Neuromodulatory techniques in veterinary behavioral medicine - Expanding treatment horizons for complex behavioral disorders

Neuromodulerende technieken in de gedragsdiergeneeskunde – Nieuwe behandelperspectieven voor complexe gedragsstoornissen

[1,2,*]S. Salden, [1,*]A. Haverbeke, [1]K. Peremans, [1,2]Y. Xu, [2,3,4]C. Baeken, [1]J. H. Saunders

[1]Department of Morphology, Imaging, Orthopedics, Rehabilitation and Nutrition, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium
[2]Department of Head and Skin, Ghent Experimental Psychiatry (GHEP) Lab, Ghent University, C. Heymanslaan 10, 9000 Ghent, Belgium
[3]Department of Psychiatry, University Hospital (UZ Brussel) Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Jette, Belgium
[4]Department of Electrical Engineering, Eindhoven University of Technology, Groene Loper 19, 5612 AP Eindhoven, the Netherlands

[*]These authors contributed equally to this work and share first authorship

Sofie.Salden@ugent.be

ABSTRACT

In this review, the emerging role of neuromodulation is explored in veterinary behavioral medicine for treating complex and refractory behavioral disorders. Conventional treatments, including environmental management, behavioral modification, and psychopharmaceuticals often fall short, necessitating alternative approaches. The potential of Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) to expand treatment options is examined, supported by two illustrative case studies. While these techniques show promise, each presents unique benefits and challenges. In this review, the need for determining appropriate use is emphasized, considering clinical context, feasibility, costs, and current scientific evidence. These findings suggest that neuromodulation could significantly enhance veterinary behavioral treatment plans, but further research is essential to further validate its efficacy and refine its application.

SAMENVATTING

In dit overzichtsartikel wordt de opkomende rol van neuromodulatie beschreven in de veterinaire gedragsgeneeskunde voor de behandeling van complexe en refractaire gedragsstoornissen. Conventionele behandelingen, waaronder omgevingsmanagement, gedragsmodificatie en psychofarmaca, schieten vaak tekort, waardoor alternatieve benaderingen nodig zijn. Verder wordt het potentieel van transcraniële magnetische stimulatie (TMS) en transcraniële gelijkstroomstimulatie (tDCS) onderzocht om de behandelopties uit te breiden, ondersteund door twee illustratieve casestudies. Hoewel deze technieken veelbelovend zijn, brengt elke techniek unieke voordelen en uitdagingen met zich mee. In het voorliggende overzicht wordt de noodzaak benadrukt om het juiste gebruik te bepalen, rekening houdend met de klinische context, haalbaarheid, kosten en de huidige wetenschappelijke evidentie. Deze bevindingen suggereren dat neuromodulatie veterinaire gedragsbehandelplannen aanzienlijk zou kunnen verbeteren, maar verder onderzoek is essentieel om de werkzaamheid verder te valideren en de toepassing te verfijnen.

INTRODUCTION

Non-invasive brain stimulation (NIBS), encompassing techniques like Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS), has emerged as a promising treatment in human neuroscience. These methods involve the application of electrical or magnetic fields to modulate neural activity in specific brain regions, and their efficacy has been demonstrated in the treatment of various neurological and neuropsychiatric conditions (Baeken et al., 2019; Eldaief et al., 2013; Lefaucheur et al., 2020). While primarily studied in human medicine, the exploration of NIBS in veterinary medicine is an emerging and promising area of research.

In companion animals, the application of NIBS remains predominantly experimental, targeting seve-ral neurological and behavioral conditions, such as refractory epilepsy and anxiety disorders (Charalambous et al., 2020; Dockx et al., 2019b; Martins et al., 2021; Nollet et al., 2003). Anxiety disorders are highly prevalent in dogs (Overall et al., 2006; Sherman and Mills, 2008; Tiira et al., 2016) and can significantly impact their welfare (Dreschel, 2010). Conventional treatments, typically combining management, behavioral modification, and psychopharmaceutical interventions, do not always provide sufficient relief. This has led to the growing interest among dog owners in exploring innovative approaches (Buller and Ballantyne, 2020). Integrating neuromodulatory techniques into treatment plans for behavioral patients could represent a significant advancement in veterinary behavioral medicine. These methods, which directly influence neural pathways and neurotransmitter systems and modulate brain function (Dockx et al., 2017b, 2018; Xu et al., 2022a; 2022b; 2023), could offer the potential to alleviate behavioral disorders and improve the overall quality of life for affected animals (Dockx et al., 2019b; Salden et al., in preparation).

