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Repetitive Transcranial Magnetic Stimulation for Refractory and Super-refractory Status Epilepticus: A Systematic Review

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ABSTRACT

Rationale: Off-label treatments are often considered to treat refractory status epilepticus (RSE) and superrefractory status epilepticus (SRSE). To investigate the efficacy of repetitive transcranial magnetic stimulation (rTMS) as a treatment for (S)RSE, we performed a systematic review.

Materials and Methods: Cessation of (S)RSE after rTMS was extracted as the primary end point from manuscripts describing patients with (S)RSE treated with rTMS. Data relevant to epilepsy history, (S)RSE type and etiology, prior treatment for (S)RSE, prior duration of (S)RSE, rTMS parameters, number of treatment sessions, duration of rTMS protocols, latency to (S)RSE cessation, recurrence rate, adverse events, and long-term outcome were collected as secondary end points.

Results: We identified 33 patients; 17 of 33 had epilepsia partialis continua; 7 of 33 had new onset RSE. Data were incomplete in 3 of 33 regarding classification and etiology; 18 of 30 had focal motor status epilepticus (SE), 9 of 30 nonconvulsive SE, and 3 of 30 convulsive SE. The most frequent etiologies were cortical malformation (8/31), stroke (5/31), and genetic mutations (5/31). Median duration of (S)RSE before rTMS was 70 days (range: two–7300, interquartile range = 148, Q1 = 32, Q3 = 180). In 25 of 33 patients (75.8%), rTMS caused cessation of (S)RSE after zero to four days. (S)RSE recurred in eight of 17 patients (47%), for whom follow-up was available. Three deaths occurred from the underlying disease.

Conclusion: rTMS caused cessation in 75.8% of patients with (S)RSE within four days, with recurrence in 47%. To determine the therapeutic potential of rTMS for patients with (S)RSE, further studies are required given the present findings stem from level IV studies and may have reporting bias.

Keywords: Efficacy, epilepsia partialis continua, refractory status epilepticus, superrefractory status epilepticus, transcranial magnetic stimulation

BACKGROUND

Status epilepticus (SE) is defined as an abnormally prolonged seizure episode, resulting from the malfunctioning of mechanisms responsible for termination, spread, or recurrence of seizures.[1–3] SE occurs in ten to 41 cases per 100,000 annually, with mortality rates of 15% to 60%.[4–6] It is more frequent in drug-resistant epilepsy (DRE), which affects 30% of people with epilepsy, and especially in those with generalized DRE.[7,8] SE also occurs in patients without an epilepsy history. New-onset refractory status epilepticus (NORSE) is a distinct entity of RSE in patients without an underlying structural, metabolic, or toxic cause.[9] Febrile infection-related epilepsy syndrome (FIRES) is a NORSE subset characterized by fever onset one to 14 days before seizures.[9] SE is a neurologic emergency requiring immediate evaluation and therapeutic intervention.[4–6] RSE is defined as recurrent seizure activity despite the use of two appropriately chosen and correctly administered antiseizure medications (ASMs), one of which must be a benzodiazepine.[4] SE can be classified as superrefractory (SRSE) when it persists for 24 hours after initiation of treatment with anesthetics or recurs despite the use of or on weaning from general anesthesia.[4]

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In clinical practice, the pharmacologic treatment of SE follows evidence-based guidelines.[5] RSE and SRSE develop in 29% to 43% and 12% to 26%, respectively, of SE cases and are associated with a mortality rate of 30% and 30% to 50%, respectively.[10,11] Despite the relatively high transition from SE into (S)RSE, current treatment guidelines for (S)RSE are lacking, and there remains a significant treatment gap. Although randomized controlled trials have not yet been conducted, various invasive and noninvasive neuromodulation techniques have been explored in patients with (S)RSE, with mixed results. None of these techniques, however, has SE as an approved indication for treatment.

We conducted a systematic review of the literature to investigate the efficacy of repetitive transcranial magnetic stimulation (rTMS) for (S)RSE. Transcranial magnetic stimulation (TMS) is a noninvasive neurostimulation technique that generates a large magnetic field (±2T) by inducing a current in a coil of copper wire.[12,13] Based on Faraday's law of electromagnetic induction, application to the scalp then leads to a weak secondary electric current in the underlying brain tissue that can modulate neural excitability.[12,13] The type and orientation of the TMS coil and the waveform of the magnetic pulse both influence the geometry of this electric field.[12] Depending on the applied stimulation parameters, TMS can be delivered repetitively using either low-frequency (LF-rTMS, ≤1 Hz) or high-frequency (HF-rTMS, ≥5 Hz) stimulation. Theta burst stimulation is a more recently introduced rTMS protocol, characterized by a shorter treatment duration and fewer variable effects than those in conventional protocols.[12] To date, rTMS has already received European Conformity marking and Food and Drug Administration approval for the treatment of depression both with and without comorbid anxiety symptoms, obsessive-compulsive disorder, substance use disorders, and migraine, and is under investigation for various other neuropsychiatric disorders.[14] Previous reports on (S)RSE treatment with rTMS have described success rates between 40% and 70%.[5,15] The exact mechanism of action is not known, but LF-rTMS may exert its effects in this population by reducing N2B subunit-containing N-methyl-D-aspartate receptor (NMDA-R) activity, enhancing γ-aminobutyric acid A receptor function, decreasing synaptic densities, elevating levels of brain-derived neurotrophic factor precursor (pro-BDNF) and dopamine, and exerting antiinflammatory effects.[16–21]

