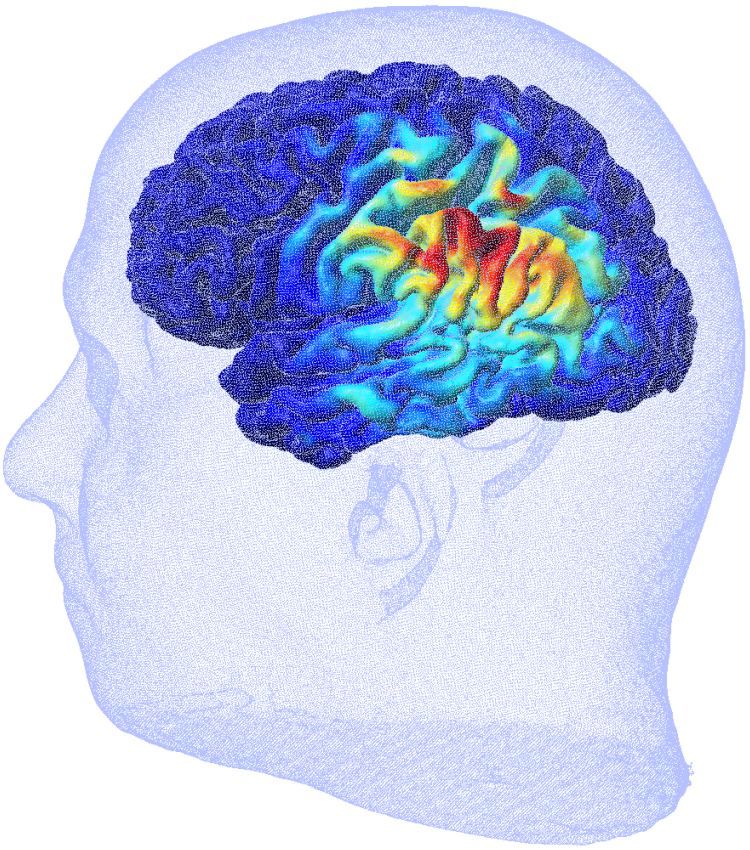

WHITE PAPER

Clinical applications of non-invasive transcranial Electrical Stimulation (tES) and Electroencephalography (EEG) by personalized, custom-made, 3D printed neurostimulators

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Development of Non-Invasive Brain Stimulation: From Research to Personalized Home Treatment

Non-invasive brain stimulation (NiBS) techniques rely on the brain's constant use of electricity to rapidly transmit information through action potentials sent along axons, which are elegant biological examples of electrical conductors. These NiBS techniques originated around 40 years ago when researchers stimulated superficial regions of the brain through the skull by applying a pulsed magnetic field via electrical currents in a metal coil on the scalp above the motor cortex, thus exploiting Faraday's law to induce an electric field as a result of an alternating magnetic field. Barker et al. provided the first example of **transcranial magnetic stimulation (TMS)**.[1] The development of stimulators capable of delivering long trains of closely spaced pulses made repetitive transcranial magnetic stimulation (rTMS) possible in the 1990s. This expanded the scope of TMS from a neurophysiological probe for exploring brain function to a tool potentially capable of exciting or inhibiting brain activity even beyond the stimulation period.

The growing scientific and clinical interest in NiBS generated by TMS also led to a revitalization of **transcranial electrical stimulation (tES)** in the late 1990's as a portable alternative to TMS. In the meantime, tES has grown into a standalone neuromodulation modality with vast clinical potential. There are several examples of electrical stimulation, among these are **transcranial direct current electrical stimulation (tDCS)**, **alternating current electrical stimulation (tACS)**, and **random noise stimulation (tRNS)**. Unlike TMS, which can produce direct neurostimulatory effect, tES usually does not generate action potentials. Instead, tES is believed to have a modulatory effect on brain function when the externally applied electric field displaces ions within neurons, **altering neuronal excitability and modulating the timing of spikes in individual neurons**.

