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Systematic Review

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Efficacy and Safety of Repetitive Transcranial Magnetic Stimulation in Epilepsy: A Comprehensive Review

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a safe, well-tolerated neuromodulation technique with proven therapeutic potential in neurological disorders. Low-frequency rTMS, in particular, has attracted considerable interest for epilepsy management. However, published evidence regarding its efficacy and adverse effects remains conflicting. This comprehensive review evaluates studies published between January 1999 and January 2026, specifically assessing the therapeutic outcomes and safety profile of rTMS in epilepsy. Beyond a conventional synthesis, our analysis incorporates a comparative assessment of sample sizes across studies and adopts a multidimensional approach to clinical evaluation. Our findings support the clinical promise of rTMS for epilepsy patients. The intervention effectively reduces interictal epileptiform discharges and exhibits a favorable safety profile: it does not impair neuropsychological function in healthy individuals, does not worsen cognitive performance—with some evidence even suggesting improvement in Stroop task performance—and serious adverse events such as provoked seizures or psychotic symptoms are exceedingly rare. The risk profile remains low across both pediatric and adult populations. Importantly, preliminary evidence indicates potential benefits for suicidal ideation, an often-overlooked comorbidity in epilepsy. Collectively, this review underscores the significant potential of rTMS in alleviating epilepsy-related complications, with uncommon and generally mild side effects. We advocate for the expanded integration of rTMS as a valuable and promising tool in future clinical research and therapeutic protocols.

Keywords: Low-Frequency rTMS, Drug-Resistant Epilepsy, Interictal Epileptiform Discharges, Neuropsychological Outcomes, Treatment Safety, Neuromodulation.

1. Introduction

Epilepsy is a significant neurological disorder affecting over 1% of the global population [1]. Its hallmarks are the occurrence of sudden and recurrent sensory, motor, autonomic, or psychological seizures. These events arise from an imbalance within the brain's cortical circuits, leading to abrupt and uncontrolled electrical discharges of neurons [2–4]. Seizures in epilepsy are broadly categorized into generalized seizures (affecting approximately 20% of patients, involving both hemispheres and impairing consciousness, with subtypes like absence and tonic-clonic), focal seizures (occurring in about 40% of patients, originating in specific cortical areas and classified as focal or multifocal), and non-convulsive epilepsy (accounting for the remaining 40%, characterized by brief losses of consciousness) [5–7].

Despite the development of over 30 antiepileptic drugs, a substantial proportion (roughly one-third) of individuals with epilepsy continue to experience drug resistance or intolerable side effects [8]. Surgical intervention, involving the removal of epileptogenic tissue or the disconnection of seizure foci, offers another avenue. However, this approach requires specialized equipment and is limited to patients with identifiable and monitorable seizure origins. Critically, surgery is not a viable option for more than half of those with epilepsy due to multifocal, diffuse, or inaccessible seizure activity. In this regard, significant efforts have been made to localize epileptic foci. The most advanced approaches in this area include simultaneous EEG-fMRI recording techniques, a portion of which were previously conducted by our research team in past years [9–21]. However, surgery remains an option when none of the non-invasive methods were effective. Furthermore, the findings of similar studies aimed at focus identification have not been substantially groundbreaking in the context of surgery. Consequently, the medical world still feels a pressing need for a non-invasive therapeutic method with greater efficacy. Consequently, non-invasive brain stimulation techniques have emerged as a significant advancement in neuroscience, offering a less invasive alternative to intracranial stimulation for various neurological conditions [22–24].

Over the past few years, extensive basic and clinical research has focused on neuromodulation methods [24], with efforts directed towards discovering safer and less invasive techniques involving targeted cortical stimulation [25]. Transcranial magnetic stimulation (TMS) has garnered increasing attention as a promising tool for modulating cortical excitability and activity [26,27]. Single-pulse and paired-pulse TMS are established as safe and valuable tools for investigating human brain neurophysiology, including cortical excitability in epilepsy [28,29]. The principle of electromagnetic induction for transcranial stimulation dates back to 1985 [30]. More recently, repetitive transcranial magnetic stimulation (rTMS), a non-invasive technique employing alternating magnetic fields to induce small electrical currents and neuronal depolarization in cortical areas [31], has gained prominence. Essentially, rTMS uses repeated magnetic pulses to regulate cortical excitability [32,33], capable of reaching depths of up to 2 cm in the brain to stimulate subcortical gray and white matter [34]. This technique is now recognized for its ability to induce long-term stimulation and lasting changes in neural activity [35–42].

Both low-frequency (LF-rTMS, $\leq$ 1 Hz) and high-frequency (HF-rTMS, $\geq$ 1 Hz) applications of rTMS have demonstrated lasting inhibitory and excitatory effects on cortical excitability, respectively, both during and after stimulation [43]. While generally safe, rTMS has been associated with transient side effects such as headaches, stimulation site pain, muscle discomfort, and tinnitus [44,45]. Although the most concerning potential adverse event, particularly in epilepsy patients, is seizures, adherence to international safety guidelines and the implementation of safe protocols can significantly mitigate these risks [46,47]. Indeed, a study by Bae et al. [42] reported a relatively low crude seizure risk of 1.4% per patient in a cohort of 280 individuals with epilepsy undergoing rTMS. The clinical potential of rTMS was further acknowledged by the Canadian Health Association in 2002 and the US FDA in 2008 [48].

Given rTMS's capacity to modulate cortical excitability, numerous clinical trials have explored its effectiveness in reducing seizure frequency in individuals with epilepsy. However, these studies have reported varied outcomes, including decreases, increases, or no change in seizure frequency across different time intervals. These discrepancies may stem from variations in patient characteristics (disease severity,

epilepsy type), stimulation parameters (frequency, intensity, coil type), and treatment protocols [49-91]. Importantly, a lack of statistical significance in individual studies does not necessarily negate the potential therapeutic benefits of rTMS for epilepsy. Therefore, a systematic review of existing research is warranted to comprehensively investigate the therapeutic effect of rTMS on epilepsy and address these conflicting findings. This study aims to systematically review the available data from the new millennium (2000-2025) to provide a robust, unbiased estimate of the effect of rTMS on epilepsy and to clarify its potential role in managing this condition.

2. Methods

2. 1. Search Strategy

A complete electronic search was conducted in PubMed, Google Scholar, Scopus, PEDro, and Medline databases to find all relevant articles investigating the effect of rTMS on parameters such as the number of seizures and the amount of IEDs in patients with epilepsy. In the initial search, keywords and phrases such as “rTMS”, “TMS”, “repetitive transcranial magnetic stimulation”, “transcranial magnetic stimulation”, “brain stimulation”, “magnetic stimulation”, “low frequency rTMS”, “high frequency rTMS”, “epilepsy”, “seizure”, “epilepsia partialis continua”, and “antiepileptic” were used.

Boolean operators (OR/AND) were also used to create different combinations of these keywords in line with the search strategy. The search was performed in the following manner:

(“epilepsy” OR “seizure” OR “antiepileptic” OR “epilepsia partialis continua”) AND (“rTMS” OR “TMS” OR “repetitive transcranial magnetic stimulation” OR “transcranial magnetic stimulation” OR “brain stimulation” OR “magnetic stimulation” OR “low frequency rTMS” OR “high frequency rTMS”).

2. 2. Eligibility criteria

We considered all original full-text articles published in English from 2000 to 2026. Studies included in this review had the following characteristics:

1) Studies that met the updated TMS safety guidelines and were published after 1999.

2) Studies that were published in English.

3) Studies that reported research results in numerical and quantitative form and avoided expressing the trend of changes in a qualitative manner.

4) Studies that included measures of TMS cortical excitability.

5) Studies in which the type of epilepsy of the patients was specified.

6) Studies in which rTMS was the only intervention examined.

7) Studies that had been conducted exclusively on human participants.

Qualitative or simulation studies, abstracts, editorials, pilot and preliminary studies, conference papers, and preprints were excluded. It is important to note that studies that did not focus solely on rTMS, those using cognitive training, technology-based interventions, transcranial direct current stimulation (tDCS), aerobic exercise, and meditation, were excluded.

2. 3. Study Selection

After an initial search in the main databases, all selected articles were independently screened by two co-authors (MNA and PP) to select articles that were fully relevant to the review topic in order to increase accuracy. This screening was based only on the main title of the articles and the text of the abstract. Having two co-authors in this search minimized the risk of bias and error. After this stage, any disagreements in the selection of studies were resolved by discussion between them (MNA and PP), resulting in an acceptable conclusion.

2. 4. Data Extraction

Information for the main table of the review article was collected by two co-authors (MNA and PP) from the selected articles found in the primary and secondary searches. Each of these co-authors independently

entered the extracted information into a personal table and, at the end, compared their results and, through discussion and re-examination, corrected and resolved any discrepancies.

3. Results

As shown in Fig. 1, a total of 1053 articles were determined by searching in the above-mentioned databases. Primarily, 824 studies were left after excluding duplicates and screening titles, abstracts, and language. This procedure removed 688, 43, and 14 articles, respectively. At the end, 79 full-texts were reviewed for eligibility, and 57 studies were finally accepted according to the inclusion and exclusion criteria (see Table 1 for details).

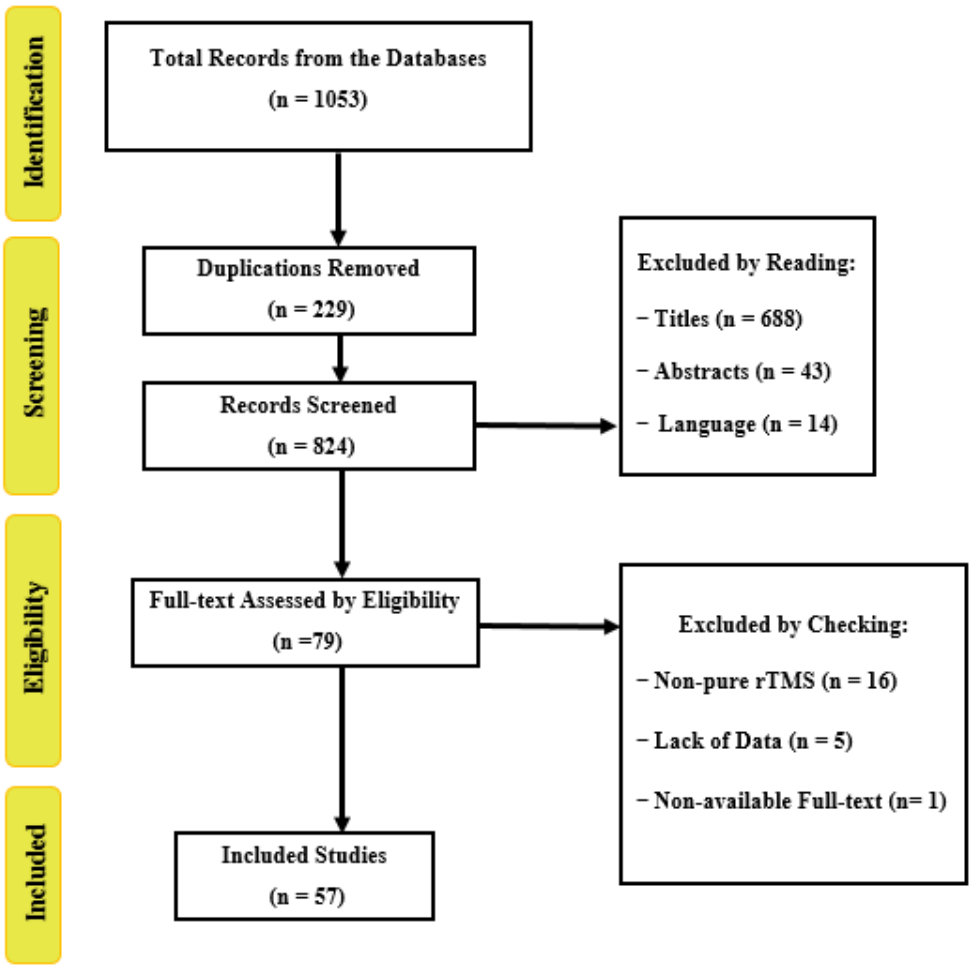

Fig 1. PRISMA flowchart showing the classification of the extracted articles related to epilepsy by repetitive Transcranial Magnetic Stimulation (rTMS) in patients with epilepsy.