TRANSCRANIAL MAGNETIC STIMULATION

Principles and mechanisms

Transcranial Magnetic Stimulation (TMS) is a technique that utilizes electromagnetic induction to generate electric currents within the brain. By applying an alternating magnetic field, an electric field is induced in the neurons beneath, thereby altering neural activity (Hallett, 2000). When TMS pulses are administered in rhythmic succession, it is referred to as repetitive TMS (rTMS) (Pell et al., 2011). The effect on neural activity depends on the frequency of the pulses and the brain region targeted, with higher frequencies generally enhancing neural activity and lower frequencies inhibiting it (Hallett, 2000; Houdayer et al., 2008). Low-frequency stimulation (LF-rTMS), defined as 1Hz or less, is believed to decrease cortical excitability and diminish neural activity. In contrast, high-frequency stimulation (HF-rTMS), defined as 5Hz or more, is linked to increased cortical excitability and heightened neural activity (Houdayer et al., 2008; Kimbrell et al., 1999; Lefaucheur et al., 2020; Speer et al., 2000, 2009). Repetitive TMS treatments are traditionally administered using multiple daily sessions over several weeks. In contrast, the same number of rTMS treatment sessions can be given over a shorter period, namely accelerated rTMS (arTMS). This method results in similar but faster clinical effects, without severe side effects (Baeken, 2018; Holtzheimer et al., 2010; McGirr et al., 2015).

In human medicine, rTMS protocols are tailored to different conditions (Lefaucheur et al., 2020). Similarly, in veterinary medicine, different rTMS protocols have been explored (Charalambous et al., 2020; Dockx et al., 2018; 2019b). For example, a five-day low-frequency rTMS (LF-rTMS) protocol has been studied for drug-resistant idiopathic epilepsy in veterinary neurology (Charalambous et al., 2020). In

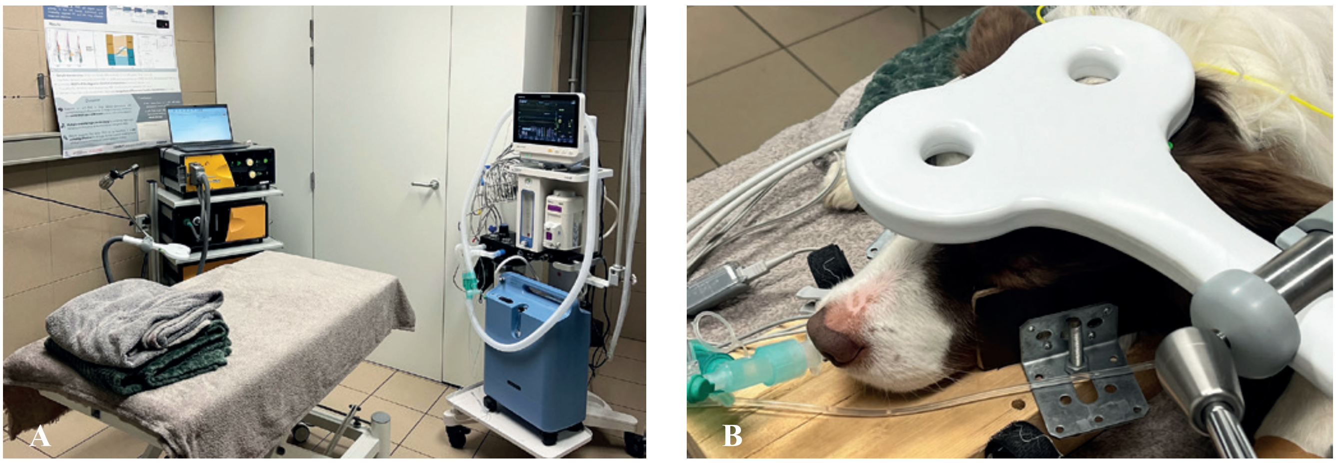

Figure 1. Setup of the TMS device (Neurosoft, Neuro-MS/D) in the Department of Morphology, Imaging, Orthopedics, Rehabilitation and Nutrition (Faculty of Veterinary Medicine, Ghent University). (A) Overall setup, including the TMS device, coil and the table where the dog will be positioned. (B) Human figure-of-eight coil used to stimulate the dog's brain.