Overall, rTMS is a safe neuromodulation technique, with 17.1% of subjects experiencing mild adverse effects (AEs).[22] The most serious AEs are seizures, which occur at a crude per-subject risk of 1.4%.[22] These documented incidents primarily originated from times before the implementation of currently applied safety regulations. A small proportion of adults may experience a transient increase in auditory threshold, although most subjects using earplugs report no changes.[23] Data on the AEs of rTMS in children are currently lacking. The single study on hearing safety in the pediatric population reports no changes in hearing, even without hearing protection.[23]

Given the potential of this noninvasive technique to address the existing treatment gap for (S)RSE, we conducted a systematic review of the literature to evaluate the efficacy of rTMS in (S)RSE.

MATERIAL AND METHODS

We reported the results following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[24]

Search Strategy

EMBASE was independently searched on March 27, 2024 by two authors (CA and KVR) using the following search strategy: "epileptic state"/exp AND "repetitive transcranial magnetic stimulation"/exp. PubMed, CENTRAL, Opengrey.eu, medRxiv, and bioRxiv also were independently explored by two authors (CA and KVR) using the subsequent search terms: (transcranial magnetic stimulation, repetitive[MeSH Terms]) AND (((((status epilepticus[MeSH Terms]) OR (NORSE)) OR (New-onset refractory status epilepticus)) OR (FIRES)) OR (Febrile infection-related epilepsy syndrome)). These methods were then used to screen conference abstracts from the American Epilepsy Society and the European Academy of Neurology meetings since 2005 on their websites. Reference lists were reviewed for studies missed during the data base search.

Study Selection

Entries lacking relevance, articles reporting duplicate data, studies on epilepsy and/or refractory epilepsy without SE, and articles focusing on animal studies were excluded. Original manuscripts, case reports, and abstracts were deemed suitable for inclusion. Studies reporting in patients with epilepsia partialis continua (EPC) were included, independently of whether a benzodiazepine was administered. Reviews were not included but were screened to identify relevant studies that had not been identified when searching the data bases. Outliers in qualitative and quantitative data were excluded to ensure reliable outcome evaluation. In case of uncertainty, the senior author was consulted (KV).

Data Extraction

Cessation or continuation of the (S)RSE episode after rTMS treatment was extracted for each patient from the manuscripts as the primary end point. The following data also were collected: age, sex, epilepsy history, (S)RSE type and etiology, prior treatment for (S)RSE, prior duration of (S)RSE, rTMS parameters, number of treatment sessions, duration of rTMS protocols, latency to (S)RSE cessation, recurrence rate, AEs, and long-term outcome. The type of (S)RSE is based on the report of the International League Against Epilepsy Task Force on Classification of Status Epilepticus.[1] Authors were contacted and asked to provide any missing data.

Quality of Evidence Assessment

According to the Grading Recommendation Assessment Development and Education (GRADE) criteria, the Oxford criteria, and the methods of Murad, two coauthors (CA and KVR) independently completed the risk-of-bias assessment of the included studies.[25–27] In case of disagreement, the senior author (KV) was involved.

Statistical Analysis

A qualitative approach was applied. Cessation or continuation of (S)RSE after rTMS served as a primary end point. Median, interquartile range (IQR), and range were computed for the duration of (S)RSE before rTMS, the duration of rTMS protocols, and the latency to (S)RSE cessation, when applicable. Correlation coefficients were calculated to evaluate the influence of specific variables on the primary outcome. In addition, post hoc subgroup analyses were conducted if deemed relevant.

RESULTS

The search yielded 163 publications (Fig. 1), 162 from the data base search and one from other sources. After the removal of six duplicates, the remaining 157 publications were screened. On applying the inclusion and exclusion criteria, 141 studies were excluded. In addition, five more manuscripts were identified through reference list searches of other manuscripts, bringing the total number of publications included in the present review to 21.

Study Selection and Level of Evidence

All included studies were classified as GRADE D and Oxford IV evidence (Supplementary Data Appendix A).[28–31] Although Murad's methods advise against using an aggregate score, we did opt to summarize the results into a composite score to enhance comprehensibility.[25] Results vary from 2 to 4 of 5 (Table 1). All included studies were retrospective and single-center studies, comprising 15 case reports and six case series, with only two studies including >two patients (Table 1). Five studies were exclusively conducted in pediatric populations; 14 studies focused solely on adults, and one study involved both age groups. Age-related data were unavailable for one of the studies. Consequently, a total of 33 patients who received rTMS treatment were included in this analysis.

Demographics and SE Classification

Data on age and sex were missing for four and seven patients, respectively; 20 adults had a mean age of 44 years (range: 18–68 years), and nine children had a mean age of seven years (range: ten months–16 years). Among the patients for whom data regarding sex were available, ten of 26 (38%) were male, and 16 of 26 (62%) were female (Table 2). Data on the type of SE were available for 30 patients, of whom 17 had EPC; 18 of 30 were classified as having focal motor SE, 8 of 30 as having nonconvulsive status epilepticus (NCSE) without coma, 3 of 30 as having convulsive SE, and 1 of 30 as having NCSE with coma (Table 2).