Following the screening and selection process, the results of the included studies were synthesized and are presented in two principal categories: focal epilepsy and generalized epilepsy. Given the heterogeneity within focal epilepsy, this group was further subdivided into two clinically important subtypes: focal cortical dysplasia-related epilepsy, as one of the most common structural causes of drug-resistant epilepsy, and epilepsia partialis continua, representing a rare but challenging manifestation of focal seizures. This classification allowed for a more systematic presentation of the findings and facilitated a clearer comparison of the therapeutic potential of rTMS across different epilepsy phenotypes.

Table 1. Repetitive Transcranial Magnetic Stimulation (rTMS) Studies for the Treatment of Epilepsy

Author	No. of Subjects	Age	Type of Study	Epilepsy Type	Coil Form/ Localisation	Frequency (Hz)	Intensity	Duration of Study	No. of Stimuli(per day)/ Repetition (Days)	Seizures/ Interictal Epileptiform Discharges	Adverse event
Tergau [49]	9	21-48	Open-label pilot study	Focal epilepsy (Refractory focal epilepsy): 2 patients= temporal 7 patients= extratemporal	Round/ Over the vertex	0.33	Not reported	4 weeks before rTMS course 5 days (rTMS course) 4 weeks after rTMS course	1000/5 days	Significant reduction/ Not recorded	Nothing reported
Menkes [75]	1	38	Case study	Focal epilepsy (A single focal cortical dysplasia in the left parasagittal parietal)	Round/ Epileptogenic focus (2 cm to the left of electrode Pz)	0.5	95% MT	4 weeks before rTMS course 4 weeks (rTMS course) 4 weeks after rTMS course	100/ Biweekly for four weeks	Significant reduction/ Significant reduction	Nothing reported
Theodore [51]	24	40 ± 14	Randomized, double-blind, sham-controlled	Focal epilepsy: 10 patients= mesial temporal foci 10 patients= lateral temporal neocortical 3 patients= frontal 1 patient= parietal	Figure-of-eight/ Epileptogenic focus	1	120% MT	8 weeks before rTMS course 1 week (rTMS course) 8 weeks after rTMS course	1800/7 days	Not significant reduction (The reduction observed was not significant)/ Not recorded	One patient reported mild discomfort during stimulation. Another patient did not complete the full week of stimulation, but continued to see positive effects.
Tergau [50]	17	29 ± 10	Multi center, crossover, placebo-controlled	Focal and generalized epilepsy: 11 patients= focal neocortical 2 patients= focal mesial temporal 2 patients= multifocal 2 patients= generalized epilepsy	Round/ Over the vertex	1 and 0.333 in real 0.666 in placebo	Not reported	Stimulation was occurred in 3 separate 5-day randomized rTMS courses (two courses with real stimulation and one course with placebo stimulation). In all rTMS courses, the subjects were examined 4 weeks before and 4 weeks after the rTMS course.	1000/15 days (3 5-day courses)	Significant reduction only for 0.333 Hz stimulation compared to baseline/ Not recorded	Nothing reported

Daniele [76]	4	29.5 ± 2.6	Open-label pilot study	Focal epilepsy: 2 patients= unifocal cortical dysplasia in frontal 2 patients= multifocal cortical dysplasia	Figure-of-eight/ Epileptogenic focus: Over the site of focal epileptic in patients with unifocal and over the Cz in patients with multifocal epilepsy	0.5	90% MT	4 weeks before rTMS course 4 weeks (rTMS course) 4 weeks after rTMS course	100/ Biweekly for four weeks	Significant reduction only by stimulation over the epileptogenic focus in patients with single focus of cortical dysplasia (improvement persisted 1 month)/ Not recorded	Nothing reported
Rossi [78]	1	34	Case study	Focal epilepsy (Focal cortical dysplasia of the right motor cortex)	Figure-of-eight/ Over the cortical dysplasia	1	90% MT	None	900/1 day	Not recorded/ Not significant reduction	Nothing reported
Brasil-Neto [52]	5	27.4 ± 14.6	Open label	Focal epilepsy: 2 patients= temporal 3 patients= frontal	Round/ Over the Cz	0.3	95% MT	3 months before rTMS course 3 months (rTMS course) 3 months after rTMS course	100/ Twice a week for 3 months	Significant reduction/ Not recorded	Nothing reported

Graff-Guerrero [83]	2	9.0 ± 2.0	Case study	Focal epilepsy (Epilepsia Partialis Continua): first patient= fronto-medial and left fronto-lateral second patient= left frontal and right parietal	Figure-of-eight/ Left frontal cortex	20	Patient 1= 50% MT Patient 2= 128% MT	1 day	600/1 day	Significant reduction in one of two patients/ Not recorded	Nothing reported
Misawa [84]	1	31	Case study	Focal epilepsy (Epilepsia Partialis Continua)	Figure-of-eight/ Over the left hand motor area (5 cm lateral to Cz)	0.5	90% MT	Stimulation was occurred in 2 separate rTMS sessions. In each rTMS session, the subject was examined up to 3 months after the rTMS sessions.	100/2 days	Significant reduction for 2 months (After each stimulation session)/ Not recorded	Nothing reported
Kinoshita [53]	7	23.3 ± 5.4	Open-label pilot study	Focal epilepsy (Focal extratemporal epilepsy)	Round/ Over the FCz or PCz	0.9	90% rMT or 100% aMT (When rMT was higher than the maximum output of the stimulator)	2 weeks before rTMS course 1 week (rTMS course) 2 weeks after rTMS course	Two patients = 810 (Because they received 1 session per day) Other patients= 1620/5 days	Not significant reduction (The reduction observed was not significant))/ Not recorded	During rTMS, two patients complained of headache. But no seisures occured during rTMS.
Fregni [54]	8	24.2 ± 9.5	Open label	Focal epilepsy: 1 patient= posterior quadrants 2 patients= temporal 1 patient= left temporal 4 patients= multifocal	Figure-of-eight/ Epileptogenic focus: Over the site of focal epileptic in patients with focal and Cz in patients with multifocal epilepsy	0.5	65% of maximum stimulator output	1 month before rTMS course 1 day (rTMS course) 1 month after rTMS course	600/1 day	Significant reduction for 1 month/ Significant reduction for 1 month	Nothing reported

Fregni [77]	21	21.9 ± 8.1	Randomized, double-blind, sham-controlled	Focal epilepsy: 17 patients= focal epilepsy 4 patients= structural multifocal epilepsy (due to malformations of cortical development)	Figure-of-eight/ Epileptogenic focus in patients with focal epilepsy and for 4 patients with MCD over the Cz.	1	70% of maximum stimulator output	1 month before rTMS course 5 days (rTMS course) 2 months after rTMS course	1200/5 days	Significant reduction for 2 months/ Significant reduction only for the active group compared to baseline for 1 month.	5 patients complained of mild headache after rTMS
Mecarelli [55]	1	22	Sham-controlled	Focal epilepsy (focal epilepsy with fixation-off sensitivity)	Round/ Over the vertex	0.33	100% rMT	Stimulation was occurred in 2 separate 5-day rTMS courses with a 4-month interval. In each rTMS course, the subject was examined 2 months before and after the rTMS sessions.	1000/10 days (2 5-day courses)	Not significant reduction/ Significant reduction after real stimulation	Nothing reported
Brighina [56]	6	37.0 ± 5.7	Case study	Focal epilepsy: 3 patients= unifocal epilepsy 3 patients= multifocal epilepsy	Figure-of-eight/ Over the cerebellar cortex	5	90% MT	4 weeks before rTMS course 4 weeks (rTMS course) 4 weeks after rTMS course	100/4 weeks	Significant reduction/ Not recorded	Nothing reported
Cantello [80]	43	36.9 ± 13.0	Randomized, double-blind, sham-controlled, crossover	Focal and generalized epilepsy: 19 patients= cryptogenic epilepsy 22 patients= symptomatic epilepsy 2 patients= generalized epilepsy	Round/ Over the vertex	0.3	100% rMT	12 weeks before rTMS course 1 week (rTMS course) 6 weeks after rTMS course	1000/5 days	Not significant reduction/ Significant reduction in one-third of patients	7/43 complained of headache associated with the rTMS,but no major adverse events were reported.

Joo [79]	35	25	Randomized	Focal epilepsy: 18 patients= unifocal epilepsy 17 patients= multifocal epilepsy	Round/ Epileptogenic focus for focal epileptic and over the vertex for multifocal epileptic	0.5	100% rMT	8 weeks before rTMS course 5 days (rTMS course) 8 weeks after rTMS course	3000 and 1500/5 days	Not significant reduction/ Significant reduction	Five patients complained of a mild and transient headache during and immediately after rTMS.
Rodriguez [57]	12	29.3 ± 15.8	Open label	Focal epilepsy (Focal neocortical epilepsy): 2 patents= temporal 4 patients= frontal 6 patients= fronto-temporal	Figure-of-eight/ Epileptogenic focus	0.5	120% MT	4 weeks before rTMS course 2 weeks (rTMS course) 8 weeks after rTMS course	900/2 weeks	Not significant reduction/ Significant reduction	One patient complained headache after rTMS. One other patient presented aseizure at the beginning of the rTMS session. Other showed a light rest tremor in the hands at the end of the first week of rTMS.
Rotenberg [85]	1	14	Case study	Focal epilepsy (Epilepsia Partialis Continua)	Figure-of-eight/ Epileptogenic focus	1	100% MT	Stimulation was occurred in 9-day rTMS sessions. In each rTMS session, the subject was examined 30 minutes before and after the rTMS sessions.	1800/9 days	Significant reduction in seizure duration only during stimulation/ Not recorded	Nothing reported
Rotenberg [86]	7	40.7 ± 21.3	Open label	Focal epilepsy (Epilepsia Partialis Continua)	Figure-of-eight/ Epileptogenic focus	20-100 or 1	100% MT (Except for one case, which was 90–100% MO)	There was no fixed schedule. 1-2 days follow-up in most cases and up to >4 months in one case	Diverse/ Different	Significant reduction, but in most cases short lasting/ Not recorded	Mild side effects include transient head and limb pain, and limb stiffening during high-frequency no exacerbation of seizures or secondary generalization

Sun [58]	60 patients in 2 groups	20.5 ± 7.0	Randomized, single-blind, controlled, parallel group	Focal epilepsy (Refractory focal epilepsy): 21 patients= frontal 26 patients= central parietal 3 patients= mesial-temporal 3 patients= neocortical-temporal 7 patients= occipital	Figure-of-eight/ Epileptogenic focus	0.5	Group1= 90% rMT Group2= 20% rMT	4 weeks before rTMS course 2 weeks (rTMS course) 8 weeks after rTMS course	1500/2 weeks	Significant reduction in group 1/ Significant reduction in group 1	Nothing reported
Thordstein [59]	1	68	Case study	Focal epilepsy (Anesthesia-refractory focal status epilepticus)	Figure-of-eight/ five sessions= right temporo-occipital three sessions= left fronto-anterior	0.5	100% of maximum stimulator output	Stimulation was occurred in 8-days rTMS sessions, the subject was examined 38 days before and 4 days after rTMS sessions.	First 2 days= 1800 Next 6 days= 3600/8 days	Significant reduction after twice daily rTMS// Not recorded	Nothing reported
Liu [60]	2	48.5 ± 2.5	Case study	Focal epilepsy (Refractory focal status epilepticus)	Figure-of-eight/ Epileptogenic focus (Patient 1= over the right centrotemporal Patient 2= over the left sensorimotor)	1	Patient 1= 70% machine output; Patient 2= 100% motor threshold	Stimulation was occurred in 1-days rTMS session, the subjects were examined 21 days before and 14 days after rTMS sessions.	Patient 1= 1200 Patient 2= 1800/1 day	Patient 1= Significant reduction Patient 2= Temporary reduction/ Patient 1= Significant reduction Patient 2= Not specified	Nothing reported