In general, NiBS serves as a valuable tool in neuroscience research, aiding in the investigation of brain functions, connectivity, and plasticity. These techniques facilitate the exploration of neural mechanisms underlying cognition, behavior, learning, memory, decision-making, and various mental health conditions. By causally interacting with brain function, researchers can map brain networks, study the effects of alterations of neuronal activity, and elucidate the brain's role in various cognitive processes, significantly improving mapping capabilities of more standard "correlative" methods such as functional MRI (fMRI) or electroencephalography (EEG).[2]

Clinically, the use of NiBS-based non-pharmacological therapeutic techniques for specific disorders with specific protocols has been approved by regulatory bodies such as the Swissmedic, the European Medicines Agency (EMA), and the Food and Drug Administration (FDA). To date, **hundreds of positive studies** have been published on the impact of tES in neurological and psychiatric conditions. Multiple

pivotal clinical trials are currently ongoing in Europe and the USA to validate the use of tES for conditions such as depression, addiction, epilepsy, and Alzheimer's disease to name a few. tES holds a significant clinical potential due to its **portability, safety profile, and vast parameter space** allowing for personalized therapeutic solutions tailored to each individual brain more accurately than in the case of, for instance, TMS or transcranial focused ultrasound stimulation. Moreover, the possibility to easily combine tES with other interventions to augment or complement their effect (e.g., drugs, behavioral interventions, physical exercise), opens an even wider range of potential clinical applications.

Introduction to tES

Generally, there are two types of electrodes used in tES: an **anode** (i.e., positive electrode) and a **cathode** (negative electrode); stimulation delivered through the anodal electrode generally increases cortical excitability, while stimulation of the cathodal electrode decreases it. The precise location and polarity of the electrodes are crucial factors in determining the effects of tES. Electrode placement depends on the desired outcome and the specific brain area targeted for stimulation. For instance, if enhancing cognitive abilities is the goal, the anode might be placed over the brain region associated with the targeted cognitive function (e.g., dorsolateral prefrontal cortex to improve working memory performance). In addition to electrode location and stimulation intensity, another important parameter is the **stimulation frequency** in tACS. Frequency-specific stimulation can modulate and increase the endogenous frequency of neuronal firing in targeted brain regions associated with a particular task.

Before stimulation, the scalp area where the electrodes will be located needs to be cleaned of any residues that might interfere with conductivity. The electrodes are usually moistened with saline solution or conductive gel to ensure good contact with the scalp, improving the conduction of electrical current. During the tES session, **the current is gradually ramped up** to the desired intensity and maintained for the specified duration. Patients might experience a mild tingling sensation or a slight itching feeling under the electrodes, but the procedure is generally painless and well-tolerated. The **duration and intensity** of tES sessions also vary according to research protocols or clinical needs. Typical sessions can range from 10 to 60 minutes, with electrical currents of an amplitude ranging from 1 to 2 milliamperes (mA). At the end of the tES session, the electrodes are removed, and excess gel or solution is cleaned from the scalp. Patients may experience residual sensations or mild redness of the skin, which generally subsides shortly after the end of the tES session.

Safety of tES

Non-invasive brain stimulation techniques have been increasingly **recognized for their safety and efficacy** in various therapeutic applications[1,3], as demonstrated by multiple FDA approvals in the US and CE marking obtained by multiple companies in the European Community. In particular, the CE mark is a certification indicating conformity with health, safety, and

environmental protection standards for products sold within the European Economic Area that has been granted to numerous NiBS devices, reflecting their adherence to stringent safety regulations. While minor side effects like scalp discomfort or headache can occur, serious adverse effects are extremely rare and most of the NiBS technologies are classified as Class 3 devices.

Safety of tES has been explored both in the context of single sessions and repeated longitudinal exposure, with no adverse events reported so far, even when stimulation was applied remotely in home settings. Swissmedic recently accepted a clinical trial for home-based tACS stimulation in mild cognitive impaired patients (BASEC2021-D0055). In a recent review paper[4], six phase I, II, and III clinical trials were analyzed for the applicability of tES in patients suffering from minimum to severe neurological disabilities. The review found that a total of 308 participants between the age of 18 - 78 years each underwent up to 60 daily sessions for a total of 6779 remote tDCS sessions without a single occurrence of a serious adverse event. In total, only three sessions (0.04%) were aborted due to discomfort, but no participant dropped out due to tolerability. In a prior review paper[5], additional cases were tested including case studies with 400 daily sessions[6] and others with up to 40 sessions performed in patients with multiple sclerosis[7], bipolar disorder[7], schizophrenia[8], depression[9], and Alzheimer's disease[10]. **Across these studies, no severe adverse events** associated with remote tES applications were reported. Long-term delivery of tES in a patient's home thus appears acceptable and safe while offering many benefits regarding protocol compliance and patient satisfaction.