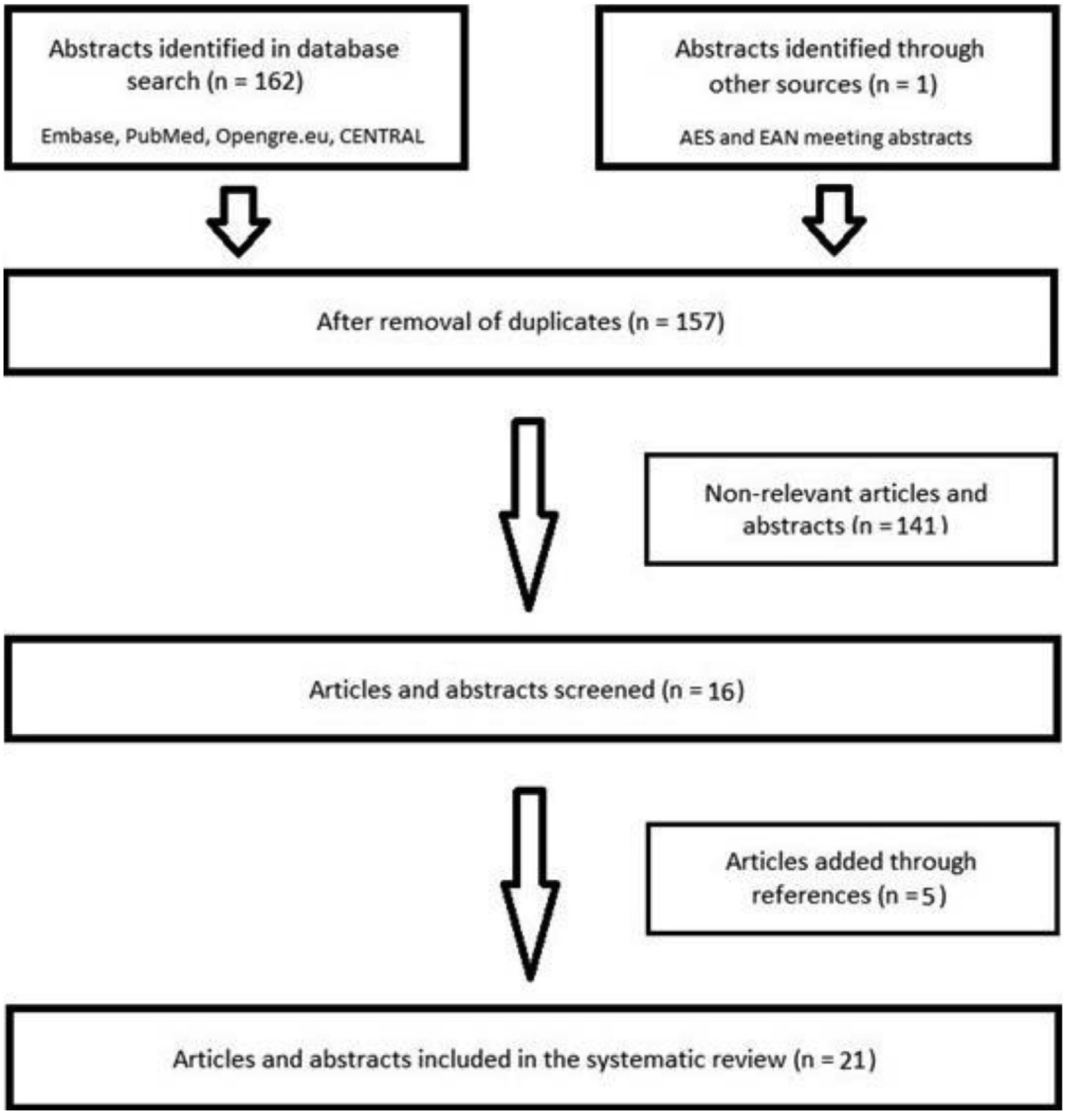

Figure 1. Flowchart of search strategy. AES, American Epilepsy Society; EAN, European Academy of Neurology.

Table 1. Study Type and Murad's Methods.[25]

Author	Study type	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total score
Guerrero et al[32]	Retrospective case series	N	Y	Y	NA	NA	NA	Y	Y	4/5
Misawa et al[33]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	Y	4/5
Morales et al[34]	Retrospective case series	N	Y	Y	NA	NA	NA	Y	Y	4/5
Schrader et al[35]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	N	3/5
Hyllienmark and Åmark[36]	Retrospective case report	Y	Y	Y	NA	NA	NA	N	N	3/5
Rotenberg et al[37]	Retrospective case series	Y	Y	Y	NA	NA	NA	Y	N	4/5
Wusthoff et al[38]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	N	3/5
Thordstein and Constantinescu[39]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	Y	4/5
Thordstein et al[40]	Retrospective case series	N	Y	Y	NA	NA	NA	N	N	2/5
Liu et al[41]	Retrospective case series	N	Y	Y	NA	NA	NA	Y	Y	4/5
VanHaerents et al[42]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	Y	4/5
Mahajan et al[43]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	N	3/5
Guzmán García et al[44]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	Y	4/5
Starnes et al[45]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	N	3/5
Agac et al[46]	Retrospective case report	N	Y	Y	NA	NA	NA	N	N	2/5
Yang et al[47]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	N	3/5
Chang et al[48]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	Y	4/5
Rodríguez-Irausquin et al[49]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	N	3/5
Lettieri et al[50]	Retrospective case series	N	Y	Y	NA	NA	NA	N	N	2/5
Rhys Potter et al[51]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	Y	4/5
Rodriguez-Villar et al[52]	Retrospective case report	N	Y	Y	NA	NA	NA	Y	N	3/5