Van Haerents [61]	1	24	Case study	Focal epilepsy (Refractory focal epilepsy)	Figure-of-eight/ At the left occipital (O1)	1	95–100% rMT	Under supervision for 35 weeks: 6 months before rTMS course 10 days (rTMS course) 2 months after rTMS course	First day= 3600 Next 9 days= 1800/10 days	Significant reduction/ Significant reduction	Nothing reported
Gersner [62]	1	25	Sham-controlled	Focal epilepsy (Temporal lobe epilepsy)	H12-Coil/ Epileptogenic focus	1	Course 1(sham stimulation)= 83% rMT Course 2(active stimulation)= 100% rMT Course 3(active stimulation)= 110% rMT	Stimulation was occurred in 3 separate rTMS course In all rTMS courses, the subject was examined 28 days before and 28 days after rTMS course.	Course 1(10 rTMS sessions)= 18000 Course 2(15 rTMS sessions)= 27000 Course 3(30 rTMS sessions)= 54000/3 days	Significant reduction/ Not recorded	The patient tolerated few minor adverse events. She reported headache, Neck pain, anxiety and mild scalp irritation.
Seynaeve [63]	11	35.0 ± 9.9	Randomized, sham-controlled, crossover	Focal epilepsy (Refractory neocortical epilepsy)	Figure-of-eight Round Sham coil/ Epileptogenic focus	0.5	90% rMT	8 weeks before rTMS course 2 weeks (rTMS course) 10 weeks after rTMS course	1500/2 weeks	Not significant reduction/ Not recorded	Two patients with increase in seizure frequency. One patient with hearing problems after stimulation. Four patients experienced fatigue. Two patients experienced fatigue with sham treatment. One patient repoeted dfficulties with concentration.

Mukherjee [64]	30	8_18	Randomized, double-blind, sham-controlled	Focal epilepsy	Figure-of-eight/ Over the vertex	0.3	100% MT	1 months before rTMS course 1 week (rTMS course) 3 months after rTMS course	600/5 days	Not significant reduction/ Not significant reduction	Side effects including scalp itching related to irritation and headaches lasting only half to two hours have been reported.
Li [81]	2	18.5 ± 2.5	Case study	Focal epilepsy (Focal cortical dysplasia)	Figure-of-eight/ Patient 1= Epileptogenic focus Patient 2= Bilateral over the motor cortex	0.5	Patient 1= 50% rMT Patient 2= 80% rMT	36 weeks (rTMS course) 16 weeks after rTMS course	1200/20 weeks with an interval of time	Significant reduction/ Not recorded	Nothing reported
Shon [65]	4	26.2 ± 1.5	Open label	Focal epilepsy (Refractory focal epilepsy)	Figure-of-eight/ Epileptogenic focus	0.5	100% rMT	4 weeks before rTMS course 2 weeks (rTMS course) 8 weeks after rTMS course	900/10 days	Significant reduction/ Not recorded	Nothing reported
Ozek [90]	10	26.6 ± 7.6	Sham-controlled	Generalized epilepsy: (Juvenile myoclonic epilepsy)	Round/ Over the vertex	0.2	120% aMT	Stimulation (active and sham) was occurred in 2 separate 5-day rTMS courses with a 3-month interval. All patients were monitored for 3 months before the first stimulation, and for 3 months after each stimulation course.	1000/5 days	Significant reduction/ Significant reduction	Nothing reported
Ashour [66]	30	Not reported	Sham-controlled	Focal epilepsy (Focal neocortical epilepsy)	Figure-of-eight/ Epileptogenic focus	0.5	90% rMT	1 months before rTMS course 1 day (rTMS course) 1 months after rTMS course	1000/1day	Significant reduction/ Not recorded	Nothing reported

Mikellides [67]	1	28	Case study	Focal epilepsy (Frontal lobe epilepsy)	Figure-of-eight/ Epileptogenic focus: over the left and right orbitofrontal cortex	1	100-120% rMT	5 weeks (rTMS course) 6 months after rTMS course under supervision in the form of maintenance sessions.	1008/ Main sessions: 15 days(Three days in 5 weeks) Maintenance sessions: 10 days with an interval of time	Significant reduction/ Not recorded	Nothing reported
Chang [87]	1	infant (10-month-old)	Case study	Focal epilepsy (Epilepsia Partialis Continua)	Figure-of-eight/ Over the motor cortex	10	50% maximum stimulator output	11 days before rTMS course 1 day (rTMS course) 3 days after rTMS course	1200/1 day	Significant reduction/ Not recorded	Nothing reported
Starnes [82]	1	48	Case study	Focal epilepsy (A focal cortical dysplasia in the left occipital lobe)	Figure-of-eight/ Epileptogenic focus: The left occipital region	1	100% rMT	2 days before rTMS course 5 days (rTMS course) 6 months after rTMS course	1800/5 days	Significant reduction/ Not recorded	Nothing reported
Carrette [68]	7	40.1 ± 13.7	open-label pilot study	Focal epilepsy (Focal neocortical epilepsy)	Figure-of-eight/ Epileptogenic focus	50	80% MT	4 weeks before rTMS course 1 week (rTMS course) 7 weeks after rTMS course	3000/4 days	Significant reduction/ Not recorded	The reported side effects were mild and transient in all subjects.
Jin [69]	4	Not reported	Open-label pilot study	Focal epilepsy (Benign epilepsy with centrotemporal spikes or rolandic epilepsy)	Figure-of-eight/ Bilateral (in both hemispheres)	1	90% rMT	3 months before rTMS course 2 weeks (rTMS course) 6 months after rTMS course	1000/10 days	Significant reduction for at least 3 months/ Not recorded	Nothing reported
Yang [70]	8	5.8 ± 1.2	Case study	Focal epilepsy (Self-limited epilepsy with centrotemporal spikes with electrical status epilepticus in sleep)	Figure-of-eight/ Over the central region (C5 or C6)	≤ 1	Not reported	1 month before rTMS course 2 weeks (rTMS course) 12 months after rTMS course	500, 1000, 1500 (depending on the frequenc)/ 10 days	Significant reduction/ Not recorded	Nothing reported

Celebi [91]	12	34.5 ± 8.8	Single-blind, placebo-controlled, crossover, pilot study	Focal and generalized epilepsy: 7 patients= focal epilepsy 5 patients= generalized epilepsy	Focal epilepsy = Figure-of-eight Generalized epilepsy = Round Focal epilepsy = Epileptogenic focus Generalized epilepsy = Over the vertex	30	80% rMT	Subjects were monitored for 8-12 weeks before and after active and sham stimulation. The treatment period was 5 consecutive days.	600/5 days	Significant reduction/ Not significant reduction	Two patients reported adverse effects after sham cTBS; headache in one and feeling restlessness in the other. Three patients reported adverse effects after active stimulation; dizziness on day two in one, headache on day two in one, and spasm in the jaw in one.
Velasco-M´erida [88]	2	21.5 ± 2.5	Case study	Focal epilepsy (Epilepsia Partialis Continua)	Figure-of-eight, and round/ Patient 1= over Cz and C3 Patient 2= over the Cz, C4, Pz, and P4	0.5	Patient 1= 100% MT Patient 2= 120% MT	1 day (rTMS course) 1 month after rTMS course	Patient 1= 1000 Patient 2= 1065/1day	Significant reduction only in patient 1/ Not recorded	Nothing reported
Wang [71]	38	31.0 ± 1.5	Randomized, double-blind, sham-controlled, crossover	Focal epilepsy	Figure-of-eight/ Cerebellar region	50	80% rMT	Stimulation was occurred in 2 separate 10-day rTMS courses with a 2-month interval. All patients were monitored for 1 month before the first stimulation course and for 2 months after each rTMS course.	2400/10 days	Significant reduction/ Not significant reduction	Moderate headache was present in 5% of patients, tinnitus in 3% of patients, and dizziness in 3% of patients.
Algoet [89]	3	35.3 ± 12.2	Case study	Focal epilepsy (Epilepsia Partialis Continua)	Figure-of-eight/ Epileptogenic focus	50	80% rMT	Assessments were recorded 15 minutes before and after each session, as well as 24 hours after the last session. 4 days (rTMS course)	3000/4 days	Not significant reduction/ Not recorded	Headache occurred in one patient.

Melus [72]	18 patients in 2 groups	38.4 ± 8.8	Randomized, single-blinded, sham-controlled, crossover	Focal epilepsy	Figure-of-eight/ Epileptogenic focus	0.5	90% rMT	Stimulation was occurred in 2 separate 5-day rTMS courses with a 3-month interval. All patients were monitored for 4 weeks before the first stimulation, and for four weeks after each stimulation course.	3000/10 days (2 5-day courses)	Significant reduction/ Not significant reduction	Nothing reported
She [73]	19	10.0 ± 1.4	Randomized, sham-controlled, crossover	Focal epilepsy	Figure-of-eight/ Over the motor cortex	1	90% rMT	One active session and one sham session were randomly assigned 6 days apart (rTMS course). Comparison of the effect of rTMS compared to baseline was performed on the same day of the experiment.	1000/2 days	Not recorded/ Significant reduction	Nothing reported
Sinha [74]	49	8.9 ± 2.9	Randomized, double-blind, sham-controlled	Focal epilepsy (Refractory focal epilepsy)	Figure-of-eight/ Epileptogenic focus	0.5	110% rMT	1 month before rTMS course 10 days (rTMS course) 8 weeks after rTMS course	1200/10 days	Significant reduction/ Not recorded	Mild side effects such as headache and scalp discomfort have been reported.

3. 1. Focal Epilepsy

Early clinical investigations on rTMS primarily focused on patients with focal epilepsies, particularly those with focal epilepsies arising from a specific lobe (unifocal) or multifocal epilepsy. These studies are primarily designed to assess the potential impact of magnetic stimulation on cortical excitability in the context of drug-resistant epilepsy. The first clinical investigation assessing the therapeutic potential of rTMS in epilepsy was reported in 1999 by Tergau et al. [49]. In this 5-day, open-label pilot study, nine patients with refractory focal epilepsy (seven with extratemporal and two with temporal lobe epilepsy) received low-frequency stimulation (0.33 Hz) consisting of 1000 pulses delivered with a round coil positioned over the vertex. Patients were monitored for four weeks prior to and up to eight weeks following the intervention. While seizure frequency returned to baseline levels within six to eight weeks, a significant reduction of 36.6% was observed during the four-week post-treatment period, corresponding to the predefined trial duration. The promising outcomes of this trial laid the groundwork for further evaluating the role of rTMS in epilepsy.

In 2003, Tergau et al. [50] further investigated the effects of rTMS on epilepsy in a larger cohort encompassing a broader spectrum of epilepsy types compared to their initial study. This multicenter, randomized, crossover, placebo-controlled trial involved 17 patients with either focal or generalized epilepsy, each undergoing three separate 5-day treatment courses (two with active stimulation and one with placebo stimulation). Low-frequency stimulation (1 Hz and 0.33 Hz in the active conditions and 0.66 Hz in the placebo condition) was delivered using 1000 pulses per session with a round coil positioned over the vertex. Patients were monitored for four weeks before and after each treatment course. A significant reduction of approximately 70% in seizure frequency was observed exclusively during and up to two weeks following the 0.33 Hz active stimulation protocol, relative to baseline.