Mechanisms of Action and Biological Effects

The vast parameter space offered by tES allows interaction with and modulation of a variety of neural substrates of the healthy and pathological brain, including but not limited to brain excitability, brain perfusion and brain metabolism, as well as "rewiring" brain connectivity and guiding recovery after injury (e.g., stroke, TBI). For instance, the application of **tDCS** has been shown to induce significant effects on cortical excitability depending on the polarity of the electric field applied; specifically, tDCS can depolarize (during anodal stimulation) or hyperpolarize (during cathodal stimulation) the resting membrane potential of neurons, therefore **altering neuronal excitability and firing rate**.[11] In conditions where a reduction of activity in a specific brain region is observed (due to physical lesion or other pathology), tDCS can be used to **increase brain activity** with effects including an increase in **cerebral blood flow** as well as **metabolism** in the targeted region.[12] tES can also affect neurotransmitter systems, including the dopaminergic, cholinergic, and serotonergic systems, **influencing cognitive processes and mood**, with particular relevance in neurological and psychiatric conditions.[13] Interestingly, there is also evidence suggesting that tES promotes an increase in the levels of neurotrophic factors such as BDNF (brain-derived neurotrophic factor), and might have effects on **synaptic plasticity** through the modulation of NMDA receptor activity and calcium influx, which are critical for modulation of synaptic strength.[14,15] This modulation of synaptic strength resembles the process of long-term

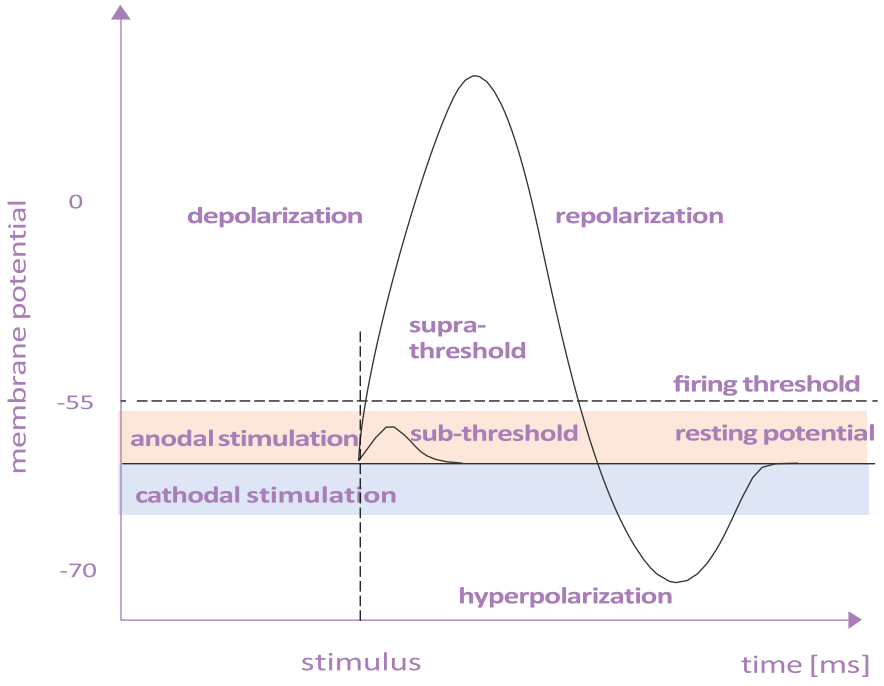
potential and long-term depression in the hippocampus during learning and memory formation.

The application of frequency-specific oscillatory stimulation –as in the case of **tACS**– has been shown to lead to **entrainment of endogenous brain waves** at a specific frequency. This opens the possibility of enhancing activity in specific frequency bands responsible for **cognitive function** (e.g., memory = theta activity between 4 Hz and 6 Hz; attention = alpha activity between 8 Hz and 12 Hz) that might be deficient in specific **neurological and psychiatric diseases**. For example, gamma activity around 40 Hz is decreased in Alzheimer's disease and dementia; traumatic brain injury (TBI) is characterized by a shift of activity in the alpha and beta band (12 – 30 Hz) and patients with depression show altered activity in the alpha band.[16–18]

Finally, **tRNS** has been suggested to **enhance cortical excitability** more diffusely than tDCS and induce longer lasting effects, which is particularly important for motor learning, attention, and visual perception.[19,20] Altogether, tES is establishing itself as one of the most promising neuromodulation approaches thanks to the diverse range of techniques and neural substrates targetable via tDCS, tACS and tRNS.