canine behavioral medicine, an accelerated high-frequency rTMS (HF-rTMS) protocol targeting the left frontal cortex is used (Dockx et al., 2017b, 2018, 2019b; Xu et al., 2022a; 2022b; 2023). This approach has shown promise for managing anxiety disorders in dogs, with recent studies highlighting its potential benefits (Dockx et al., 2019b; Salden et al., in preparation). Further details on this protocol will be discussed below.

TMS protocol for anxiety in dogs

At the Department of Morphology, Imaging, Orthopedics, Rehabilitation, and Nutrition of the Faculty of Veterinary Medicine (Ghent University), the Transcranial Magnetic Stimulation (TMS) protocol employed is an accelerated high-frequency repetitive TMS (aHF-rTMS). The aHF-rTMS is applied over the left frontal cortex using a human figure-of-eight coil (Figure 1). The precise target, i.e. the left frontal cortex, is identified through neuronavigation (Dockx et al., 2017a) using external anatomical landmarks: two-thirds of the distance from the tip of the nose to the occiput and approximately 0.5 cm to the left of the sagittal midline (Xu et al., 2024) (Figures 2 and 3).

Each aHF-rTMS session consists of five consecutive stimulation sessions conducted within one day. The protocol involves stimulating at a frequency of twenty Hz with forty trains of 1.9 seconds each, separated by a twelve-second inter-train interval, resulting in a total of 1560 pulses per session. Sessions are separated by a ten-minute interval. The stimulation intensity is set at 110% of the motor cortex threshold (MCT), which is determined as described by Dockx et al., (2019a). This aHF-rTMS protocol is performed at least twice, with a four-week interval between treatments, as recent trials have indicated a higher response rate with this schedule (Salden et al., in preparation).

All aHF-rTMS sessions are conducted under general anesthesia using a fixed protocol (Dockx et al., 2017), conducted by a team of professional veterinary anesthesiologists of the Department of Small Animals, Faculty of Veterinary Medicine, Ghent University. Premedication includes butorphanol (Dolorex, MSD Animal Health, the Netherlands), administered either directly intravenously via an intravenous catheter at 0.2 mg/kg when possible, or otherwise intramuscularly at 0.4 mg/kg followed by placement of an intravenous catheter. Dogs are induced with propofol (PropoVet Multidose, Abbott Laboratories, United Kingdom) at 2-3 mg/kg and midazolam (Dormazolam; Dechra Pharmaceuticals, United Kingdom) at 0.2 mg/kg intravenously. In cases where butorphanol is inadequate, such as unknown multi-drug resistance 1 (MDR1) gene status in collie breeds or extremely anxious or aggressive dogs, dexmedetomidine (Dexdomitor, Orion Corporation, Finland) at approximately 10 µg/kg intramuscularly may be used as an alternative

