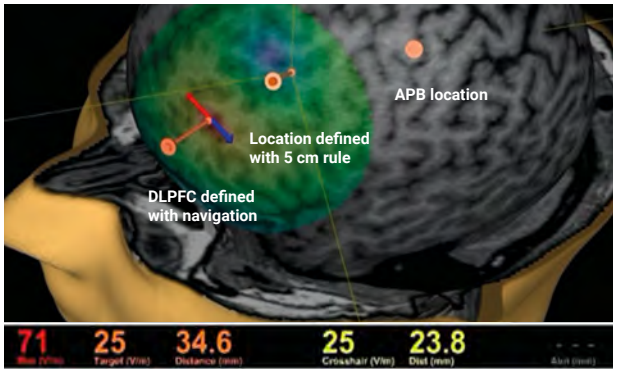
What is SmartFocus® nTMS?

Nexstim NBT® System with SmartFocus® nTMS technology uses sophisticated navigation tools to visualize the location, orientation, and magnitude of the maximum stimulating E-field induced when the TMS coil is activated.

SmartFocus® nTMS takes into account the unique shape and conductivity of each patient's brain and the positioning of the coil and uses this information to determine the location and orientation of the maximum induced E-field in the brain. In addition, advanced algorithms enable the stimulation dose to be quickly and accurately determined for each patient using their own neurophysiological readings. This all makes SmartFocus® a truly personalized and accurate nTMS therapy–as explained on the following pages.

Where to Stimulate?

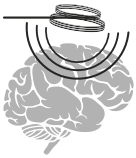
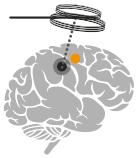
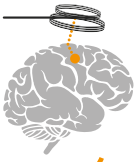
In depression treatment, TMS is often targeted to the left dorsolateral prefrontal cortex (DLPFC). PET imaging studies in patients diagnosed with major depressive disorder (MDD) have shown lower metabolism, compared to controls, in their left DLPFC regions, which supports the concept of using TMS as a therapy to increase the excitability of the left DLPFC.[1]



How to Target the DLPFC?

Navigation enables accurate targeting of the DLPFC. Without neuronavigation, research shows that the correct area is only targeted in approximately 30% of patients.[2] Studies show that without navigation, treatments are unintentionally being delivered on average 2 cm posterior to the DLPFC.[3]

SmartFocus® nTMS – a Paradigm Shift in TMS Therapy for Depression

Features	Stand-Alone TMS	TMS with Coil Navigation	SmartFocus® nTMS
Head/brain image display from MRI	–	✓	✓
Coil localization/positioning	–/✓	✓	✓
Individual modeling of brain conductivity	–	–	✓
E-field orientation shown on cortical anatomy	–	–	✓
Navigation of E-field in cortex	–	–	✓
Integrated motor response (EMG) measurement	–	–	✓
Accuracy clinically proven	–	–	✓
Fully integrated system	–	–	✓
Single & repetitive TMS	✓	✓	✓

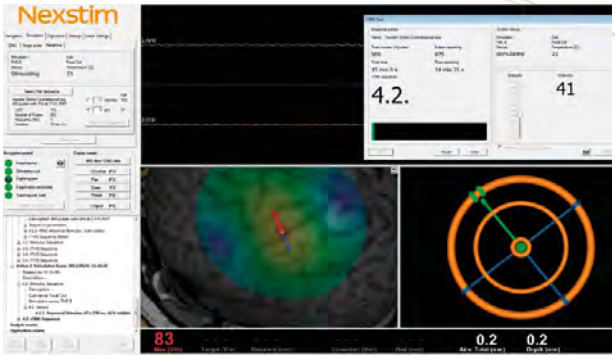
Technology	Applications – Current Focus			
	Depression		Chronic neuropathic pain	
Therapy	Europe	U.S.	Europe	U.S.
Navigated Brain Therapy (NBT)	CE marked	FDA cleared • 3 min theta burst 50 Hz • 19 – 37.5 min conventional	CE marked	Not FDA cleared. For investigational use only

Why Settle for 30% Accuracy?