In a randomized, double-blind, sham-controlled trial, Theodore et al. [51] evaluated the effects of rTMS in 24 patients with focal epilepsy, including cases of mesial and neocortical temporal lobe epilepsy as well as frontal and parietal lobe epilepsy. Patients were monitored for eight weeks before and eight weeks after the intervention. During the treatment phase, they underwent daily sessions of low-frequency rTMS at 1 Hz for one week, consisting of 1800 pulses per day delivered at 120% of the motor

threshold using a figure-of-eight coil positioned over the epileptogenic focus. This protocol did not result in a statistically significant reduction in seizure frequency when compared with baseline or sham stimulation.

In contrast, Brasil-Neto et al. (2004) [52] reported more favorable outcomes in an open-label trial, including five patients with focal epilepsy localized to a specific lobe (two with temporal and three with frontal lobe epilepsy). In this study, low-frequency stimulation (0.3 Hz) was applied using a round coil positioned over the Cz at 95% of the motor threshold, administered twice weekly for three months. Participants were monitored for three months before the intervention and followed for three months afterward. Although the degree of seizure reduction varied among individuals, a mean reduction of 22.8% was observed across the cohort.

Subsequently, Kinoshita et al. (2005) [53] conducted an open-label study in seven patients with focal extratemporal epilepsy. A 5-day treatment protocol over one week was applied, delivering 1620 pulses per session (810 pulses in two participants) at 0.9 Hz and 90% of the motor threshold using a round coil positioned over the FCz and PCz. Patients were monitored for two weeks before and two weeks after the intervention. Similar to the trial by Theodore et al., no significant reduction in seizure frequency was observed.

In the same year, Fregni et al. [54] conducted a 1-day open-label study in eight patients with focal epilepsy, including four with epilepsy localized to specific lobes and four with multifocal epilepsy. Low-frequency rTMS (0.5 Hz) was applied at 65% of maximum stimulator output, delivering 600 pulses with a figure-of-eight coil positioned over the epileptogenic focus in patients with focal epilepsy and over the Cz in those with multifocal epilepsy. Patients were monitored for one month before and one month after the intervention. Active stimulation was associated with a significant reduction in seizure frequency, with decreases of 57.3% and 51.2% observed at 15 and 30 days post-treatment, respectively, compared with the pre-treatment baseline. Moreover, significant reductions in interictal epileptiform discharges were noted, with decreases of 46.4% and 42.1% at the same time points.

In 2006, Mecarelli et al. [55] conducted a sham-controlled study involving a 22-year-old patient with focal epilepsy characterized by sporadic seizures originating from the temporo-parieto-occipital region. The intervention consisted of two separate 5-day sessions of low-frequency rTMS (0.3 Hz) delivered four months apart, with 1000 pulses per session administered via a round coil at 100% of the resting motor threshold. The patient was monitored for two months before and after each rTMS course. While the stimulation protocol did not produce a reduction in seizure frequency, it was associated with a decrease in interictal epileptiform discharges following active stimulation. Within the same year, Brighina et al. [56] evaluated the impact of high-frequency rTMS on six patients with focal epilepsy, including three individuals with unifocal and three with multifocal seizure foci. The intervention consisted of 100 pulses per session at 5 Hz and 90% of the motor threshold, delivered to the cerebellar cortex via a figure-of-eight coil over four weeks. Participants were closely monitored for four weeks before and four weeks after the treatment course. The protocol resulted in an average seizure frequency reduction of 52.9% within the study cohort.

In continuation of the investigations, Rodriguez et al. (2008) [57] reported comparable outcomes in an open-label trial involving 12 patients with focal epilepsy localized to specific lobes. Participants received a two-week course of low-frequency stimulation consisting of 900 pulses at 0.5 Hz and 120% of the motor threshold, delivered with a figure-of-eight coil over the epileptogenic focus. This protocol failed to yield a significant reduction in seizure frequency. However, a marked effect on cortical excitability was observed, as evidenced by a 54.9% reduction in interictal spikes as a type of interictal epileptiform discharge following active stimulation.

In 2012, Sun et al. [58] conducted a randomized, single-blind, sham-controlled trial involving 60 patients with focal epilepsy localized to specific lobes. Participants were stratified into two groups according to their motor threshold level for rTMS and subsequently received low-frequency stimulation (0.5 Hz) targeted to the epileptogenic zone. The intervention was delivered over two weeks, consisting of 1500 pulses per session administered with a figure-of-eight coil. Patients were monitored for four weeks before the intervention and for eight weeks thereafter. The findings demonstrated that, while the therapeutic response varied between groups, individuals with a higher motor threshold exhibited a

statistically significant reduction in both seizure frequency and interictal epileptiform discharges following rTMS treatment. In the same year, Thordstein et al. [59] reported a case study involving a middle-aged patient with focal epilepsy (anesthesia-refractory focal status epilepticus), in which an 8-day rTMS treatment protocol was administered. Low-frequency stimulation (0.5 Hz) was delivered at 100% of maximum stimulator output using a figure-of-eight coil; however, stimulation parameters varied across the course. Specifically, 1800 pulses per day were applied during the first two days, followed by 3600 pulses per day for the subsequent six days. In addition, the stimulation site was altered over the course of treatment, with the coil positioned over the right temporo-occipital region during the initial five sessions and shifted to the left fronto-anterior region during the final three sessions. The patient was monitored for 38 days before and four days after the intervention. Notably, a significant reduction in seizure frequency was observed only during the latter phase of the protocol, coinciding with the higher stimulation intensity (3600 pulses/day).

In 2013, Liu and colleagues [60] presented a brief case study exploring the short-term effects of rTMS in two patients with focal epilepsy. The intervention consisted of a single stimulation session in which low-frequency rTMS at 1 Hz was delivered to the epileptogenic foci using a figure-of-eight coil. Stimulation intensity varied between the two cases, with one patient receiving 1200 pulses and the other 1800 pulses. Clinical monitoring was performed 21 days before and 14 days after the intervention. The outcomes revealed a marked reduction in seizure frequency in one patient, whereas the other did not exhibit significant improvement. These divergent responses highlight the variability of individual outcomes in rTMS treatment and underscore the limitations of drawing firm conclusions from such small-scale observations. Stated otherwise, the limited sample size and heterogeneous response preclude drawing definitive conclusions regarding the efficacy of this protocol. Nonetheless, two additional case studies [61,62], conducted one year apart, provide further insight, as outlined below.

In 2015, Van Haerents et al. [61] reported a 10-day interventional study in a 24-year-old patient with focal epilepsy. Low-frequency repetitive stimulation (1 Hz) was applied using a figure-of-eight coil at 100% of the resting motor threshold over the left occipital cortex. On the initial day, 3,600 pulses were delivered, followed by 1,800 pulses per day across the subsequent nine sessions. The patient was

prospectively monitored for six months before treatment and for two months thereafter. The intervention was associated with a sustained reduction in seizure frequency (lasting up to nine months post-treatment) as well as a marked decrease in interictal epileptiform discharges.

One year later, Gersner et al. [62] reported a sham-controlled study in a patient with temporal lobe epilepsy. The protocol comprised three independent rTMS courses, with clinical evaluations performed 28 days before and 28 days after each intervention. The stimulation paradigms consisted of 10 sessions during the first course, 15 during the second, and 30 during the third, all delivered at a low frequency of 1 Hz within a single day. The coil was precisely positioned over the epileptogenic focus. Notably, each intervention was associated with a substantial reduction in seizure frequency, ranging from 50% to 70%, underscoring the potential therapeutic relevance of targeted low-frequency rTMS in refractory epilepsy.

Despite these promising results, two subsequent investigations failed to demonstrate significant clinical improvements. Seynaeve et al. [63] in the same year reported less favorable outcomes. In a randomized, sham-controlled crossover trial including 11 patients with focal epilepsy, the investigators evaluated the impact of coil type on treatment efficacy. The intervention consisted of a 2-week course of low-frequency rTMS (0.5 Hz, 1500 pulses per session) delivered at 90% of the resting motor threshold using both figure-of-eight and round coils, targeted over the epileptogenic foci. Patients were observed for 8 weeks before treatment and for 10 weeks thereafter. Unlike the preceding studies, this trial did not demonstrate any significant reduction in seizure frequency, irrespective of the coil type employed. Similarly, Mukherjee et al. (2018) [64] in a randomized, double-blind, sham-controlled trial of 30 patients with focal epilepsy, administered low-frequency stimulation (0.3 Hz, 600 pulses per session at 100% of the motor threshold) over a 5-day course within a one-week treatment period using an octagonal coil. When seizure frequency during the 1-month baseline was compared with that of the 3-month follow-up, no significant differences emerged.

Together, these findings highlight the need to clarify stimulation parameters and patient-related factors that may contribute to treatment responsiveness. While some trials failed to establish clear clinical benefits, several subsequent studies consistently provided compelling evidence supporting the efficacy

of rTMS, reporting statistically significant improvements in seizure outcomes [65–71]. Among these, one of the earliest significant contributions was made in 2019, when Shon et al. [65] presented an open-label clinical investigation involving four patients with focal epilepsy. In this trial, low-frequency rTMS (0.5 Hz) was administered at 100% of the motor threshold, delivering 900 pulses via a figure-of-eight coil directly over the epileptogenic foci. The treatment was distributed across a 10-day course within two weeks, with participants undergoing baseline monitoring for four weeks before stimulation and follow-up assessments for eight weeks thereafter. Importantly, the intervention was associated with a significant reduction in seizure frequency, an effect that remained evident throughout the entire follow-up period, underscoring the potential durability of rTMS-induced clinical benefits.

Building upon earlier reports of beneficial outcomes, Ashour et al. (2020) [66] further reinforced the therapeutic potential of rTMS through a sham-controlled study in 30 individuals with neocortical focal epilepsy. Using an octahedral coil, patients underwent a 1-day session of low-frequency stimulation (0.5 Hz) at 90% of the resting motor threshold, each comprising 1000 pulses. Clinical monitoring over a month pre- and post-intervention period revealed striking effects: seizure frequency was reduced by 87.5% in the active treatment group, compared with a 50% reduction in the sham group. These findings are aligned with the growing body of studies reporting significant clinical improvements.

Another notable step forward was marked in 2021, Mikellides et al. [67] reported a case study involving a 28-year-old man with frontal lobe epilepsy who underwent rTMS targeted at the epileptogenic focus (over the left and right orbitofrontal cortex) using a figure-of-eight coil with a stimulation frequency of 1 Hz (Fig. 2). The main treatment phase lasted for five weeks, during which the patient received stimulation three times per week. Following this initial course, a prolonged six-month stabilization phase was implemented, consisting of weekly sessions during the first month, biweekly sessions in the second month, and monthly sessions for the remaining four months. Remarkably, the extended stimulation protocol was associated with a sustained and clinically meaningful reduction in seizure frequency.