Q1 = Does the patient(s) represent(s) the whole experience of the investigator (center), or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?
Q2 = Was the exposure adequately ascertained?
Q3 = Was the outcome adequately ascertained?
Q4 = Were other alternative causes that may explain the observation ruled out?
Q5 = Was there a challenge/rechallenge phenomenon?
Q6 = Was there a dose–response effect?
Q7 = Was FU long enough for outcomes to occur?
Q8 = Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?
N, no; NA, nonapplicable; Y, yes.

Etiology, Treatment Before rTMS, and SE Duration Before rTMS

Information regarding etiology was lacking for three of 33 patients. Cortical malformations were the most frequent cause (8/30), followed by stroke (5/30), genetic mutations (5/30), Rasmussen's encephalitis (2/30), traumatic brain injury (1/30), and metabolic causes (1/30) (Table 2). NORSE was identified in seven cases, two of which met the criteria for FIRES. Among the 24 patients for whom data on previous treatment were available, the mean number of ASMs administered for (S)RSE was four (range: two–nine); 13 patients received steroids, 12 anesthetics, eight intravenous immunoglobulins (IVIG), five ketogenic diet (KD), three immunomodulatory drugs, and two plasma exchange or plasmapheresis, and one was given electroconvulsive therapy (ECT) (Table 2).

Data on (S)RSE duration before rTMS were available for 20 of 33 patients (Table 3). The median duration was 70 days (range: two–7300 days), with an IQR of 148 days (Q1 = 32 days, Q3 = 180 days). For patients with non-EPC (S)RSE, the median duration was 45 days (range: two–180 days), with an IQR of 69 days (Q1 = 21 days, Q3 = 90 days). Among the 17 patients with EPC, the median duration was 180 days (range: 28–7300 days), with an IQR of 658 days (Q1 = 45 days, Q3 = 730 days).

Parameters

Most patients (15/33) underwent treatment using a figure-of-eight coil; one patient was treated with a round coil (Table 4). Data for the remaining patients were unavailable. Information about rTMS parameters was provided in 75.8% of cases (25/33). Treatment protocols exhibited a high variability among patients, with the number of trains (series of consecutive magnetic pulses delivered to the brain) varying from one to 120 per day and train durations fluctuating between 0.05 seconds and 3600 seconds (Table 4). Frequencies ranged from 0.5 Hz to 100 Hz (Table 4). More specifically, three of 25 patients (12%) underwent HF-rTMS; 16 of 25 (64%) received LF-rTMS, and six of 25 (24%) underwent a combination of both (Table 4). Moreover, the duration of treatment protocols varied significantly (median = 3.5 days, IQR = 9 days, Q1 = 1 day, Q3 = 10 days), with some patients receiving a single session and others having treatment for four weeks (Table 4).

Primary Outcome

In 25 of 33 patients (75.8%), rTMS ceased (S)RSE, in 17 of 22 patients (77.3%) with RSE, and in 8 of 11 (72.7%) with SRSE. When analyzed by age groups, rTMS caused cessation of (S)RSE in five of nine children (55.6%) and in 17 of 20 adults (85%). In terms of SE classification, rTMS ceased (S)RSE in 13 of 18 of patients with focal motor SE (72.2%), in six of eight patients with NCSE without coma (75%), in two of three cases of convulsive SE (66.7%), and in one of one case of NCSE with coma (100%). Cessation of (S)RSE was observed in 15 of 20 individuals (75%) previously diagnosed with epilepsy and in five of seven patients (71.4%) with NORSE.

Table 2. Patient Demographics, Status Classification, and Previous Treatment.