Nexstim NBT® System with SmartFocus® nTMS technology is the only FDA-cleared TMS system with MRI-based E-field navigation and electromyography (EMG). SmartFocus® nTMS uses advanced algorithms based on mathematical modeling, taking into account both the shape and the composition of each patient's individual brain.

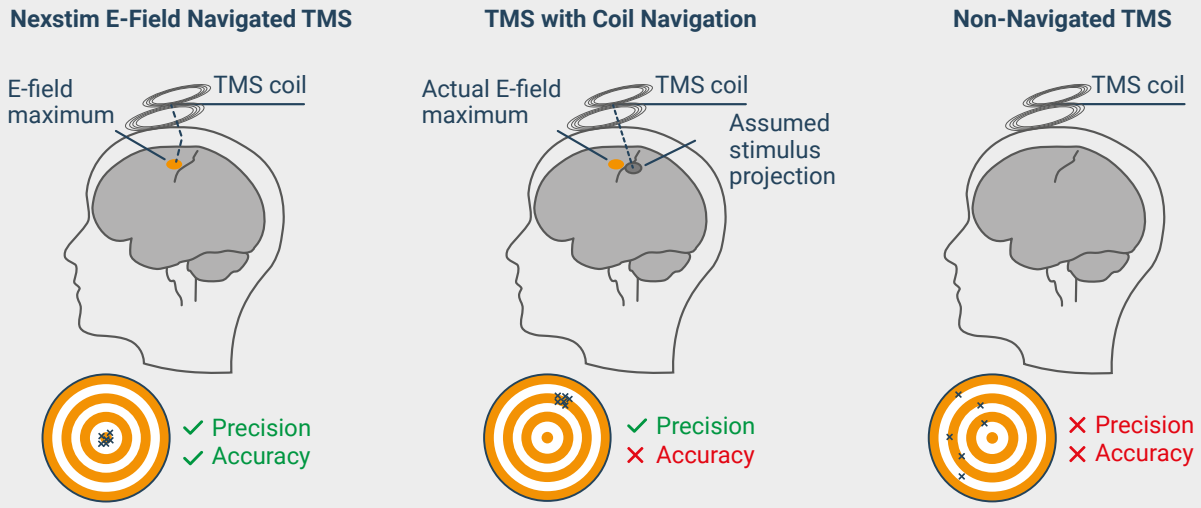
SmartFocus® nTMS displays the location and orientation of the maximum induced E-field in a 3D rendering, built from the patient's own MRI head scan. The multi-sphere model has been scientifically validated to accurately determine the location and orientation of the maximum induced E-field in the brain and hence to target the stimulation to the intended spot with accuracy in the millimeter range.

Without knowing the location of the maximum stimulating E-field in the brain, there is a risk of missing the target 70% of the time.[2]



Screenshot from Nexstim SmartFocus® software: E-field navigated technology allows the user to interact with the 3D brain model as it guides the user toward the intended target.

Nexstim E-Field Navigation vs. Other TMS Technologies



Coil navigation assumes that the stimulation projects perpendicularly from the coil. It does not account for the refraction of the stimulating electromagnetic field caused by bone and brain matter. Nexstim's E-field navigation takes that refraction into account. Only through visualization of the stimulating E-field it is possible to achieve the precision and accuracy necessary to confirm the right dose is being delivered to the right location.

[1] Bench C. J. et al. The Anatomy of Melancholia – Focal Abnormalities of Cerebral Blood Flow in Major Depression. Psychol Med. 1992 Aug 22;(3): 607–15.
[2] Herwig U. et al. The Navigation of Transcranial Magnetic Stimulation. Psychiatry Res. 2001 Nov 30;108(2): 123–31.
[3] Ahdab R. et al. Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. Clin Neurophysiol 2010; 40: 27–36.

How to Stimulate?