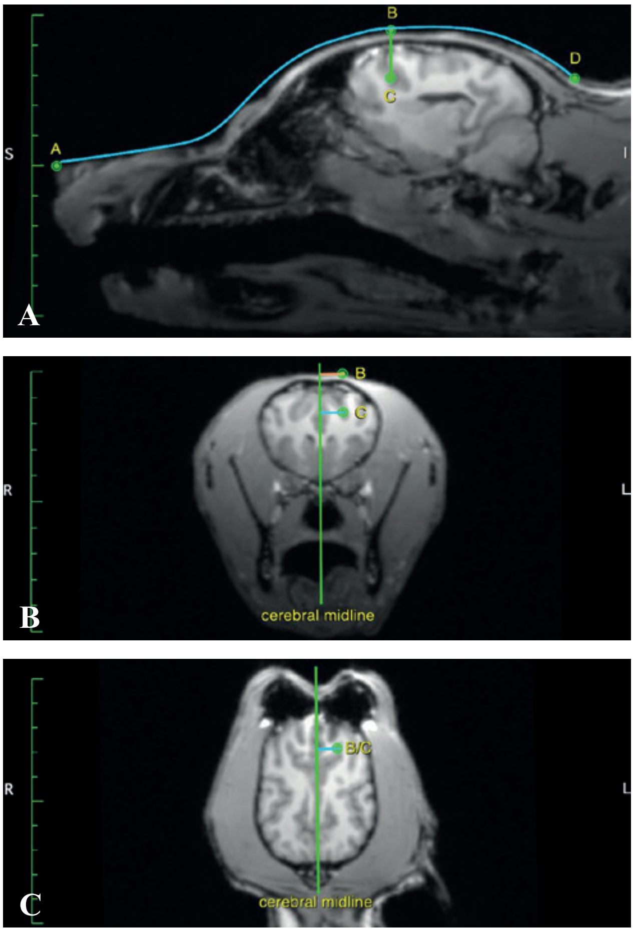

Figure 2. (A) localization of the left frontal cortex on a structural MRI image in the (A) sagittal view, (B) transversal view, and (C) dorsal view.
A: the nose tip; B: the left frontal cortex's external position on the skull; C: the center of the left frontal cortex; D: the occiput; A-D: the middle line of the cerebrum (from: Xu et al., 2024).

for premedication. Anesthesia is maintained with isoflurane (Isoflo, Zoetis, Belgium) in oxygen using a circular system after endotracheal intubation. After the stimulation, the recovery is performed in a quiet environment in proximity with the owners and if needed facilitated with atipamezole (Antisedan, Orion Corporation, Finland) at half the previously administered volume of dexmedetomidine intramuscularly.

Case study: TMS in a dog with anxiety

Background and history

A four-year-old female neutered Bearded collie was presented to the Faculty of Veterinary Medicine (Ghent University) with severe anxiety, lethargy, extreme stress, and panic as a response to noise. Due to the severity of the complaints, the dog was enrolled in an ongoing clinical trial involving an rTMS treatment (Salden et al., in preparation). Prior to the rTMS treatment, a single-photon emission computed tomo-