Clinical Applications and Opportunities

While tDCS is the most studied tES technique when it comes to clinical applications, growing evidence also exists for tACS and tRNS, with recent guidelines reporting overall promising clinical efficacy for tES across neurological and psychiatric conditions.[21]



Modulation of membrane resting potential by tES. Neuronal subthreshold depolarization by anodal tES increases neural excitability. Hyperpolarization under the cathode inhibits neuronal excitability.

In **depression**, multiple studies have shown that tDCS can safely and significantly reduce depressive symptoms.[22] Similarly, in **stroke rehabilitation**, tDCS has been used to enhance **motor recovery**, with very promising results especially when combined with behavioral interventions.[23,24] In the context of **migraine**, tDCS over the ventrolateral prefrontal cortex has been shown to reduce the intensity and frequency of migraine attacks.[25] Similarly, for **chronic pain**, tDCS applied to the motor cortex can provide significant pain relief by modulating pain processing pathways and reducing the excitability of regions involved in pain perception.[26]

tACS, which delivers alternating current at specific frequencies, has recently experienced a surge in interest as possibly the most promising tES technique, particularly for **cognitive enhancement** and the treatment of conditions with a clear alteration of oscillatory brain dynamics.[27] For instance, recent work has shown its potential to boost memory in elderly individuals with a transient **restoration of memory** capacity similar to young adults.[28] It has also shown strong results in modulating **OCD**[29], in reducing **epileptiform activity**[30], in mitigating depressive symptoms[31], and promising initial evidence of its effect in **Alzheimer's disease and dementia**.[32–34]

Finally, tRNS, characterized by the application of random electrical noise, is a relatively newer technique and its clinical applications are less studied; however, given its effect on brain plasticity and long-lasting effects, initial evidence is emerging for its effect in conditions including **schizophrenia**[35] and chronic **cortical blindness**[20], with further ongoing studies in other conditions.

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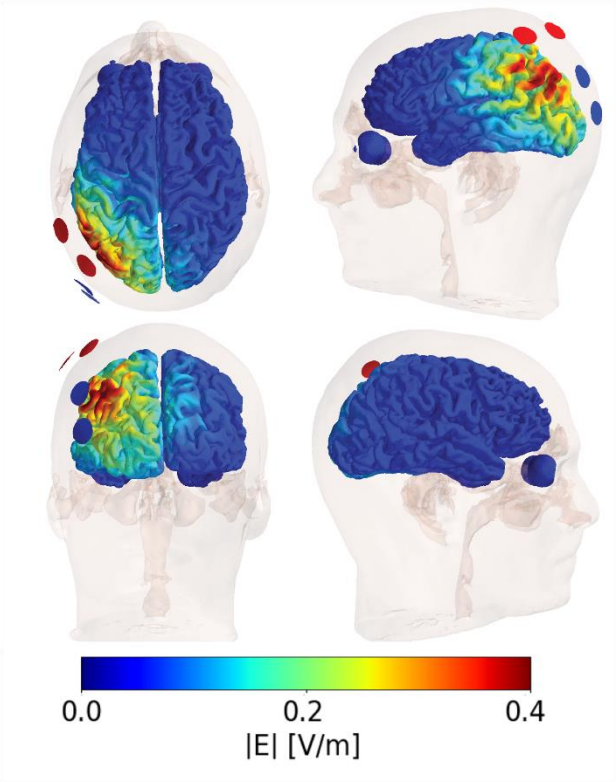
Bottneuro is at the forefront of portable, personalized brain diagnostics and treatment for patients with neurological and psychiatric conditions. Their customized headset allows for simultaneous recording and modulation of brain oscillatory activity, enabling unprecedented interaction with individual brain patterns. Bottneuro's precision technology is proving crucial in enabling research and validation of potential treatments for conditions such as Alzheimer's disease, depression, and pain, bringing personalized neuromodulation to patients' home.

For a more detailed list of potential applications and promising results across neurological and psychiatric conditions, please contact Bottneuro.

Beyond treating disorders, NiBS methods are investigated for their potential to **enhance cognitive abilities in healthy individuals**, for instance improving **memory, attention, language, and motor functions**[36,37], with promising applications in educational settings, skill learning, and for promoting **brain health and healthy aging** in general.

Personalization and Precision Neuromodulation

Recently, major research efforts have been aimed at personalization to increase the precision and robustness of tES treatments. The spatial distribution of electrical fields in the brain depends on both the electrode positions and subject anatomy.[38,39] Even for the same electrode montage and stimulation parameters, **inter-subject anatomical variations change the induced fields**[40,41] and thus the effects of tES across patients[42].