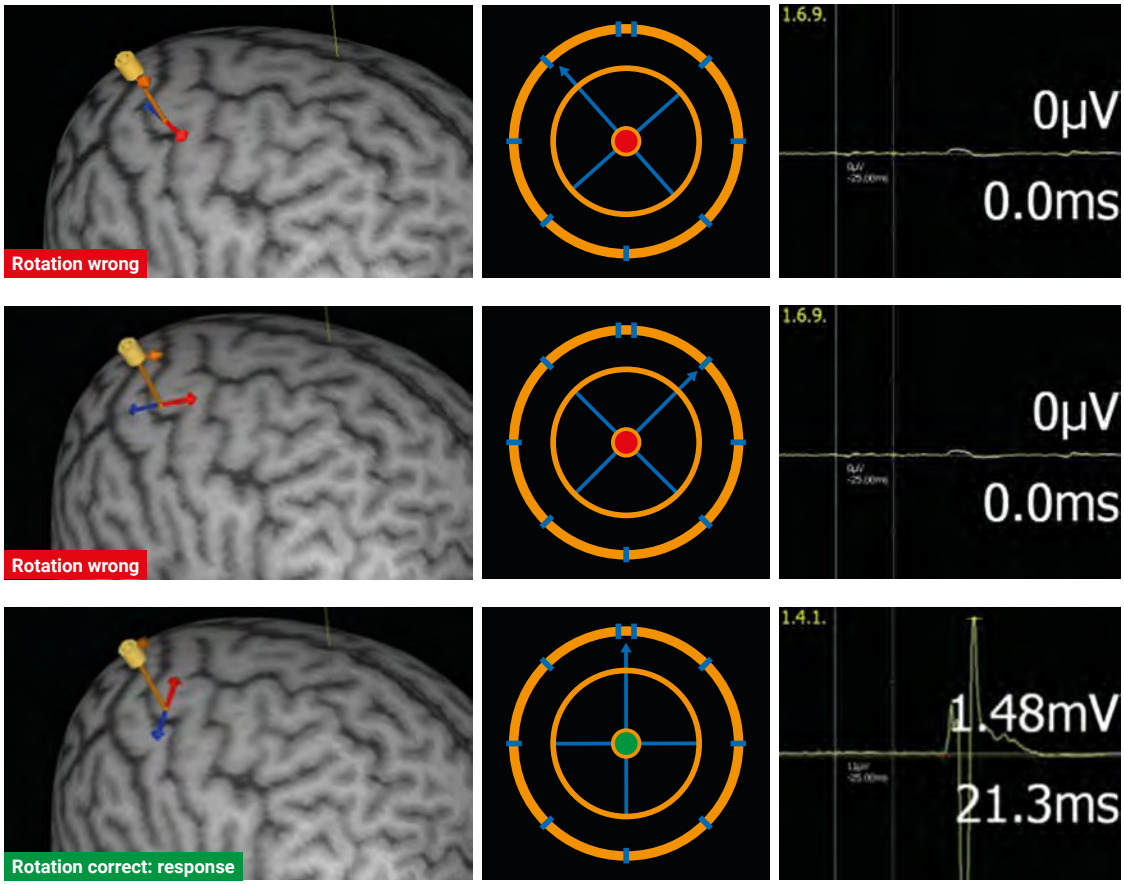
There are several factors affecting stimulation in addition to head shape and size: the location of the coil, orientation of the coil, tilting angle of the coil, distance from the coil. Small variations in ideal coil positioning (e.g., 10 degrees) produce significant differences (up to 1–2 cm) in stimulus location (other gyrus).

So even if you are on target, if your TMS system is not calculating all these factors there is a very good chance that you are not, in fact, achieving optimal neuronal modulation. Nexstim SmartFocus® nTMS takes these factors into account in addition to the patient's brain shape and conductivity. In other words, it calculates the E-field location and orientation. As the operator moves, turns or tilts the coil—even slightly—the system shows the updated location, orientation, and E-field data in real time and guides the operator to find the right positioning for the coil.

SmartFocus® nTMS Takes Into Account:

- Location of the coil
- Tilting angle of the coil
- Distance between target and coil
- Orientation of the coil
- Coil rotation
- Head shape and size

Example: The Impact of Coil Rotation



Note: A similar effect is seen with variations in coil tilting angle.