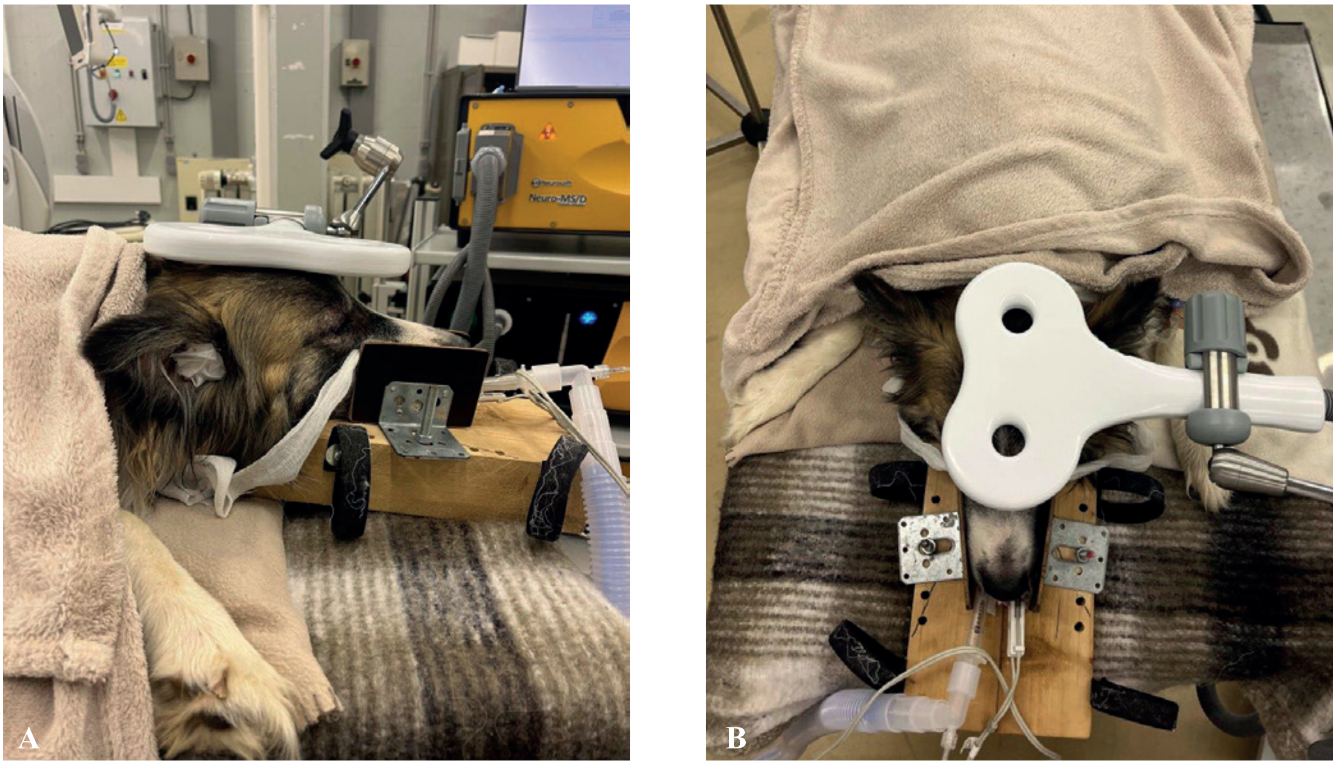

Figure 3. A dog undergoing the aHF-rTMS treatment over the left frontal cortex at the Department of Morphology, Imaging, Orthopedics, Rehabilitation and Nutrition (Faculty of Veterinary Medicine, Ghent University).

graphy (SPECT) brain scan was performed and results revealed significant hypoperfusion in the left frontal lobe, a finding consistent with observations by Vermeire et al. (2009).

TMS pipeline

Following the prescribed rTMS protocol, the dog underwent two aHF-rTMS sessions separated by four weeks. During this trial, multiple SPECT scans were acquired to follow up brain alterations (Salden et al., in preparation). If the results were beneficial, it was recommended to perform maintenance rTMS sessions depending on the individual evolution of the dog.

Results

After enrolment in the trial, the dog's behavior showed significant improvement. She showed less fearful behavior, more confidence, more energy, resumed playing behavior, and her panic responses were substantially diminished. SPECT scan results showed improvement of the left frontal hypoperfusion. After the study, the dog received maintenance rTMS treatments every six months.

Discussion

In this case, the potential of rTMS as a potential treatment for canine anxiety is highlighted. The protocol successfully alleviated the dog's initial symptoms, and ongoing maintenance sessions every six months helped sustain these improvements, underscoring the importance of continuous treatment for long-term anxiety management. This approach mirrors human rTMS therapy, where periodic sessions are used to prevent relapse and maintain therapeutic benefits (Senova et al., 2019).

The dog initially showed major hypoperfusion of the left frontal lobe, which improved after the rTMS sessions. This improvement supports the hypothesis that the aHF-rTMS may enhance neural activity in the left frontal cortex, as demonstrated in healthy dogs (Dockx et al., 2017b, 2018; Xu et al., 2022b) and in cases of canine anxiety (Dockx et al., 2019b). While hypofrontality may play a role in the observed clinical response, it is important to note that not all patients show hypofrontality, and thus, this factor may not be universally applicable.