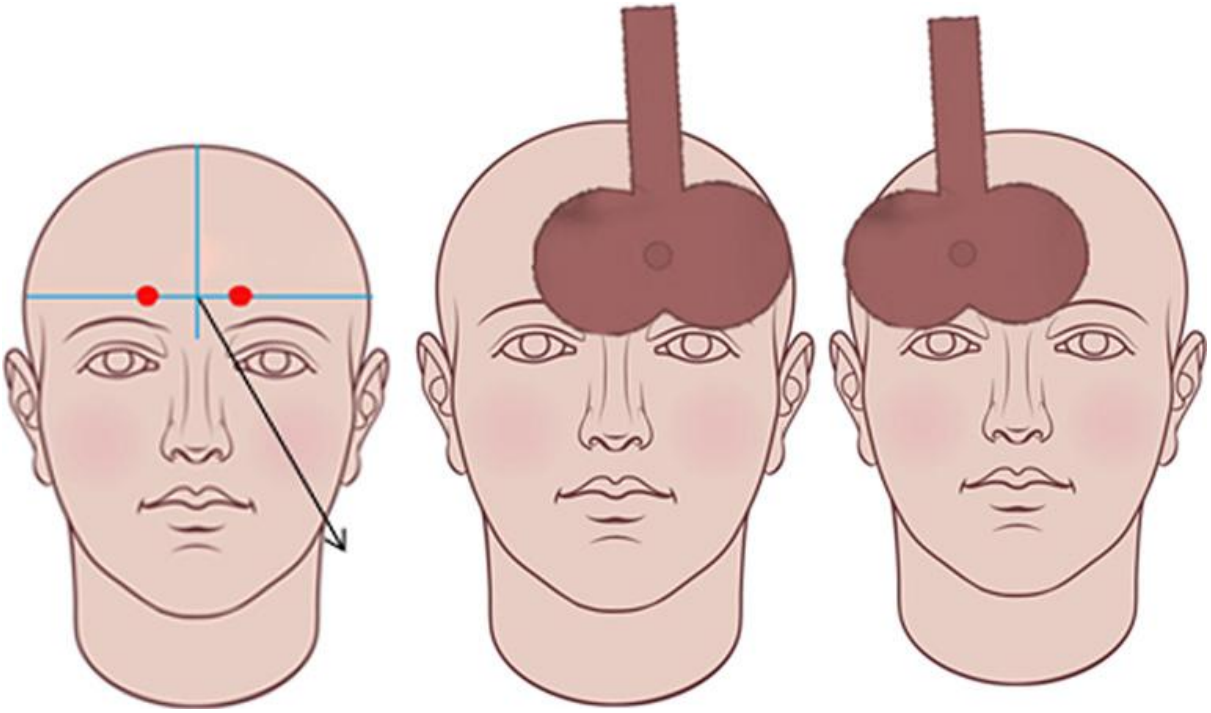

Fig. 2. "This figure illustrates the precise method for positioning and orienting the Transcranial Magnetic Stimulation (TMS) coil used in this study. (A) Targeting the Stimulation Sites (Fp1 & Fp2): This panel details the anatomical targeting process based on the standardized 10–20 electroencephalogram (EEG) system. First, the midline point 'Fpz' was located by measuring 10% of the total distance from the nasion (bridge of the nose) to the inion (bony prominence at the back of the skull) along the scalp's midline. From the Fpz point, measurements were then taken laterally (to the left and right) along the scalp, each equal to 5% of the total head circumference. The endpoints of these lateral measurements define the exact target locations for stimulation: Fp1 (left hemisphere) and Fp2 (right hemisphere). (B) Left Hemisphere Coil Orientation: This panel shows the specific angle and position (tangential to the scalp) at which the TMS coil was placed over the Fp1 target site on the left side of the head. (C) Right Hemisphere Coil Orientation: This panel shows the specific angle and position (tangential to the scalp) at which the TMS coil was placed over the Fp2 target site on the right side of the head. [Key Takeaway: This standardized, measurement-based protocol ensured accurate and consistent stimulation of the prefrontal cortical regions (Fp1/Fp2) across all participants.]" Taken from [67] with permission.

Continuing this line of promising evidence, Carrette et al. in 2022 [68] conducted an open-label pilot study to assess the therapeutic potential of rTMS in patients with focal neocortical epilepsy. The investigation included seven individuals who underwent a 4-day treatment course administered within one week. The stimulation protocol consisted of continuous theta-burst stimulation (cTBS) at 50 Hz, delivered at 80% of the resting motor threshold, for a total of 3,000 pulses via a figure-of-eight coil positioned over the epileptogenic focus. Clinical outcomes were evaluated by comparing seizure frequency during a 4-week baseline period with that of a 7-week follow-up phase. The findings revealed a substantial reduction in seizure burden, with mean weekly seizure frequency decreased by approximately 60% during follow-up relative to baseline, thereby underscoring the potential efficacy of high-frequency cTBS in this patient population.

Complementing these findings, an additional open-label pilot study in the same year reported convergent evidence on the potential benefits of rTMS. Jin et al. [69] applied low-frequency rTMS at 1 Hz and 90% of the resting motor threshold via a figure-of-eight coil bilaterally over the centrotemporal cortex in four patients with focal Rolandic epilepsy. The intervention consisted of 10 sessions administered over two weeks. Patients were closely monitored for three months before the treatment and subsequently followed for six months post-intervention. Comparative analyses between the baseline and follow-up periods revealed a significant reduction in seizure frequency, with therapeutic benefits persisting for at least three months after the conclusion of treatment.

In the following year, Yang et al. [70] expanded this line of research by conducting a two-week treatment protocol involving ten sessions of low-frequency rTMS in eight patients with focal epilepsy (Self-limited epilepsy with centrotemporal spikes with electrical status epilepticus in sleep). Stimulation was administered with a figure-of-eight coil positioned over the central cortical region. Participants underwent a one-month baseline monitoring phase before intervention and were followed longitudinally for twelve months post-treatment. Results revealed a significant reduction in seizure frequency, further reinforcing the therapeutic potential of rTMS as a sustained intervention for focal epilepsy (Fig. 3).

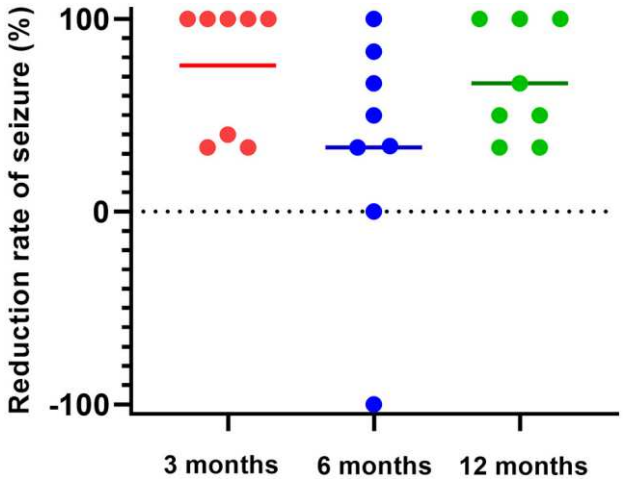

Fig. 3. "Long-term reduction in seizure frequency following repetitive transcranial magnetic stimulation (rTMS). The bar graph shows the clinical response for eight patients over three time points after treatment. At 3 months post-rTMS, five patients (62.5%) were completely seizure-free, while the other three experienced a reduction of less than 50% (red bars). By 6 months post-treatment, the response evolved: four patients maintained a reduction greater than 50%, two patients showed a reduction of approximately 30%, one patient's seizure frequency returned to pre-treatment levels, and one patient experienced an increase in seizures (blue bars). At the 12-month follow-up, three patients remained seizure-free, three patients sustained a reduction greater than 50%, and two patients maintained an approximate 30% reduction (green bars)." Taken from [70] with permission.

In the following year (2024), Wang et al. [71] advanced this line of research through a randomized, double-blind, sham-controlled crossover study. In this study, patients underwent two separate 10-day courses of rTMS, spaced two months apart, in which continuous theta-burst stimulation (cTBS) at 50 Hz was applied to the cerebellum using a figure-of-eight coil. Each session delivered 2,400 pulses at 80% of the resting motor threshold intensity. Participants were monitored for one month before the initial intervention and for two months after each stimulation period. The results demonstrated a significant reduction in seizure frequency, accompanied by a transient decrease in interictal epileptic discharges, thereby highlighting both the therapeutic potential and the temporal dynamics of cerebellar-targeted rTMS in focal epilepsy (Fig. 4).

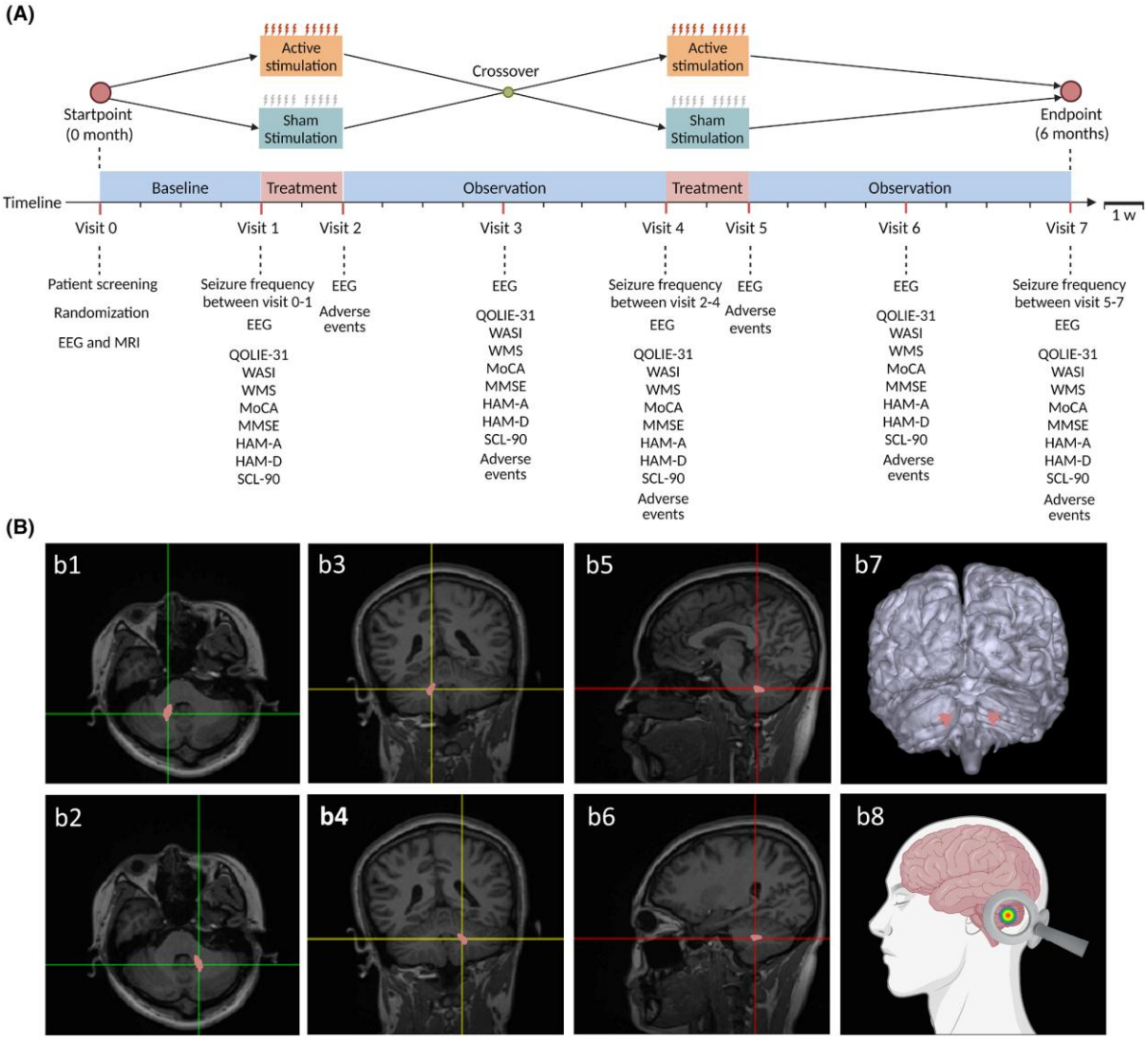

Fig. 4. "Study timeline and schematic of targeted cerebellar stimulation. (A) Trial timeline illustrating the crossover study design. (B) Visualization of neuronavigated continuous theta-burst stimulation (cTBS) applied to

the cerebellum. The target was planned using a 3D reconstruction of an individual's MRI scan. Representative MRI slices from one patient display the stimulation target in transverse (b1–b2), coronal (b3–b4), and sagittal (b5–b6) views. The cerebellar dentate nucleus (CDN), the deep cerebellar target (b1–b7), is situated within the white matter near the vermis and the fourth ventricle's roof. A double-cone coil (b8) was positioned to direct the stimulation at the CDN. Abbreviations: cTBS, continuous theta-burst stimulation; EEG, electroencephalogram; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; QOLIE-31, Quality of Life in Epilepsy Inventory; SCL-90, Symptom Checklist-90; WASI, Wechsler Abbreviated Scale of Intelligence; WMS, Wechsler Memory Scale." Taken from [71] with permission.