Personalizing the Stimulation Level

The effects of TMS are always dependent on the brain's sensitivity level to stimulation. This state is unique for each patient but can easily be measured with Nexstim's SmartFocus® nTMS technology by rapidly defining the patient's resting motor threshold (MT) via the integrated EMG. This gives you confidence that you are treating the intended location with a personalized dose to minimize any risk associated with overstimulation.

Accuracy Validated in Neurosurgery

The unparalleled accuracy of Nexstim's underlying SmartFocus® nTMS technology has been validated in neurosurgery in over 96 peer-reviewed articles, covering over 4,194 patients, and is now available to the mental health community for treatment of major depressive disorder.

Promising Initial Results: 74% Response Rate and 42% Remission Rate [4]

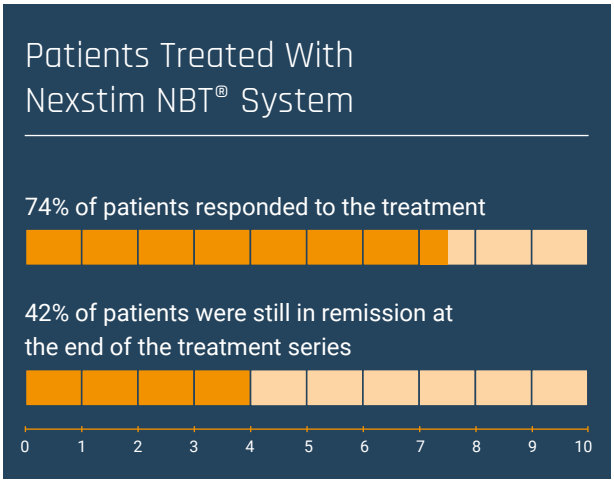
In early 2019, centers worldwide using Nexstim NBT® System with SmartFocus® nTMS began contributing to a multi-institutional, multi-indication data registry.

In October 2020, Nexstim reported the clinical outcomes of the first 108 patients to have completed SmartFocus® navigated rTMS therapy for treatment of major depressive disorder (MDD) at clinical sites in the United States.

42% of the patients completing the treatment achieved clinical remission and 74% obtained a clinical response at the end of treatment. While only a small sample, this study exemplifies the potential of using SmartFocus® navigated rTMS technology instead of non-navigated rTMS, which yields response rates of 50% and remission rates of 33% for the treatment of MDD.

The results are based on the patient-reported outcome measures on Beck's Depression Inventory (BDI) and Patient Health Questionnaire-9 (PHQ-9).

According to the registry data, patients also reported that the experience of receiving the treatment was generally very positive, as reflected by a mean score of 8.81 on a scale of 0 to 10.



[4] The report can be found here: www.nexstim.com/research/white-papers

Researching Deeper Brain Structures With Nexstim SmartFocus® nTMS

Decay by distance is an innate property of all TMS—whether labeled focal or deep. A TMS pulse is strongest at the surface of the cortex and decays with distance from the coil. As such, the maximum depth of stimulation that is reached depends on stimulation intensity.

Increasing stimulation intensity has multiple effects. Not only does the dose at deeper targets increase, the entire volume of the stimulation field enlarges as well. The dose at deeper structures and the volume of the stimulating electric field can both be visualized in the NBT® software.

Why Was Nexstim Founded?

Nexstim was established in 2000 with the aim of adding navigation capabilities to existing transcranial magnetic stimulation (TMS) technology. The founders believed that making TMS visible with the help of navigation is a crucial aspect for TMS technology to become a safe and effective clinical tool for patient treatment.

Before Nexstim was established, figure-of-eight coils were widely used. However, their positioning was often merely based on external landmarks on the head, which meant that the anatomical target in the brain remained inaccurate.[5]

A trend then emerged of using figure-of-eight coils together with navigation and individualized targeting. Nexstim was founded at this time and introduced the field to a unique concept: combining navigation technology with powerful stimulation field visualization capabilities.