Author	Age (y)	Sex	EP/NO	Seizure type	Epilepsy etiology	SE etiology	A/Re/P/CS	SE classification	SE subclassification	Treatment before rTMS
Guerrero et al[32]	7	F	EP	Focal motor	R focal cortical atrophy	Known	Re	Focal motor	EPC	TPM, VPA, PHT, and PRM
	11	M	EP	Focal motor	R focal cortical atrophy	Known	Re	Focal motor	EPC	CLB, VPA, PHT, and OXC
Misawa et al[33]	31	F	EP	Focal motor	Focal cortical dysplasia	Known	Re	Focal motor	EPC	CZP and PHT
Morales et al[34]	8	F	EP	Focal motor	Neuronal ceroid lipofuscinosis	Known	P	Focal motor	EPC	LZP FPHT, OXC, LEV, PB, LTG, and ZNS Coenzyme Q and carnitine
	16	M	EP	Focal to bilateral tonic clonic	Congenital R parietal infarct	Known	Re	NCSE without coma	Focal sensory without impairment of consciousness	CLB and LTG
Schrader et al[35]	48	NR	EP	Focal motor	Not known	Not known	NA	Focal motor	EPC	NR
Hyllienmark and Åmark[36]	5	M	EP	Generalized	Dravet syndrome	Known	P	Convulsive	Generalized convulsive	LEV, TPM, and VPA LC, MDZ, and TP
Rotenberg et al[37]	14	M	EP	Focal motor	Rasmussen's encephalitis	Known	A	Focal motor	EPC	LZP and DZP FPHT, OXC, LEV, and VPA IVIG and CSS
	42	NR	NO	NA	NA	Known (hypoglycemia)	A	Focal motor	EPC	NR
	56	NR	NO	NA	NA	Known (stroke)	A	Focal motor	EPC	NR
	33	NR	NO	NA	NA	Not known	NA	Focal motor	EPC	NR
	18	NR	NO	NA	NA	Not known	NA	Focal motor	EPC	NR
	46	NR	EP	Focal motor	Resected cortical vascular malformation	Known	Re	Focal motor	EPC	NR
	NR	NR	NO	NA	NA	Known (stroke)	Re	Focal motor	EPC	NR
Wusthoff et al[38]	29	F	EP	Focal to bilateral tonic clonic	Parry Romberg syndrome and Rasmussen's encephalitis	Known	A	NCSE without coma	Focal with aphasic status	PHT, LEV, PB, VPA, TPM, PGB, and PGB PTB, MDL, and DSF IVIG and CSS 10 ECT sessions 2 times plasmapheresis
Thordstein and Constantinescu[39]	68	F	NO	NA	NA	Known (HSV encephalitis)	A	NCSE without coma	Focal with impaired consciousness	DZP CBZ and VPA PROP and MDL Acyclovir and CSS
Thordstein et al[40]	2	M	EP	Focal motor	Alpers disease	Known	P	Focal motor	EPC	NR
	6	F	EP	NR	Cortical malformations	Known	CS	NA	NA	NR
Liu et al[41]	46	M	EP	Focal to bilateral tonic clonic	Chronic encephalomalacia	Known	Re	Convulsive	Generalized convulsive	PB, PGB, LTG, LPHT, LCM, and LEV PTB, MDL, and PROP KD
	51	M	EP	Focal motor Focal to bilateral tonic clonic	Not known	Not known	NR	Focal motor	Repeated focal motor seizures	LZP LTG, LEV, FBM, and LCM VNS magnet
Van Haerents et al[42]	24	M	EP	Focal motor Focal to bilateral tonic clonic	Progressive myoclonic epilepsy	Known	P	NCSE without coma	Focal without impairment of consciousness	ZNS, LTG, PB, and PHT IV anesthetics CSS

(Continues)

Table 2. *Continued*

Author	Age (y)	Sex	EP/ NO	Seizure type	Epilepsy etiology	SE etiology	A/Re/ P/CS	SE classification	SE subclassification	Treatment before rTMS
Mahajan et al[43]	63	F	NO	NA	NA	Not known	A	NCSE without coma	Focal with impaired consciousness	Multiple ASMs IV anesthetics CSS
Guzmán García et al[44]	23	F	EP	Generalized	Traumatic brain injury	Known	Re	NCSE without coma	Focal with impaired consciousness	LEV, PB, LCS, and PER IV anesthetics IVIG and CSS KD
Starnes et al[45]	48	M	EP	Focal	Focal cortical dysplasia	Known	Re	NR	NR	Multiple ASMs
Agac et al[46]	33	M	EP	Generalized	Not known	Known (autoimmune)	A	Focal motor	EPC	Multiple ASMs CSS and RTX Plasma exchange
Yang et al[47]	22	F	NO	NA	NA	Not known	NR	Focal motor	EPC	LZP and DZP LCS, LEV, PHT, CBZ, OXC, VPA, PB, BEV, and GBP PROP, MDZ, PTB, and KET MP, PRED, IVIG, and RTX KD and pyridoxine
Chang et al[48]	10mo	F	EP	Focal motor	POLG1 mutation	Known	P	Focal motor	EPC	LZP, DZP, and MDZ LEV, PTB, FPHT, OXC, CZP, LCS, PHT, TPM, and VGB IVIG and CSS KD Resection
Rodríguez-Irausquin et al[49]	23	M	NO	NA	NA	Known (COVID-19 infection with febrile peak)	A	NR	NR	Multiple ASMs Anesthetics Antibiotics Immunomodulation drugs (tocilizumab, anakinra) KD
Lettieri et al[50]	NR	M	NO	NA	NA	Known (ICH)	Re	NCSE without coma	NR	Multiple ASMs IVIG and CSS
	NR	M	NO	NA	NA	Known (iCVA)	Re	NCSE without coma	NR	Multiple ASMs IVIG and CSS
	NR	NR	NO	NA	NA	Not known	NA	NCSE with coma	NR	Multiple ASMs IV anesthetics IVIG and CSS
Rhys Potter et al[51]	58	M	EP	Focal motor Focal to bilateral tonic clonic	Periventricular nodular heterotopia	Known	Re	Focal motor	EPC	CBZ, TPM, and PB

(Continues)

Table 2. *Continued*

Author	Age (y)	Sex	EP/NO	Seizure type	Epilepsy etiology	SE etiology	A/Re/P/CS	SE classification	SE subclassification	Treatment before rTMS
Rodriguez-Villar et al[52]	54	F	NO	NA	NA	Not known	A	Convulsive	NR	LEV, VPA, PHT, and LCS MDZ, PROP, and TP MP