TRANSCRANIAL DIRECT CURRENT STIMULATION

Principles and mechanisms

Transcranial Direct Current Stimulation (tDCS) is a non-invasive neuromodulation technique that applies an electrical current via electrodes on the scalp. This method is generally painless and relatively simple to administer (Fregni et al., 2021; Lefaucheur et al., 2017; Woods et al., 2016). The anode (positive electrode) is thought to enhance cortical excitability by depolarizing neurons, while the cathode (negative electrode) is thought to decrease excitability through hyperpolarization. This modulation of neuronal membrane potentials is believed to enhance or suppress spontaneous neuronal firing rates, thereby facilitating or inhibiting specific brain functions. However, tDCS faces criticism regarding the reproducibility of these effects and some concerns about the technique have been raised (Filmer et al., 2019). Further research is still needed to fully understand and validate the underlying working mechanisms and potential indications of tDCS.

tDCS protocol for anxiety in dogs

The transcranial Direct Current Stimulation protocol used at the Department of Morphology, Imaging, Orthopedics, Rehabilitation and Nutrition at the Faculty of Veterinary Medicine (Ghent University) derived from practical experience and human research, involves placing the anode over the left frontal cortex and the cathode on the right cervical region (Figures 4 and 5). For the neuronavigation technique to identify the left frontal cortex, the authors refer to Xu et al. (2024). Stimulation parameters are set at 2 mA for thirty minutes daily for twenty days. The electrodes are pre-cut to approximately 5 x 5 cm to ensure focal stimulation, and the areas for stimulation are shaved to reduce resistance and improve gel adhesion. Owners are carefully instructed on how to apply the treatment at home and are shown how to place and secure the electrodes using a bandage to prevent displacement. They are advised to ensure daily application for twenty days, supervise the dog during treatment, and immediately cease stimulation if the dog shows signs of discomfort or adverse reactions. During the initial thirty seconds and the final thirty seconds of stimulation, owners are informed that the dog might experience mild tingling, itching, or burning sensations. Measures such as using a cone are recommended to prevent the dog from removing the electrodes. Adequate gel application is emphasized to prevent mild burns, and owners are advised that mild skin redness after the treatment is normal. Still, persistent or severe redness or burns require immediate contact with the veterinary team.

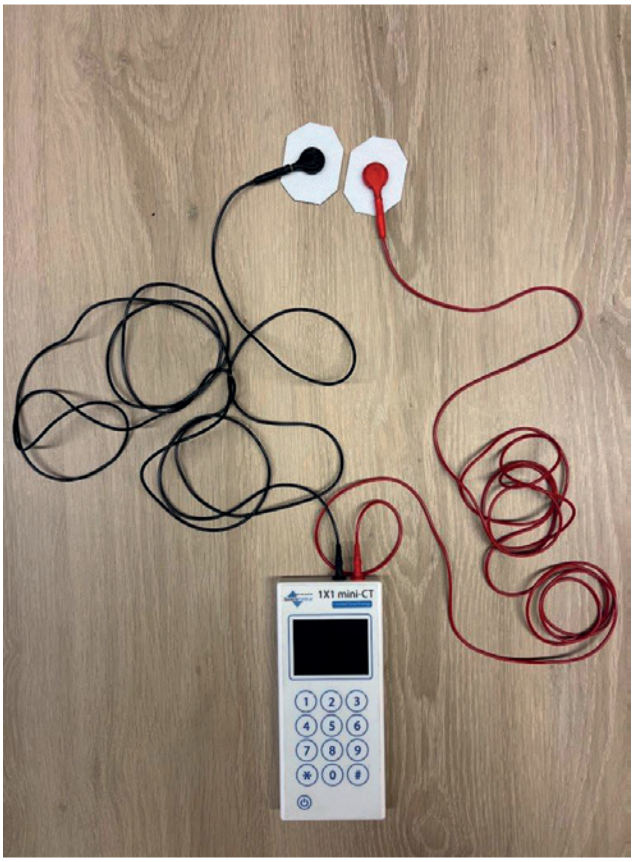

Figure 4. Setup of the 1X1 mini-CT (Soterix Medical Inc.), a tDCS-device, at the Department of Morphology, Imaging, Orthopedics, Rehabilitation and Nutrition (Faculty of Veterinary Medicine, Ghent University). Overview of the device connected to two electrode pads.