Most recently, in 2025, three independent investigations were conducted, marking one of the most productive periods in this line of research [72–74]. Collectively, these studies provide further insights into the clinical applicability of rTMS in focal epilepsy and reinforce its potential as a promising therapeutic approach. The first of these recent investigations, conducted by Melus et al., evaluated the effects of rTMS in a cohort of patients with focal epilepsy in the form of a randomized, placebo-controlled, double-blind crossover study. In this study, participants underwent a 10-day treatment course, during which low-frequency stimulation at 0.5 Hz and 80% resting of the motor threshold was delivered via a figure-of-eight coil positioned over the epileptogenic focus. The intervention was administered 2 separate 5-day rTMS courses with a 3-month interval, with a total of 3000 pulses per session. Patients were monitored for 4 weeks prior to the intervention and followed for 4 weeks thereafter. This protocol led to a notable decrease in seizure frequency, most prominently in the first two weeks after stimulation, providing further confirmation of the modulating effects of rTMS on cortical excitability in focal epilepsy [72]. Building upon these findings, the next study was explored by She et al. [73] investigated the immediate effects of rTMS in a cohort of 19 patients with focal epilepsy. In this randomized, sham-controlled crossover study, participants received a single active session and a single sham session, separated by a six-day interval. Low-frequency stimulation (1 Hz) at 90% of the motor threshold was delivered in 1,000 pulses via a figure-of-eight coil targeting the motor cortex. Comparisons with baseline measures on the same day revealed a significant reduction in interictal epileptiform discharges, highlighting the acute modulatory impact of rTMS on cortical excitability (Fig. 5).

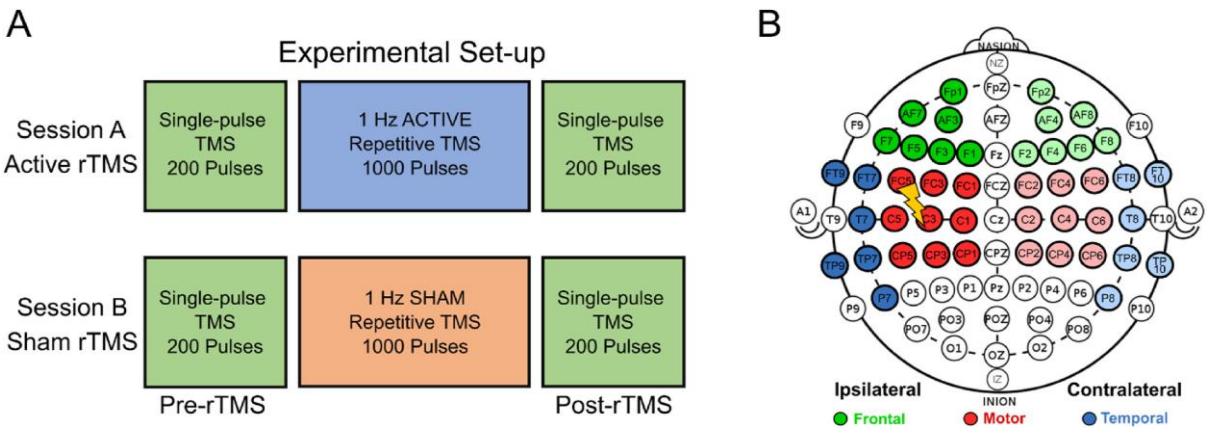

Fig. 5. Panel A illustrates the experimental timeline. Participants underwent single-pulse TMS combined with EEG (spTMS-EEG) targeting the motor cortex (indicated by green boxes) both before and after receiving a series of either active (blue) or sham (orange) repetitive TMS (rTMS) sessions. The order of these active or sham sessions was randomized for each participant. Panel B details the high-density EEG setup and analysis. The hemisphere directly stimulated by rTMS is labeled 'ipsilateral,' while the opposite hemisphere is 'contralateral.' Key regions analyzed for brain activity included the frontal (green), motor (red), and temporal (blue) areas in both hemispheres (Taken from [73] with permission).

The final investigation in this series, conducted by Sinha et al. [74], provided further insights into the therapeutic potential of rTMS in focal epilepsy. In this randomized, double-blind, sham-controlled crossover study, 49 patients received 1200 pulses of low-frequency stimulation at 0.5 Hz and 110% of the resting motor threshold, administered via a figure-of-eight coil over the epileptogenic focus across a 10-day treatment course. Participants were carefully monitored for one month prior to the intervention and followed for eight weeks post-treatment. The active rTMS sessions were associated with a marked clinical benefit, with over 50% seizure reduction observed in 76% of patients, thereby reinforcing the growing body of evidence supporting rTMS as a promising modulatory strategy in focal epilepsy. This study investigated the efficacy of transcranial magnetic stimulation (TMS) in reducing seizure frequency. Patients were randomly assigned to either an active TMS treatment group or a sham (placebo) control group. Both groups were assessed before and after the intervention period. However, post-therapy the active TMS arm showed significantly lower median weekly seizure frequency compared to the sham arm, indicating a specific therapeutic effect of the magnetic stimulation beyond a placebo response (Fig. 6).

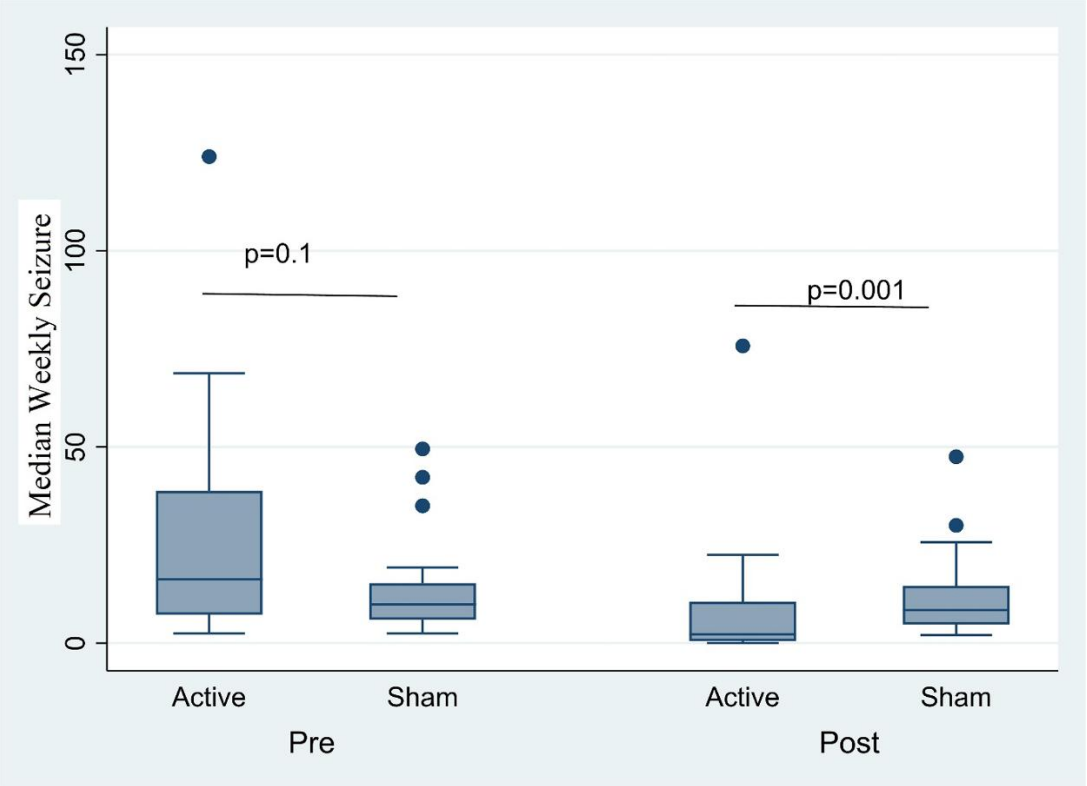

Fig. 6. Box-and-whisker plots illustrating the median weekly seizure frequency at baseline and after therapy for both the active treatment and control groups (Taken from [74] with permission).

3. 2. Focal Cortical Dysplasia

Among the structural etiologies of focal epilepsy, focal cortical dysplasia stands out as one of the most prevalent and therapeutically challenging causes. Focal cortical dysplasia is characterized by localized malformations of cortical development that give rise to highly epileptogenic zones, often resistant to pharmacological treatment and sometimes even refractory to surgical resection. Given the limited efficacy of conventional interventions in many cases, non-invasive neuromodulatory techniques such as rTMS have been explored as potential adjunctive strategies. Several studies have specifically examined the application of rTMS in patients with focal cortical dysplasia-related epilepsy, aiming to suppress cortical hyperexcitability and achieve meaningful seizure reduction [75–82].

Menkes et al. [75] reported very positive results from a case study in which low-frequency (0.5 Hz) magnetic stimulation at 95% motor threshold intensity was applied as 100 pulses, biweekly for four weeks, with a round coil over the epileptogenic focus (2 cm to the left of electrode position Pz) in a patient with single focal cortical dysplasia in the left parasagittal parietal (a type of

structural focal epilepsy). The patient was monitored for 4 weeks before and after the treatment. The number of seizures recorded during the month of treatment showed a significant 70% reduction. This effect, although at a lower percentage, was also sustained during the month after treatment. Furthermore, this stimulation was associated with a 77% reduction in the frequency of interictal spikes, as a specific type of IEDs. After this successful outcome in patients with focal cortical dysplasia, other investigators began to focus on the subpopulation of patients with structural focal epilepsy disorder. [76–82].

In 2003, Daniel et al. [76] repeated Menkes' protocol with minor changes in an open-label pilot study of 4 patients with focal cortical dysplasia, as a type of structural focal epilepsy (2 patients with unifocal cortical dysplasia in the frontal lobe and 2 patients with multifocal cortical dysplasia). The magnetic stimulation used in this study was low-frequency (0.5 Hz) with 90% of motor threshold intensity in the form of 100 pulses, biweekly for four weeks, with a figure-of-eight coil over the epileptogenic focus in patients with unifocal epilepsy and over the Cz in patients with multifocal epilepsy. The patient was monitored for 4 weeks before and after treatment. Following this protocol, only a significant reduction in seizure frequency was observed in patients with single focus cortical dysplasia. The improvement was sustained both during the month of treatment and up to one month after the end of the treatment course.

Years later, Fregni et al. [77] conducted a randomized, double-blind, sham-controlled trial involving 21 patients with malformations of cortical development, including 17 with focal epilepsy and 4 with multifocal epilepsy. Participants underwent a 5-day treatment course in which low-frequency rTMS (1 Hz) was applied at 70% of maximum stimulator output. Stimulation consisted of 1200 pulses per session delivered with a figure-of-eight coil, positioned over the epileptogenic focus in patients with focal epilepsy and over the Cz in those with multifocal epilepsy. Patients were monitored for one month before and two months following the intervention. Active rTMS significantly reduced seizure frequency, with the effect persisting for at least two months. In addition, a significant reduction in epileptiform discharges was observed immediately after treatment and at week four post-intervention, but only in the active stimulation group.