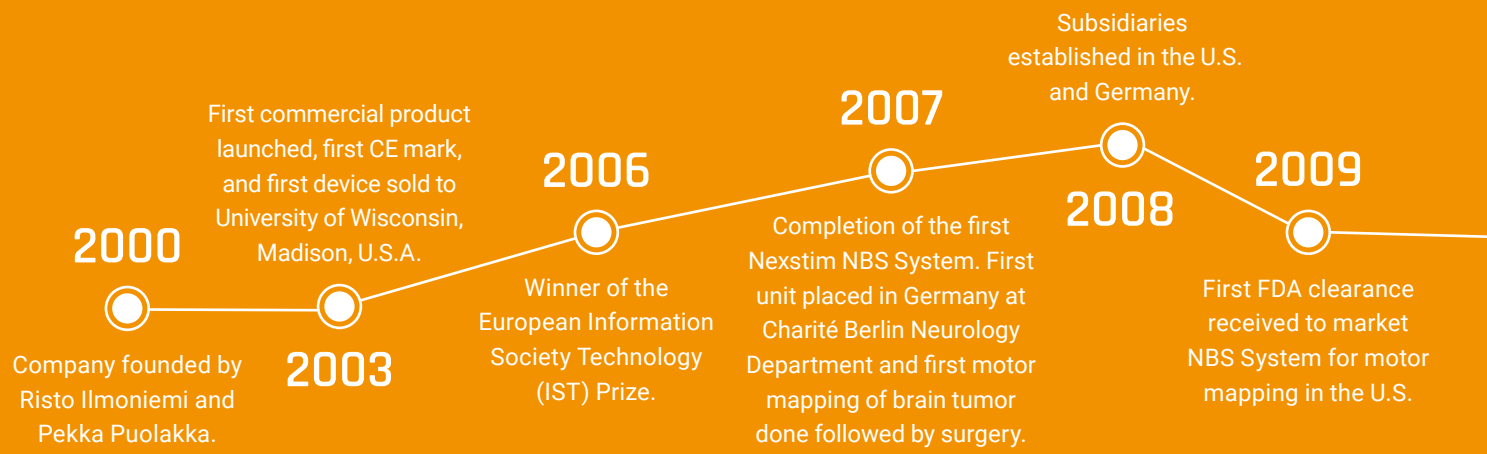
Nexstim: Making the TMS Visible and Reproducible

The company founders, led by Professor Risto Ilmoniemi, were researchers at Helsinki University of Technology, which has a long tradition of commercial innovation in the fields of biomagnetism and neuroscience.

In the 1990s, Professor Ilmoniemi was already well known for his work with multichannel magnetoencephalography (MEG) instruments, in which small magnetic fields produced by neuronal activity are localized, visualized, and analyzed. By engineering a reverse application to MEG, Ilmoniemi began designing TMS advancements

[5] Krieg S (Ed.), Navigated Transcranial Magnetic Stimulation in Neurosurgery. 2017. Springer International Publishing,

Key Milestones:



that provided similar visualization and localization tools, allowing a user to see where they were stimulating using a patient's own MRI. This advanced approach is termed "E-field navigated TMS." In 2000, Nexstim was established to bring this technology into the clinical practice.

The pin-point accuracy of Nexstim's first FDA-cleared technology led to a paradigm shift in the way neurosurgical cases are planned and performed, re-defining what is truly possible. Since its inaugural year, Nexstim has continued to expand its offerings and has been shown to offer unparalleled accuracy in both therapeutics and pre-procedural clinical brain mapping.

Over time, we at Nexstim learned that accurate, consistent TMS can only be provided by integrating all system components so that the software controls and communicates with the hardware. To ensure that we offer high-quality and reliable tools, we manage all aspects of manufacturing ourselves, including the design and precision manufacturing of tools as well as the system integration process.

We are proud to have a long tradition rooted in the research fields of biomagnetism and neuroscience throughout the Helsinki area universities. With this historical background, Nexstim is committed to collaborating with renowned researchers worldwide in several fields, including neurosurgery, radiation oncology, neurology, psychiatry, physical rehabilitation, and many others. We are dedicated to helping our researchers explore new indications through science-based technological advances and facilitating their efforts to conduct multi-center studies. Nexstim prides itself on offering award-winning, high-quality products that focus on making nTMS visible, accurate, and reproducible.

2012

FDA clearance received to market NBS System for speech mapping in the U.S. CE mark registration received for NBT® for treatment of major depressive disorder (MDD).