A, acute; BEV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; CS, status epilepticus in defined clinical syndrome; CSS, corticosteroids; CZP, clonazepam; DSF, desflurane; DZP, diazepam; EP, patient with epilepsy; F, female; FBM, felbamate; FPHT, fosphenytoin; GBP, gabapentin; HSV, herpes simplex virus; ICH, intracranial hemorrhage; iCVA, ischemic cerebrovascular accident; IV, intravenous; KET, ketamine; L, left; LC, lidocaine; LCS, lacosamide; LEV, levetiracetam; LTG, lamotrigine; LZP, lorazepam; M, male; MDL, midazolam; MP, methylprednisone; NA, nonapplicable; NO, new onset; NR, not reported; OXC, oxcarbamazepine; P, progressive; PB, phenobarbital; PER, perampanel; PGB, pregabalin; PHT, phenytoin; POLG1, DNA polymerase subunit γ 1; PRED, prednisone; PROP, propofol; PTB, pentobarbital; R, right; Re, remote; RTX, rituximab; TGB, tiagabine; TP, thiopental; VGB, vigabatrin; VPA, valproate; ZNS, zonasamide.

No statistically significant correlations were found between the primary outcome parameter and the patient's age, (S)RSE etiology, prior duration of (S)RSE, rTMS parameters, or the number of treatment sessions. (S)RSE cessation or continuation was not associated with previous administration of IVIG, KD, or steroids. A subgroup analysis in patients in whom (S)RSE cessation was achieved (n = 25) revealed a strong correlation (Spearman correlation coefficient = 0.693, p-value = 0.004) between the duration of rTMS protocols and the subsequent duration of long-term seizure control.[53]

The latency-to-seizure cessation after the initiation of rTMS varied widely, ranging from an immediate effect to an effect after one day in RSE (median = 0 days, IQR = 0 days, Q1 = 0 days, Q3 = 0 days) and from an immediate effect to an effect observed after five days in SRSE (median = 2 days, IQR = 3.5 days, Q1 = 0 days, Q3 = 3.5 days) (Table 3).

Follow-up (FU) information after (S)RSE cessation was not provided in seven of 25 patients (28%); recurrence information after rTMS treatment was not provided in eight of 25 patients (32%). Among the remaining patients with available FU information, (S)RSE recurred in eight of17 patients (47%) within a time frame ranging from 20 minutes to 3 minutes (Table 3). Of these, three of eight patients (37.5%) experienced recurrence within 20 to 30 minutes, and seven of eight patients (87.5%) had EPC (Table 3). Importantly, within the group of patients in whom (S)RSE cessation (n = 25) was reached, a strong correlation (Spearman correlation coefficient = 0.606, p-value = 0.01) between the duration of rTMS protocols and the recurrence of (S)RSE was found.[53]

In one patient (5.6%), (S)RSE did not recur, but epileptic seizures did. Moreover, in four of 18 patients (22.2%), (S)RSE resolved, although epileptic seizures continued with a significantly reduced frequency. In four of 18 cases (22.2%), complete cessation of both (S)RSE and epileptic seizures was achieved, maintaining seizure freedom for durations up to 12 minutes.

In the RSE group, recurrence data were missing for five of 17 patients (29.4%). Of the remaining patients, eight of 12 (66.7%) experienced recurrence. In the SRSE cohort, recurrence information was unavailable for three of eight patients (37.5%). The remaining five patients did not experience SRSE recurrence. For patients with NORSE (n = 7), recurrence details were lacking in three patients. Among the others, two of four (50%) had recurrences. In the subgroup of patients with a prior epilepsy diagnosis, recurrence data were unavailable for four patients. Of the remaining patients, six of 11 (54.5%) experienced recurrence.

(S)RSE recurrence led to additional therapeutic interventions, including hemispherectomy, adjustments to vagus nerve stimulation (VNS) parameters, chronic cortical stimulation (CCS), responsive neurostimulation, and additional rTMS sessions. The latter consistently (three of three) caused extended periods of seizure freedom after treatment, surpassing the effect of the initial administration of rTMS.

AEs and Long-Term Outcome

Documentation on AEs was available in 26 of 33 cases (Table 3). One patient reported increased leg pain and a mild headache, whereas another experienced scalp, arm, and leg pain. In both cases, symptoms were only present during rTMS and resolved spontaneously afterward. Long-term outcome data were limited; FU information >6 minutes was only provided for four patients with a positive outcome (Table 3). Among them, two patients

Table 3. Cessation of SE, Latency to Abortion, Duration of Status/Before Treatment, AEs, and Long-Term Outcome.