In order to investigate the effect of rTMS on patients with structural focal epilepsy disorder, Rossi et al. [78] conducted a case study on a patient with Focal cortical dysplasia of the right motor cortex, which is a type of structural focal epilepsy. In this one-day study, low-frequency magnetic stimulation (1 Hz) at 90% of motor threshold was applied over the cortical dysplasia in the form of 900 pulses using a figure-of-eight coil. This type of epilepsy manifests as myoclonic jerks in the patient's left hand. There was almost no change in the total number of seizures before and after rTMS session. The only significant change was in the amplitude of myoclonia, which decreased by about 30% on average.

In 2007, Joo et al. [79] conducted a randomized clinical study involving 35 patients with focal epilepsy, of whom 18 presented with unifocal (6 of the 18 had focal cortical dysplasia) and the remainder with multifocal epilepsy. All participants underwent an 8-week baseline monitoring period prior to the intervention and continued to be observed for 8 weeks post-treatment. The therapeutic protocol consisted of a 5-day course of low-frequency rTMS (0.5 Hz) delivered at 100% of the motor threshold using a round coil, with stimulation targeted over the epileptogenic focus in unifocal cases and over the cortex in multifocal cases. Within each treatment arm, patients were further stratified to receive either 1500 or 3000 pulses per session. Despite the structured design and relatively high stimulation dose, no significant reduction in seizure frequency was observed. Nonetheless, the intervention yielded a statistically significant decrease in interictal epileptiform discharges, suggesting a potential modulatory effect of rTMS on cortical excitability independent of seizure outcomes.

Cantello et al. [80] also published the results of their randomized, double-blind, sham-controlled crossover study on 43 patients with focal (41 patients) and general (2 patients) epilepsy. Most patients had neocortical epilepsy, the cause of which was stated to be structural damage, so it is classified as a structural focal epilepsy. Since there are two different types of epilepsy, stimulation was applied over the vertex of the brain in order to ensure the same experimental conditions. The experimental protocol was performed over 5 days, in which in the active mode, stimulation was performed by a low-frequency round coil (0.3 Hz) with an intensity of 100% of the motor threshold in the form of 1000 pulses. Subjects were monitored for 12 weeks before and 6 weeks after the treatment course. Although the seizure frequency in the active group experienced a significant decrease compared to baseline in the third week

after the treatment course, overall, similar to the study by Joo et al. [79], there was no significant change in seizure frequency and interictal epileptic discharges were only significantly reduced in one-third of patients.

In 2019, Li et al. [81] conducted a case study in which low-frequency stimulation (0.5 Hz) was administered over a 36-week treatment period, with 1200 pulses per session delivered using a figure-of-eight coil. Two patients participated: one diagnosed with focal cortical dysplasia and the other with sleep-related epilepsy. For the first patient, stimulation targeted the epileptogenic focus due to its clear localization. In contrast, for the second patient, who lacked a distinct epileptogenic focus, stimulation was applied to the M1 area of both hands. The protocol, even with bilateral inhibitory stimulation of the output of the common motor pathways, in both patients demonstrated significant cortical control and antiepileptic effects.

In another case study, Starnes et al. [82] examined the effects of rTMS on focal cortical dysplasia. Low-frequency (1 Hz) magnetic stimulation at 100% resting motor threshold was delivered as 1800 pulses per session to the epileptogenic focus (in the left occipital region) of a 48-year-old patient with a focal cortical dysplasia in the left occipital lobe using a figure-of-eight coil over a 5-day period. One month after this initial treatment, the patient achieved seizure freedom. Subsequent maintenance sessions were administered for 2 to 3 days every 2 to 4 months, resulting in a seizure-free period of six months. At the final follow-up, 17 months after the initial intervention, the patient reported only mild seizures occurring approximately every two weeks (Fig. 7).

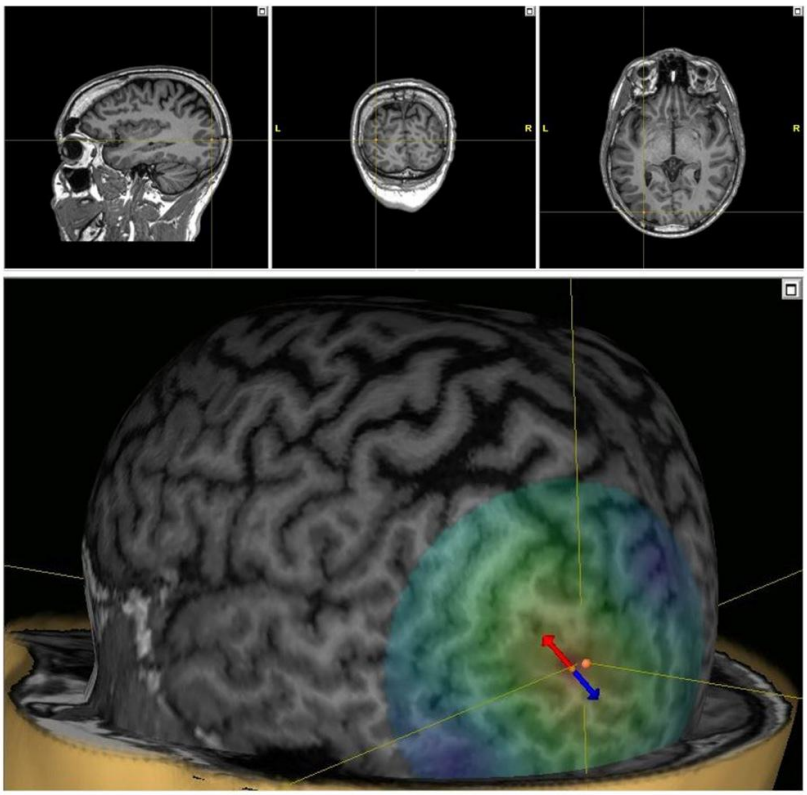

Fig. 7. "MRI-guided targeting for Transcranial Magnetic Stimulation (TMS). (A) Anatomical Localization: Stereotactic TMS targeting is planned using a patient's own magnetic resonance imaging (MRI) scans. The target site within the brain is precisely mapped across three standard anatomical planes—transverse, coronal, and sagittal (top row). (B) 3D Simulation: A three-dimensional reconstruction of the patient's brain anatomy provides a comprehensive view for treatment planning (bottom panel). The white arrow represents the primary axis of the TMS coil's electromagnetic dipole. The red and blue arrows visualize the direction of the electric field induced in the brain tissue by the TMS pulse, with red indicating the cathodal (negative) direction and blue indicating the anodal (positive) direction" (Taken from [82] with permission).

3. 3. Epilepsia Partialis Continua

The initial parts of this review summarized studies on focal epilepsy and structural focal epilepsy. The next section addresses reports on epilepsia partialis continua. Epilepsia partialis continua represents a particularly challenging and rare subtype, characterized by continuous focal motor seizures or repetitive muscle contractions that may persist for hours, days, or even longer. Given its unique pathophysiological features and therapeutic refractoriness, Epilepsia partialis continua has increasingly attracted attention as a potential target for non-invasive neuromodulatory approaches such as rTMS. In this context, several preliminary studies have investigated the feasibility and clinical outcomes of applying rTMS in patients with Epilepsia partialis continua, aiming to reduce seizure burden and improve quality of life [83–89].

In a 2004 case report, Graff-Guerrero et al. [83] administered 600 pulses of high-frequency (20 Hz) stimulation to the left frontal cortex using a figure-of-eight coil in two patients diagnosed with epilepsia partialis continua. Of these, only one demonstrated a clinically significant reduction in seizure frequency. Misawa et al. (2005) [84] reported a case involving a patient with epilepsia partialis continua who received two separate sessions of low-frequency magnetic stimulation. Each session consisted of 100 pulses applied at 0.5 Hz and 90% of the motor threshold using a figure-of-eight coil targeting the left hand motor cortex. Monitoring over the subsequent three months after each session revealed a marked reduction in seizure frequency for approximately two months following each intervention.

Rotenberg et al. (2008) [85] initially described a case study involving a 14-year-old adolescent with epilepsia partialis continua who underwent rTMS treatment consisting of 1800 pulses at 1 Hz and 100% motor threshold intensity, delivered via a figure-of-eight coil to the identified epileptogenic focus over a 9-day course. The following year, he performed an open-label study in a larger sample of seven patients with the same condition. Although uniform research parameters and TMS devices (including treatment duration, frequency, and number of pulses received) were not applied across subjects, the overall reduction in seizure frequency was more pronounced and lasted longer than in the single-case report. In the first trial, only seizure duration was significantly reduced during the treatment course, whereas in the second study, 70% of participants exhibited a reduction in seizure frequency that persisted beyond the treatment course (30 minutes after the treatment course to more than a day) [86]. Other research has been conducted in the same field, the findings of which are summarized below [87–89].

After summarizing the studies conducted up to 2009, more recent studies in the same field have been published between 2022 and 2025, providing further evidence for the effects of rTMS in focal epilepsy (specifically, partial continuous epilepsy). For instance, in 2022, Chang et al. [87] conducted a case study involving a 10-month-old infant with epilepsia partialis continua. The patient received high-frequency rTMS at 10 Hz with an intensity of 50% maximum stimulator output, delivering 1200 pulses in a 1-day treatment course using a figure-of-eight coil positioned over the motor cortex. Evaluation of seizure frequency, across an 11-day pre-treatment baseline and a 3-day post-treatment follow-up,

revealed a significant short-term benefit, with seizure frequency diminishing rapidly and disappearing within two days, although recurrence was noted shortly thereafter.

Similarly, in a 2024 case report, Velasco-Merida [88] applied one-day low-frequency rTMS (0.5 Hz) to two patients with epilepsia partialis continua using both round and figure-of-eight coils. Stimulation protocols varied slightly between the patients in terms of intensity, pulse count, and coil placement. Clinical follow-up over one month highlighted differential responses. The first patient experienced an early reduction in seizure frequency within 24 hours, accompanied by subjective improvement in severity, though these benefits were not sustained. By contrast, the second patient did not show measurable changes in seizure frequency, but reported notable functional improvements, including absence of twitches, increased calmness, and better hand use, persisting for one month.

In addition to the aforementioned study, Algoet et al. (2025) [89] examined the effects of rTMS in three individuals diagnosed with epilepsia partialis continua. The study highlighted that variations in stimulation parameters were associated with distinct clinical outcomes. Stimulation was applied to the epileptogenic focus using a figure-of-eight coil with continuous theta burst stimulation (50 Hz, 80% resting motor threshold, 3000 pulses across four days). Despite this intensive regimen, the study failed to demonstrate significant or lasting improvements in seizure frequency.

3. 4. Generalized Epilepsy

Up to this point, the majority of studies have focused on focal epilepsy and its specific subtypes, such as epilepsia partialis continua and structural focal epilepsy, providing valuable insights into the modulatory potential of rTMS within localized cortical networks. However, epilepsy is a highly heterogeneous disorder, and generalized epilepsy represents another major clinical entity with distinct pathophysiological mechanisms and therapeutic challenges. To address this, a smaller but noteworthy body of research has examined the application of rTMS in generalized epilepsy, aiming to explore whether its beneficial effects could extend beyond focal syndromes. The following section highlights two representative studies in this domain [90,91].