2014

Pre-surgical mapping outcome papers show positive outcomes in clinical patient care. The company was awarded a spot on the Red Herring European Top 100 list and was also included in Wired UK's hottest startups 2014 list. CE mark received for NBT® for treatment of chronic neuropathic pain.

2017

FDA clears NBT® System for marketing and commercial distribution in the U.S. for the treatment of MDD.

2018

SmartFocus® nTMS for depression treatment launched in the U.S.

Nexstim SmartFocus® Solution for Your Clinic

1. Patient consultation & prescription of TMS therapy and MRI scan

2. MRI scan

Typical scan time for this T1-weighted MRI is 5–10 minutes.
Contact Nexstim Representative regarding discount pricing of MRIs.

3. 1st SmartFocus TMS therapy session

Cortical mapping and 3–37.5 minutes of treatment (depending on the protocol) with nurse/TMS technician/physician:

- MRI scan uploaded to Nexstim System: 3D model of patient's brain is created
- Determination of individual stimulation location for therapy
- Determination of individual stimulation intensity
- Placing the coil on the identified therapy target
- First rTMS session: treatment with the determined protocol (3–37.5 minutes)
- All information above saved to patient's individual session file and ready for next time

4. Therapy series: 20–30 sessions with nurse/technician

- 5 days/week, 4–6 weeks with determined protocol (FDA-cleared protocols include iTBS (3 min) & 10 Hz (19–37.5 min))
- Consultation appointments with clinician when needed, usually 0–2 times during the therapy series

4a iTBS protocol: 10–15 min/session with nurse or TMS technician

- Patient file opened, patient seated, patient's head co-registered with MRI, coil placed on target
- Therapy is started: 50 Hz, total sequence duration 3 min

4b Conventional protocol: 30–50 min/session with nurse or TMS technician

- Patient file opened, patient seated, patient's head co-registered with MRI, coil placed on target
- Therapy is started: 10 Hz, total sequence duration 19–37.5 min

Possible Side Effects[6]

The most common side effects reported during clinical trials are mild headache (~50% of TMS treatment group) and scalp pain or discomfort (35.8%). Patient may feel twitches in the muscles during magnetic stimulation. This is a common sensation, but not hazardous. In addition, there is a small risk of mild skin irritation at the location where the muscle electrode sensors have been placed. Cortical magnetic stimulation runs the risk of inducing seizures, although they are rare. In ordinary clinical use, the estimated risk of seizure is approximately 1 in 30,000 treatments (0.003%) or 1 in 1,000 patients (0.1%).

[6] Janicak PG. et al. (2008). Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder: A Comprehensive Summary of Safety Experience from Acute Exposure, Extended Exposure, and During Reintroduction Treatment. J Clin Psychiatry, 69(2): 222–232.

SmartFocus® nTMS is also widely used for conducting research in the following fields (among others):

- Optimization of new protocols
- Tinnitus
- TMS-EEG
- Spinal cord injury
- Motor rehabilitation
- Cervical myelopathy