Patient specific electric field distribution. *Biophysical modeling by SimNIBS estimates the subject-specific impact of multi-electrode tES*

An important innovation is the use of **biophysical modeling** to simulate the propagation of electrical fields through the brain. A volume conductor model of each patient's head can be created by **segmentation of anatomical MRI images**.[43,44] Then, finite element method (FEM) simulations can be performed with tools such as SimNIBS[45] to calculate the electric field distribution as a result of a given electrode montage and stimulation parameters.[46] These **patient-specific simulations support the selection of an electrode montage and stimulation parameters** to enable the desired electrical field to reach the target region and minimize off-target stimulation. This optimization procedure can account for the complex trade-offs between electrical field strength and focality[47] for each patient's unique anatomy, treatment protocol, and targeted brain area or network.

Custom-made Miamind® Neurostimulator

The Miamind® Neurostimulator is registered at Swissmedic and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK as a custom-made device according to ANNEX XIII EU-MDR. The custom-made Miamind® Neurostimulator contains up to **34** (32 + CMS + DRL) **freely placeable electrodes** for repetitive **tES and EEG** recordings in clinics and at-home. Each device is custom-made to account for the **patient's unique anatomy** according to the prescription of the treating physician. To ensure comfortable fit, good electrode-scalp contact and precise location of the electrodes, each device is 3D printed based on provided **anatomical MRI scans**.

Custom-made Miamind® Neurostimulator.
Portable tES & EEG device for repetitive diagnostic and treatment assessments at home

The session parameters (including mode, duration, intensity, etc.) are predefined by the treating physician and preinstalled on the device. The patient can start, pause, and terminate the session by themselves; however, no session parameters can be modified on the device itself. This ensures that the patient receives the intended therapy only.

The custom-made Miamind® Neurostimulator is powered by a provided KNOX-secured tablet, protecting against use for any non-intended purposes. The tablet guides the patient through the session and, if desired, **automatically uploads EEG** data after a session ends to a predefined server via the included 5G connection.

Session parameters are preinstalled onto the custom-made Miamind® Neurostimulator according to the treating physician's prescription. During each use of the custom-made Miamind® Neurostimulator the same session is applied. A session consists of a predefined sequence of EEG recordings and tES steps.

EEG recordings are performed with **32 + reference** (CMS) electrodes at **500 samples per second (SPS)**. All recorded EEG data is stored in European data format (EDF) and can be remotely accessed.

For each **tES** step, up to 8 out of 32 electrodes can be individually activated at one time. These active electrodes can have different, customized stimulation parameters. The intensity can be set **up to 2 mA per electrode** with a **maximum of 4 mA** for the absolute sum of all electrode currents at any given time. These limits comply with the **scientific safety guidelines of**

Prof. Christoph Michel, University of Geneva

Home-based medical care for diagnostic assessment and treatment is witnessing a growing demand. Bottneuro has innovated a system that provides convenient and user-friendly remote monitoring of brain activity through a portable EEG device with integrated transcranial electrical stimulation. The key strength of the system lies in the creation of a personalized electrode cap, meticulously tailored to the patient's MRI. This customization is essential for crafting individualized models of electric fields, enabling precise control over anatomical variations. It guarantees accurate EEG source imaging and ensures optimal dosing for targeted brain stimulation in the desired regions.

tES applications.[3] Each active electrode can be selected individually to apply either DC or AC. The waveform can be freely adjusted (sinusoidal, rectangular, pulsed DC, AC with DC offset, etc.). For tACS, the available frequency range is **20 Hz to 80 Hz**.

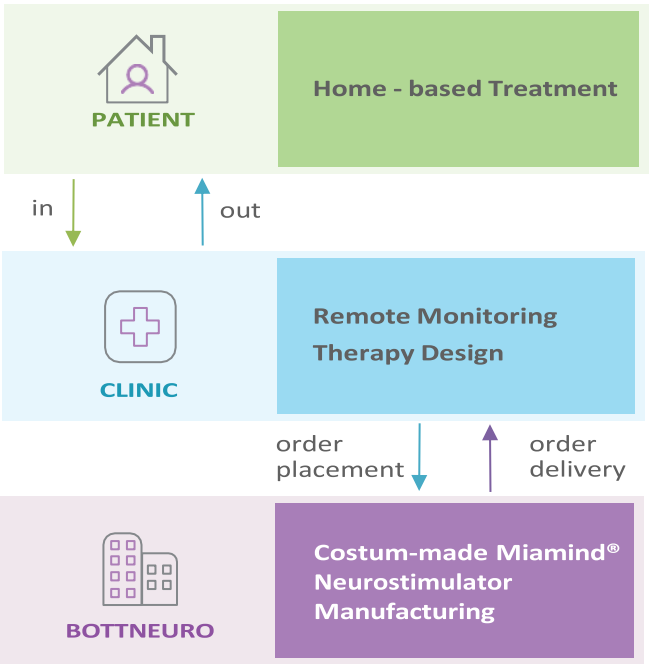
Bottneuro can provide support to the treating physician to define a personalized electrode montage and session parameters using simulated electrical field distributions in the patient's brain based on the MRI scans (see Personalization and Precision Neuromodulation).