Author	SE cessation	Latency from rTMS to SE cessation	Prior treatment for (S)RSE	(S)RSE recurrence	AEs	Long-term outcome
Guerrero et al[32]	No	NA	1 y	NA	No AE	Surgical procedures refused by parents Patient kept on same ASM regimen
	Yes	24 h	4 wk	Yes	No AE	SE recurrence after 2 wk Hemispherectomy performed with 6-mo seizure freedom
Misawa et al[33]	Yes	After first session	15 y	Yes	No AE	Gradual recurrence of EPC after 1 mo Second rTMS session 3 mo later, with EPC suppressed for ±2 mo
Morales et al[34]	No	NA	4 mo	NA	No AE	No clinical improvement after ECT Patient died 3 mo later
	No	NA	6 mo	NA	Increased leg pain and mild headache	Further rTMS or ECT refused Epilepsy surgery evaluation: inconclusive intraoperative corticography
Schrader et al[35]	Yes	NR	4 wk	No	No AE	Average seizure-h/wk decreased 62% from baseline during 8-wk FU period
Hyllienmark and Åmark[36]	Yes	NR	NR	NR	NR	NR
Rotenberg et al[37]	No	NA	6 mo	NA	No AE	NR
	Yes	After first session	NR	Yes	No AE	SE recurred after 30 min
	Yes	After second session	NR	Yes	No AE	SE recurred after 20 min
	Yes	After second session	NR	Yes	No AE	SE recurred after 20 min
	Yes	After single session	NR	No	No AE	Seizures absent for 2 d Further FU unavailable
	Yes	After single session	20 y	Yes	No AE	SE reoccurrence within 3 mo Second rTMS session: SE improved and remained suppressed at 4 mo FU
	No	NA	NR	NA	Scalp, arm and leg pain	Patient sedated and intubated 1 d after rTMS for unknown reason
Wusthoff et al[38]	No	NA	3 mo	NA	NR	KD started Mental status improved, continued moderate expressive aphasia, returned to living at home with husband
Thordstein and Constantinescu[39]	Yes	4 d	43 d	No	No AE	Gradual improvement, 7 wk in hospital MRI: slight regression of pathologic findings EEG: no epileptiform activity 2.5 mo later: A couple of possible nightly seizures have been noted
Thordstein et al[40]	Yes	NR	NR	NR	No AE	Long-term FU unavailable
	Yes	NR	NR	NR	No AE	Long-term FU unavailable
Liu et al[41]	Yes	After first session	21 d	No	No AE	88% reduction in seizure frequency in 72 h after rTMS PB and PTB successfully weaned EEG background and mental status gradually improved Patient discharged to rehabilitation center on D 47
	Yes	After first session	9 d	Yes	No AE	89% reduction in seizure frequency in 48 h after rTMS SE recurrence after 3 d Adjustment VNS setting with decrease in seizure frequency
VanHaerents et al[42]	Yes	First few days of treatment	5 mo	No	No AE	After 1 mo, start Modified Atkins diet Maintenance rTMS session 1 mo later Five additional rTMS sessions after 7 mo due to increase interictal activity on EEG Continued seizure freedom after 9 mo after initial rTMS on lower ASM doses
Mahajan et al[43]	Yes	After first session	>24 h	No	No AE	Improvement of EEG background and clinical findings in days after rTMS Long-term FU unavailable
Guzmán García et al[44]	Yes	After second session	45 d	No	No AE	Discharge on D 67 Long-term FU unavailable
Starnes et al[45]	Yes	NR	NR	No	No AE	Seizure-free at 12 mo after rTMS Discontinuation of 1 ASM; reduction of another

(Continues)

Table 3. *Continued*

Author	SE cessation	Latency from rTMS to SE cessation	Prior treatment for (S)RSE	(S)RSE recurrence	AEs	Long-term outcome
Agac et al[46]	Yes	NR	NR	NR	No AE	NR
Yang et al[47]	No	NA	NA	NA	NR	Treated with RNS
						On D 97, significant decrease in clinical seizures
						Some of the ASMs reduced
Chang et al[48]	Yes	After first session	1.5 mo	Yes	No AE	SE recurrence after 2 d
						Palliative care
						Patient died at home aged 17 mo
Rodríguez-Irausquin et al[49]	Yes	After first sessions	49 d	NR	No AE	Improved level of consciousness
						EEG activity almost normalized at time of discharge
						Long-term FU unavailable
Lettieri et al[50]	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
Rhys Potter et al[51]	Yes	After first session	±2 y	No	No AE	Improvement during 2 wk after rTMS
						Chronic cortical stimulation for further treatment
Rodriguez-Villar et al[52]	No	NA	NA	NA	NR	KD and ECT unsuccessful
						VNS on D 67 with SRSE cessation
						Anoxic event due to mucus plug in tracheostomy
						Patient died 1 y later

MRI, magnetic resonance imaging; NA, not applicable; NR, not reported; PB, phenobarbital; PTB, pentobarbital.

received additional rTMS treatment and remained seizure-free for 7 and 9 minutes, respectively. One patient remained seizure-free at 12-minute FU, which allowed discontinuation of one ASM and the reduction of another. CCS was chosen as a further treatment for this patient, in whom long-term FU data were available. After rTMS treatment, three deaths (9%) were reported but deemed unrelated to the treatment and attributable to the underlying disease.

DISCUSSION

We used systematic review methods to evaluate the efficacy of rTMS in patients with RSE or SRSE. This review revealed a cessation of (S)RSE in 75.8% of all reported cases, with a cessation of 55.6% in children and 85% in adults. The median duration of (S)RSE was 45 days for non–EPC-related SE and 180 days for patients with EPC, with a median latency to cessation of <24 hours. (S)RSE recurred in 47% of patients, with a higher prevalence among those with EPC and those who only received a single session of rTMS.