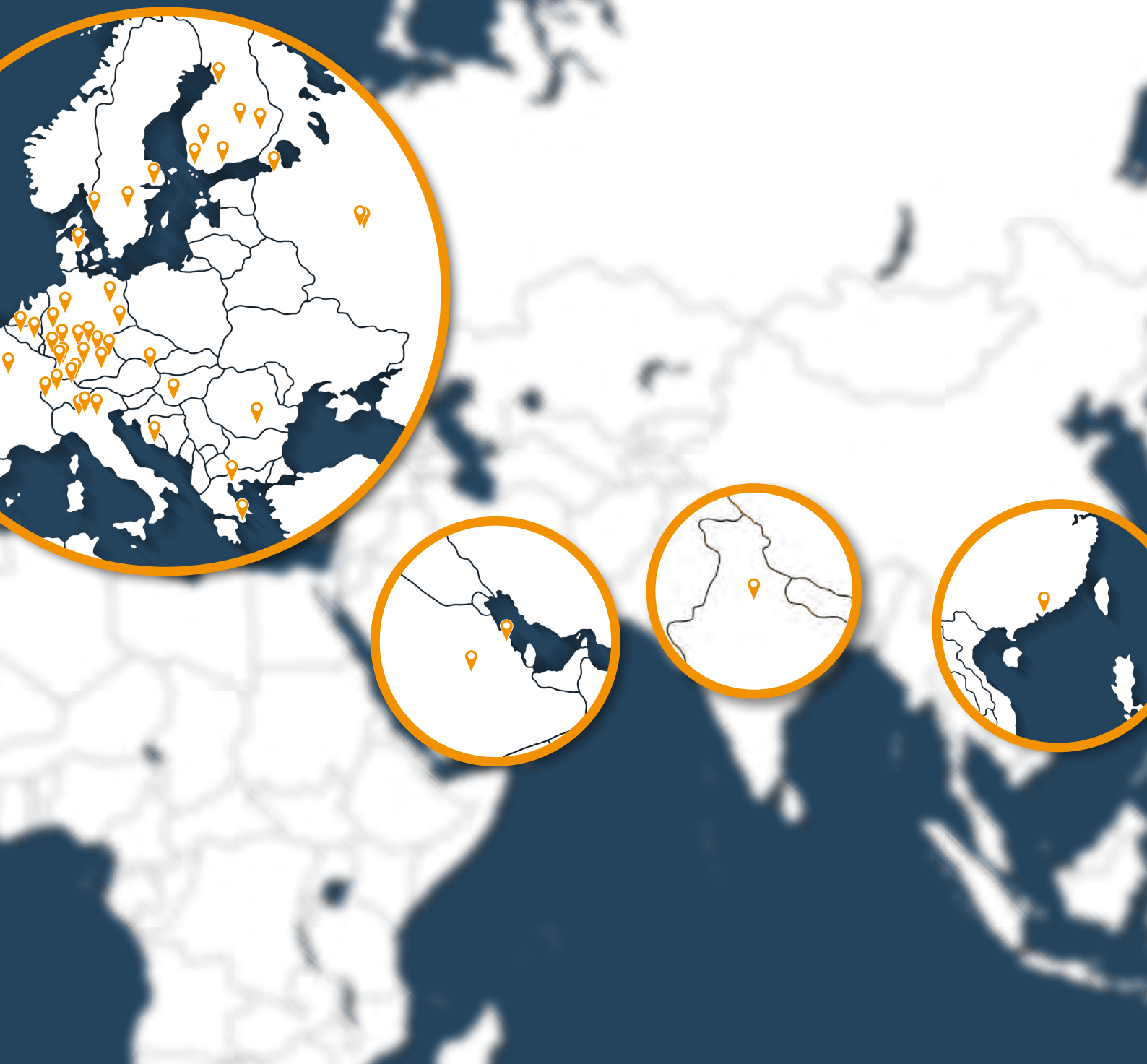
Nexstim TMS Systems are not FDA cleared or CE marked for the applications listed above.
Please visit **https://nexstim.com/research/literature** for further information and available publications.

Nexstim SmartFocus® nTMS Is Used Around the World Both in Therapy and in Neurosurgical Diagnostics

Nexstim SmartFocus® nTMS Technology Is Used in These Countries:

Austria	Croatia	Greece	Italy	Sweden
Belgium	Finland	Hong Kong/China	Romania	Switzerland
Canada	France	Hungary	Russia	UK
Denmark	Germany	India	Saudi Arabia	U.S.A.

For questions about payment plans and reimbursement in your country, please contact: info@nexstim.com.



Outreach and Marketing Support

Nexstim will assist you in marketing and communication activities to draw attention to the new services offered at your clinic.