The initial protocol includes daily treatments for twenty days. Clinical effects are expected within two to three weeks. If a positive response is observed after this period, the protocol suggests stimulating daily for at least two more weeks after the dog's behavior is stabilized. Following this, two options are available for maintenance: (1) gradually tapering the treatment while closely monitoring the dog, or (2) stopping the treatment while thoroughly monitoring the dog. In the event of a relapse, the protocol calls for an immediate resumption of daily treatments for at least one month.

Case study: tDCS in a dog with anxiety

Background and history

An Akita Inu female, neutered dog with a history of severe anxiety, fear aggression, and social anxiety towards both humans and other dogs, participated in a recent rTMS trial (Salden et al., in preparation). The owners, hesitant to use psychopharmaceuticals, found that traditional environmental management and behavioral modification techniques were insufficient. Consequently, they enrolled the dog in the rTMS trial, which yielded substantial improvements such as more relaxed behavior, less aggression, more confidence, and more affection. After the study, the dog received maintenance rTMS treatments twice per year. However, when the TMS device malfunctioned, the dog's behavior quickly deteriorated. The decision was made to try tDCS. At the start of the tDCS treatment, the dog was eleven years and eight months old.

tDCS pipeline

Following the prescribed tDCS protocol, initial instructions were provided to the owners on administering home-based tDCS. The treatment involved

Figure 5. Dog undergoing the first tDCS treatment at the Department of Morphology, Imaging, Orthopedics, Rehabilitation and Nutrition (Faculty of Veterinary Medicine, Ghent University). The anode (red electrode) is placed over the left frontal cortex and the cathode (black electrode) on the right cervical region. The electrodes are fixed using bandages to avoid displacement.

daily sessions for twenty days, after which the owners were advised to continue daily treatments until the dog's behavior stabilized for more than two weeks. Subsequently, a gradual reduction in frequency was recommended, closely monitoring the dog's condition throughout.

Results

Initially, the dog exhibited fearful behavior during electrode placement but gradually adapted and tolerated the tDCS treatment well. Within one week, the owners observed the first signs of improvement. The dog appeared more relaxed and interacted more positively with other dogs. After two weeks, the dog's behavior closely mirrored the improvements seen after rTMS treatment, with owners describing the dog as happy, energetic, affectionate, and eager for walks. Following the initial twenty-day treatment period, the owners began reducing the treatment frequency as advised. After one month, treatments were administered every other day, without signs of relapse. By the third month, they had further reduced to once every four to five days. The dog maintained consistent, improved behavior without signs of relapse throughout this period. The owners continued this maintenance regimen of once every four to five days for several months.

Discussion

In this case, the potential of tDCS is highlighted as an alternative treatment for canine anxiety. While both tDCS and rTMS proved effective for this dog, tDCS offered the advantage of home-based administration, which can reduce stress associated with veterinary visits and eliminate anesthesia risk. The sustained improvement of behavior with a reduced frequency of tDCS suggests potential for long-term management of anxiety with fewer sessions over time. However, future studies should investigate optimal maintenance schedules and the threshold for treatment reduction.

GENERAL DISCUSSION

Neuromodulation is emerging as a promising frontier in veterinary behavioral medicine, particularly for treating complex and refractory behavioral disorders. In this review, the potential of neuromodulation techniques, including repetitive Transcranial Magnetic Stimulation and transcranial Direct Current Stimulation are explored to expand treatment options. While both techniques offer unique advantages and challenges (Table 1), the choice between them should be guided by the clinical context, cost considerations, feasibility, and the existing body of scientific evidence.

Repetitive Transcranial Magnetic Stimulation has been extensively studied in healthy dogs (Dockx et al., 2017b, 2018; Xu et al., 2022a; 2022b; 2023; Salden et al., in preparation), with its efficacy documented in canine anxiety disorders (Dockx et al., 2019b; Salden et al., in preparation). This robust research base makes rTMS a promising option in veterinary behavioral applications. However, the initial cost of acquiring a rTMS device and the learning curve associated with its operation are notable disadvantages. Additionally, rTMS requires anesthesia, which introduces its own risks and side effects.