Important! Bottneuro does not make any treatment recommendations for a specific patient. Supporting material and simulations provided by Bottneuro do not replace a medical evaluation by the physician and should only be used as supporting material in defining a patient-specific therapy based on an overall medical examination and the medical history of each patient. Modeling and simulations are approximations only based on best available knowledge and current scientific standards.

Manufacturing of the custom-made Miamind® Neurostimulator requires a full head T1- & T2 weighted MRI scan from the patient (minimum 3 Tesla scanner with entire scalp, ears, and C3- vertebrae in the field-of-view). To ensure a good fit and patient comfort, ears and other soft tissue should only be minimally deformed during MRI acquisition.

Patient Journey

The treating physician evaluates the applicability and safety of the custom-made Miamind® Neurostimulator for their patient's specific condition. Bottneuro provides a non-exclusive list of exclusion criteria for tES and the application of the custom-made Miamind® Neurostimulator (e.g. open wounds on the head, any kind of electric implants, and any exclusion criteria for MRI). Based on the patients' medical history and the medical expertise of the treating physician, brain regions to stimulate are identified. Multiple techniques, including neuroimaging (MRI, fMRI, PET), brain mapping (EEG, MEG), clinical assessment and neuropsychological evaluation, as well as research of published protocols from scientific literature can be used to identify brain regions to stimulate.



Bottneuro can provide information about the current scientific literature, technical capabilities of the Miamind® Neurostimulator, and modeling of electrical field distribution in the

patient's brain based on the provided MRI scans. Based on a holistic consideration of the patient's suitability and specific condition, the treating physician defines a patient-specific therapy.

The treating physician orders the custom-made Miamind® Neurostimulator (prescription form available at Bottneuro). Within 30 days, the custom-made Miamind® Neurostimulator is manufactured according to the physician's prescription and delivered to the treating physician. The Miamind® Neurostimulator transport box includes all required material to conduct the session including the Instructions for Use with a detailed explanation on how to set up and conduct the session.

Prior to each session, the included tablet must be fully charged. To ensure low electrode impedance, any residue which may interfere with the electrode-scalp connectivity should be removed. Therefore, it is advised that patients wash and dry their hair prior to the session. The Miamind® Neurostimulator runs an impedance check prior to each session and will start only if impedance is below a predefined threshold. To begin a session, the Miamind® Neurostimulator is put on and conductive gel (included) is applied to each electrode by a trained third party using the Miamind® Gel Adapter (included). The session can then be started in the Miamind® tablet app. Once started, the session runs automatically and does not require any further input from the patient or a third party. The session can be paused by pressing the button on the Miamind® Neckpiece and resumed by clicking the same button again. An acoustic signal indicates the end of the intervention. In the Miamind® tablet app, the session is ended by clicking *Send*. This uploads the recorded data to the server and returns the Miamind® tablet app to the initial stage. The session is now over and the Miamind® Neurostimulator can be taken off. Remaining residual conductive gel in the electrodes must be cleaned with water.

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Miamind® is a product by Bottneuro

Disclaimer: *Bottneuro does not make any treatment recommendations. All presented information is solely for informational purposes about tES, the custom-made Miamind® Neurostimulator, and its potential application only. The healthcare provider takes full responsibility for the patient-specific therapy. The support offered by Bottneuro does not replace a holistic consideration of the technology and its suitability for an individual patient. It is solely the physician's responsibility to examine if there are any contraindication for the application of the Miamind® Neurostimulator for each specific patient. There is no guarantee that any list, description, references, or any other enumeration is final. Bottneuro does not take any responsibility for the scientific veracity of any of the cited references and studies. The custom-made Miamind® Neurostimulator should only be used with prescription by a board certified physician after thorough examination of the patient's medical history and its suitability for the intended therapy. Bottneuro is solely the manufacturer of the custom-made Miamind® Neurostimulator based on the physician's prescription.*

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