1. Providing communication and marketing materials

We provide you with free materials that you can use in your own media channels (website, social media, brochure, flyer, etc.) This includes the following materials:

- Texts with the most important information for patients (long and short versions, key messages, and FAQs)
- Patient video about preoperative motor and language mapping
- Images (pictures of the NBT® System, system screen shots, mood pictures, and logos)

2. Clinic-specific patient brochure

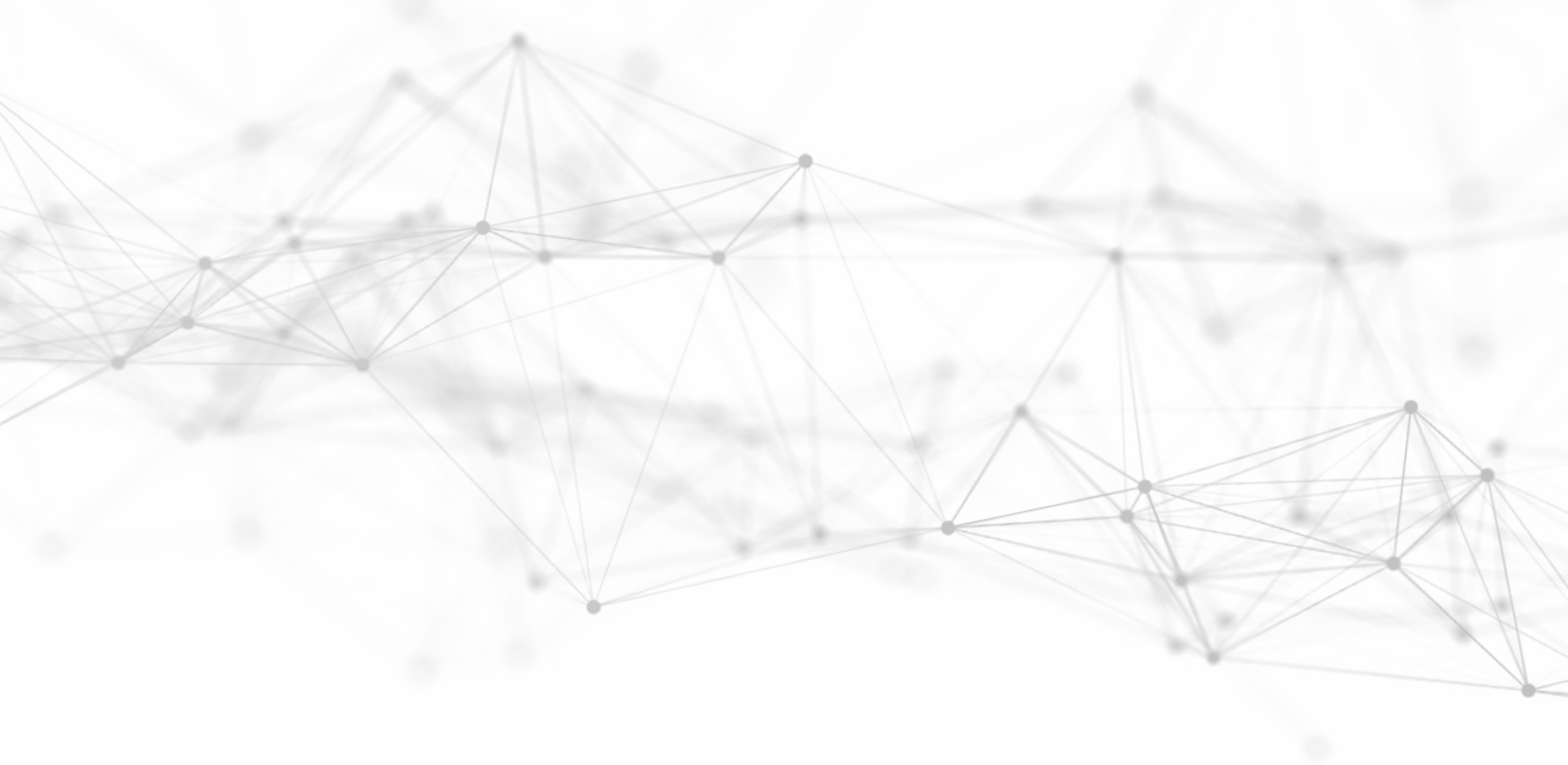
We create informational brochures for patients with your clinic's logo and contact details.

3. Digital campaigning

We offer digital marketing campaign support to help you reach patient groups in your clinic's region. The terms of Nexstim support will be discussed separately, based on your needs.

Reimbursement Support

Nexstim provides resources to assist in the reimbursement process, including guidance on coding and billing.



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