In contrast, transcranial Direct Current Stimulation is still in its early stages in veterinary medicine, with limited peer-reviewed studies available. This lack of rigorous scientific evidence poses a challenge, especially when compared to the more established rTMS. Although the dog in the second case tolerated tDCS well, broader evaluations are needed to assess potential side effects and long-term safety in a larger cohort of dogs before endorsing its widespread use. Despite these limitations, tDCS offers several practical advantages: the device is relatively inexpensive, does not require anesthesia, and can be administered at home by dog owners.

At Ghent University, the primary focus is on rTMS as a treatment for canine anxiety. rTMS may offer a valuable alternative or complement when standard treatments are ineffective or contraindicated, particularly when traditional methods, such as environmental management, behavioral modification, and pharmacological interventions, fall short. Prior to an HF-rTMS treatment, the process begins with a comprehensive behavioral consultation, including questionnaires and owner-submitted videos, to assess the dog's suitability for rTMS. If the dog is deemed to be a candidate, a single-photon emission computed tomography (SPECT) brain scan is performed to identify any functional imbalances and determine its suitability for the treatment (Vermeire et al., 2011; Salden et al., in preparation). This is followed by two rTMS sessions as specified above. During the rTMS treatment period, a trigger-free period and low-stimulation environment are recommended for eight weeks. The first behavioral changes are typically expected after two to three weeks, with more responders after the second session than the first (Salden et al., in preparation). If a dog responds well after the entire process, maintenance rTMS sessions can be scheduled based on the individual needs of the dog. This personalized approach aims to enhance treatment outcomes for dogs with challenging behavioral issues.

The transition from empirical findings to evidence-based practices in veterinary medicine is an ongoing and complex journey. While the current evidence for rTMS and tDCS in dogs is still emerging, the authors are committed to advancing towards evidence-based care. Achieving optimal outcomes for complex behavioral patients necessitates a collaborative effort, where working closely with dog owners to explore and apply the most effective treatment strategies is crucial. While the current clinical emphasis is on rTMS, due to its stronger evidence base in both human and veterinary medicine, the authors acknowledge that the path to evidence-based solutions is a continuous process of learning and improvement. For any inquiries or further information, feel free to contact the author team.

CONCLUSION

Neuromodulation techniques such as rTMS and tDCS hold promise for veterinary behavioral medicine, each with distinct benefits and challenges. rTMS is well-researched and precise, but costly and requires anesthesia, while tDCS is more affordable and easier to use at home but needs more scientific validation.

Given the rapid advancements in human neuromodulation, there is a strong potential for these techniques to benefit veterinary patients as well. To realize

Table 1. Comparison of rTMS and tDCS treatment modalities, focusing on veterinary medicine.

	rTMS	tDCS
Mechanism	Current induction: uses electromagnetic induction to generate electric currents in the brain	Current injection: uses a constant, low electrical current delivered directly to the brain
Precision and depth	High precision in targeting specific brain regions Can reach deeper brain structures (Baeken et al., 2014; Sydnor et al., 2022)	Lower precision of the current distribution, depending on anatomical features (Opitz et al., 2015) Limited to cortical surface areas and no penetration in deeper brain regions
Feasibility and applicability	Non-invasive, but anesthesia required Requires specialized equipment and trained personnel Higher costs and less accessible	Non-invasive, no anesthesia required Relatively simple equipment, easier to use Lower costs and more accessible, possibility of home-based administration
Evidence-based	Strong evidence in both human and veterinary medicine (Lefaucheur et al., 2020; Salden et al., in preparation)	Emerging evidence, still being researched in human psychiatry and starting in veterinary medicine (Lefaucheur et al., 2017; Martins et al., 2021)
Side effects	Generally well tolerated, but can cause discomfort, headaches, or scalp pain in human medicine In veterinary medicine mainly anesthesia-related side effects	Generally well tolerated, can cause itching, tingling, or mild burning sensations during the sessions (Brunoni et al., 2011; Matsumoto and Ugawa, 2017)

this potential, further research and collaboration in the field of veterinary neuromodulation are essential. By fostering a collaborative research environment, the authors aim to advance the integration of these innovative techniques into clinical practice, ultimately enhancing patient care and outcomes.

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A complete reference list is available from the corresponding author.