A pivotal extension of rTMS research into generalized epilepsy was reported by Ozek et al. in 2020 [90]. In this sham-controlled study, ten patients with generalized epilepsy underwent stimulation with a round coil positioned over the vertex. The treatment protocol consisted of two separate 5-day courses, delivered three months apart, in which low-frequency stimulation at 0.2 Hz and 120% of the motor threshold was applied at 1000 pulses per session. Patients were monitored for three months prior to and following the intervention. Notably, this protocol resulted in a clinically meaningful 30–50% reduction in both seizure frequency and interictal epileptiform discharges, thereby underscoring the potential of rTMS as a promising adjunctive approach in the management of generalized epilepsy.

In line with the growing interest in extending rTMS applications beyond focal epilepsy, another study sought to evaluate its efficacy in patients with generalized epilepsy. Celebi et al. (2023) [91] performed a single-blind, placebo-controlled crossover trial including 12 participants (five with generalized epilepsy and seven with focal epilepsy). The stimulation protocol consisted of 600 high-frequency pulses at 30 Hz, delivered at 80% of the resting motor threshold. A round coil was applied over the cortical region in patients with generalized epilepsy, whereas a figure-of-eight coil was used to target the epileptogenic foci in patients with focal epilepsy. Participants were closely monitored for 8–12 weeks before and after both active and placebo stimulation. This study demonstrated a significant reduction in seizure frequency, thereby reinforcing the therapeutic potential of rTMS not only in focal but also in generalized epilepsies.

4. Discussion

Repetitive transcranial magnetic stimulation (rTMS) has emerged over the past two decades as a promising non-invasive neuromodulatory approach for drug-resistant epilepsy. The present review synthesized a wide range of studies (spanning early pilot reports to recent randomized controlled trials) that evaluated rTMS across different epilepsy syndromes, including focal epilepsy, focal cortical dysplasia-related epilepsy, epilepsia partialis continua, and generalized epilepsy. Collectively, the evidence points toward a modulatory effect of rTMS on cortical excitability, with a substantial subset of trials demonstrating clinically meaningful reductions in seizure frequency and interictal epileptiform

discharges. Nevertheless, conflicting results remain, highlighting the complexity of translating rTMS into standardized therapeutic protocols.

Across the body of literature reviewed, 30 studies reported statistically significant clinical benefits of rTMS, 6 reported no measurable effects, and 7 yielded mixed outcomes depending on the selected clinical or electrophysiological endpoints. This distribution underscores two critical points: (1) rTMS has demonstrable therapeutic potential in epilepsy, and (2) its effects are highly context-dependent, influenced by epilepsy subtype, stimulation parameters, study design, and patient characteristics.

Early investigations, such as those by Tergau et al. [49], established the feasibility of rTMS in modulating seizure frequency. Subsequent studies expanded to larger cohorts and diverse epilepsy phenotypes, producing both promising and inconsistent results. More recent contributions, particularly between 2019 and 2025, have provided stronger evidence from controlled designs and refined stimulation protocols, supporting rTMS as a viable adjunctive treatment in carefully selected patients.

4. 1. rTMS in Focal Epilepsy

The majority of studies targeted focal epilepsies, given their prevalence and the relative ease of localizing epileptogenic zones. Overall, focal epilepsy appears most responsive to rTMS, but heterogeneity in outcomes reflects substantial methodological variability. Several trials demonstrated striking reductions in seizure frequency (up to 70–80% in some cases), particularly with low-frequency (≤1 Hz) stimulation delivered directly over the epileptogenic focus using figure-of-eight coils. For instance, studies by Fregni, Sun, and Van Haerents[54,58,61], highlighted both short-term and durable seizure reductions, often accompanied by parallel decreases in interictal epileptiform discharges . More recent investigations (e.g., Shon, Ashour, Mikellides, Carrette, Jin, and Yang [65–70]) further strengthened this evidence by demonstrating sustained seizure control over weeks to months, suggesting that repeated or maintenance stimulation may prolong therapeutic benefit. Conversely, several randomized, sham-controlled trials, such as those conducted by Theodore, Seynaeve, and Mukherjee [51,63,64], failed to demonstrate significant clinical improvement despite rigorous methodology. These discrepancies point to multiple influencing factors:

1. Stimulation parameters: Frequency, pulse number, and intensity appear to critically shape outcomes. While most positive trials employed low-frequency inhibitory protocols (0.3–1 Hz), a few studies also suggested potential benefits of theta-burst or cerebellar-targeted paradigms.

2. Coil type and positioning: Figure-of-eight coils provided more focal stimulation and often yielded superior outcomes compared to round coils, which generate diffuse magnetic fields. Nevertheless, the optimal coil type may vary depending on seizure localization.

3. Duration and repetition of stimulation: Longer or repeated treatment courses were more often associated with sustained clinical benefits, whereas single-session or very brief protocols tended to produce transient or inconsistent effects.

4. Patient-specific factors: Variabilities in cortical excitability, structural lesions, and seizure networks likely influence responsiveness.

Taken together, these findings suggest that rTMS in focal epilepsy holds significant therapeutic promise, particularly when tailored to individual neurophysiological characteristics and delivered with optimized stimulation parameters.

4. 2. rTMS in Focal Cortical Dysplasia

Focal cortical dysplasia represents one of the most refractory forms of structural epilepsy, often resistant to both pharmacological therapy and surgical resection. Consequently, the application of rTMS in this subgroup has attracted special attention.

Case studies and small trials (Menkes, Daniel, Li, and Starnes [75,76,81,82]) reported encouraging results, with seizure reductions ranging from 30% to complete seizure freedom, sometimes sustained for months under maintenance stimulation. Larger controlled studies, such as those by Fregni and Joo [77,79], provided more systematic evidence of both clinical and electrophysiological improvements. Importantly, Fregni et al. (2006) [77] demonstrated not only reductions in seizure frequency but also significant decreases in interictal epileptiform discharges persisting up to two months. Nevertheless, results were not universally positive. Rossi's and Joo's investigations [78,79], for example, showed

little to no impact on seizure frequency despite measurable changes in interictal epileptiform discharges. Cantello's large randomized sham-controlled trial [80] further highlighted the inconsistency, with only a subset of patients experiencing meaningful benefit. These findings suggest that rTMS may exert a modulatory effect on cortical excitability in focal cortical dysplasia, but seizure outcomes remain variable. Structural heterogeneity of dysplastic lesions, network-level epileptogenicity, and challenges in coil positioning over deeply seated or multifocal abnormalities likely contribute to this variability. Standardizing stimulation protocols and stratifying patients based on lesion characteristics may enhance the clinical utility of rTMS in this subgroup.

4. 3. rTMS in Epilepsia Partialis Continua

Epilepsia partialis continua, a rare and often intractable epilepsy subtype, poses unique therapeutic challenges. Evidence for rTMS in epilepsia partialis continua is limited to case reports and small open-label series, yet the results are instructive.

Several reports (Graff-Guerrero, Misawa, Rotenberg, Chang, Velasco-Merida [83–88]) documented seizure reductions or symptomatic improvements following both low- and high-frequency rTMS. Rotenberg's early series [85] demonstrated reductions in seizure duration and frequency in most patients, while Chang's infant case study [87] revealed short-term seizure cessation. However, sustained seizure control was uncommon, and responses were inconsistent across patients. The most recent contributions (Algoet et al., 2025 [89]) employing continuous theta-burst stimulation failed to demonstrate lasting clinical benefits, raising questions about the durability of rTMS in epilepsia partialis continua. Still, even transient improvements in such refractory cases may hold clinical relevance, particularly when combined with other therapeutic modalities. Overall, the evidence suggests that while rTMS can modulate cortical excitability in epilepsia partialis continua, optimization of protocols and further systematic trials are needed before firm conclusions can be drawn.

4. 4. rTMS in Generalized Epilepsy

Research into rTMS for generalized epilepsy remains comparatively sparse. Early and recent studies (Ozek, Celebi [90,91]) suggest that rTMS may also hold therapeutic potential in this domain, albeit with

less robust evidence than for focal epilepsy. Ozek et al. [90] demonstrated 30–50% reductions in seizures and interictal epileptiform discharges following vertex stimulation, while Celebi et al. [91] extended these findings by showing significant seizure reductions in both generalized and focal subgroups. Notably, these studies used relatively low stimulation frequencies (0.2–0.5 Hz), indicating that inhibitory protocols may also be effective in modulating diffuse epileptogenic networks. Nevertheless, the challenges of applying focal stimulation to generalized epileptic syndromes remain significant. Further research is required to determine whether rTMS acts directly on generalized networks or indirectly via modulation of thalamo-cortical circuits.

4. 5. Clinical Implications

Despite the inconsistencies, the cumulative evidence supports rTMS as a potentially valuable adjunct in epilepsy management, particularly for patients with focal epilepsy refractory to medication and surgery. The consistent demonstration of rTMS-induced reductions in interictal epileptiform discharges across multiple studies strengthens the biological plausibility of its therapeutic effects. Moreover, the safety profile of rTMS has been favorable, with adverse effects typically mild and transient.

Importantly, several recent studies have highlighted the potential for durable clinical benefits when rTMS is delivered in extended or maintenance protocols. This aligns with emerging understanding of rTMS as a plasticity-inducing intervention, where repeated stimulation may promote long-term reorganization of epileptogenic networks.

4. 6. Future Directions

Moving forward, several priorities should guide the field. A consensus on standardized protocols for stimulation frequency, intensity, pulse number, coil type, and treatment duration is urgently needed. Furthermore, large-scale, multicenter, randomized sham-controlled trials are required to establish efficacy, identify predictors of response, and refine clinical indications. It is also a priority to identify biomarkers—such as cortical excitability thresholds, lesion characteristics, or network connectivity—to enable patient stratification for precision targeting and improved response rates. Finally, exploring

rTMS in combination with pharmacological agents, neurostimulation devices, or surgical interventions may yield synergistic effects and should be a key focus.

5. Conclusion

This comprehensive review systematically synthesizes the entire body of research to date on the application of rTMS in epilepsy, establishing itself as the most complete and definitive reference on the topic. By exhaustively covering all prior investigative work, we not only map the existing landscape but also introduce a novel analytical framework by categorizing and comparing outcomes based on specific rTMS stimulation protocols—a methodological refinement not previously undertaken in the literature. The analysis confirms the considerable therapeutic promise of rTMS while candidly addressing its current challenges. Robust evidence, particularly from studies on focal epilepsy and focal cortical dysplasia, consistently supports the modulatory capacity of rTMS to reduce seizure frequency and suppress epileptiform activity. However, the heterogeneity of results, especially evident in randomized sham-controlled trials, clearly highlights the critical need for standardized protocol optimization and refined patient stratification to achieve reliable efficacy. Preliminary findings in more complex conditions, such as epilepsia partialis continua and generalized epilepsy, are encouraging and warrant targeted exploration. Collectively, rTMS emerges from this synthesis as a safe, non-invasive, and neurobiologically grounded intervention with significant potential to complement the management strategy for drug-resistant epilepsy. To translate this potential into established clinical practice, future research must prioritize large-scale, rigorously designed clinical trials, deeper mechanistic investigations, and studies with long-term follow-up. By providing an unprecedented protocol-oriented comparison and a complete aggregation of existing evidence, this review serves as the essential foundation for guiding the next critical phase of research and clinical application.

Author Contributions

M.N.A. and P.P. conceptualized the study, designed the methodology, conducted the systematic literature search, curated the data, and drafted the original manuscript. E.E. provided senior supervision, contributed extensively to the critical revision of the manuscript for vital intellectual content, and

performed the final linguistic polishing and editing of the text. L.R and H.S.Z. contributed to the critical analysis, interpretation of findings, and substantive intellectual revision of the manuscript. H.S.Z. also provided final approval for publication. Additionally, all necessary figures were extracted, curated, and integrated from the reviewed literature by E.E. All authors reviewed, discussed, and approved the final submitted version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Competing Interests

The authors declare that they have no competing financial interests or personal relationships that could be perceived to have influenced the work reported in this paper.

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