A review by Zeiler et al on rTMS for (R)SE included 21 patients and reported a cessation in 71.4%.[15] The study population predominantly comprised patients with focal (R)SE (18/21), of whom 57.1% were patients with EPC.[15] Seizure cessation was achieved immediately or within 24 hours. (R)SE recurred in 73.3% of cases, especially in patients with EPC.[15] It was concluded that rTMS significantly affected acute seizure control in focal (R)SE.[15] Although the results of the present review confirm those findings, our study also extends the scope by including patients with SRSE, various other types of SE, diverse etiologies, and patients with NORSE. This broader inclusion is particularly relevant given higher mortality rates are associated with (S)RSE and in the absence of established clinical treatment guidelines for its management.

This review found that rTMS ceased RSE in 77.3% and SRSE in 72.7% of cases. Recurrence occurred in 66.7% of RSE cases but not in SRSE. We showed that rTMS achieved cessation in 66.7% of convulsive SE cases and in the one patient with NCSE with coma. This finding is particularly relevant given that within the SE population, generalized convulsive SE and NCSE with coma are associated with the highest mortality rates, reaching up to 60%.[4–6] Our results also revealed comparable efficacy of rTMS across different etiologies of (S)RSE.

Our results suggest that this neuromodulation technique is equally efficacious in patients with preexisting epilepsy and NORSE, with approximately 75% cessation in both groups. Recurrence occurred in 54.4% and 50% of patients, respectively. Inflammation is believed to play a significant role in NORSE and FIRES, as evidenced by elevated proinflammatory markers in the cerebrospinal fluid and serum of individuals affected compared with other types of SE.[9,54,55] Genetic sequencing in patients with FIRES has identified multiple noncoding polymorphisms in the interleukin (IL)-1 receptor antagonist gene, contributing to uncontrolled IL-1–driven inflammation, which is proved to be proconvulsant in animal models.[9] Unfortunately, ASMs indicate limited efficacy in NORSE, which is often associated with high mortality, DRE, and poor cognitive and functional outcomes.[56,57] The antiinflammatory properties of rTMS may partially account for its superior efficacy to conventional treatments in this patient population. rTMS exerts its antiinflammatory effects through multiple mechanisms, including reducing proinflammatory cytokines while enhancing antiinflammatory cytokines in both cortical and subcortical tissue.[58] In addition, rTMS decreases the expression of mGluR5

Table 4. *rTMS Parameters.*

Author	Coil placement	Frequency	Percentage of rMT/ MSO	Train duration	Number of sessions/d	Total treatment period	Type of coil
Guerrero et al[32]	L frontal cortex	20 Hz	128% rMT	2 s	15 with ISI 58 s	1 d	Figure-of-eight
	L frontal cortex	20 Hz	50% MSO	2 s	15 with ISI 58 s	1 d	Figure-of-eight
Misawa et al[33]	Seizure focus	0.5 Hz	90% rMT	200 s	1	2 d with interval of 3 mo	Figure-of-eight
Morales et al[34]	L motor cortex	1 Hz and 6 Hz	100% MSO	1 Hz: 600 s 6 Hz: 5 s	D 1 Session 1: 4 at 1 Hz Session 2: 10 at 6 Hz with ISI 25 s + 1 at 1 Hz D 2 4 at 1 Hz	2d	Round
	Seizure focus	1 Hz and 6 Hz	76% MSO	1 Hz: 900 s 6 Hz: 5 s	Session 1: 1 at 1 Hz Session 2: 10 at 6 Hz with ISI 25 s + 1 at 1 Hz	1 d	Figure-of-eight
Schrader et al[35]	Seizure focus	0.5 Hz	100% rMT	900 s	2 with ISI 3 min	4 wk (2 times/wk)	NR
Hyllienmark and Åmark[36]	NR	NR	NR	NR	NR	NR	NR
Rotenberg et al[37]	Seizure focus	1 Hz	100% rMT	1800 s	1	9 d	Figure-of-eight
	Seizure focus	1 Hz	100% rMT	1800 s	3 with ISI NR	1 d	NR
	Seizure focus	1 Hz and 20 Hz	100% rMT	1 Hz: 1600 s 20 Hz: 2 s	Session 1: 1 at 1 Hz Session 2: 40 at 20 Hz with ISI NR + 1 at 1 Hz	1 d	NR
	Seizure focus	1 Hz and 6 Hz	100% rMT	1 Hz: 1600 s 6 Hz: priming	2 with ISI NR	1 d	NR
	Seizure focus	1 Hz	100% rMT	2000 s	1	1 d	NR
	Seizure focus	1 Hz and 100 Hz	90%–100% MSO	1 Hz: 1600–1800 s 100 Hz: 0.05–1.25 s	15 at 100 Hz + 1 at 1 Hz	1 d	Figure-of-eight
	Seizure focus	1 Hz and 20 Hz	100% rMT	1 Hz: 1800 s 20 Hz: 4 s	Session 1: >20 at 20 Hz Session 2: 1 at 1 Hz	1 d	NR
Wusthoff et al[38]	NR	NR	NR	NR	NR	NR	NR
Thordstein and Constantinescu[39]	D 1–4, 6, and 8 R temporo-occipital region D 5 and 7 L fronto-anterior region	0.5 Hz	100% MSO	3600 s	D 1 and 2: 1 D 3–8: 2 with ISI NR	8 d	Figure-of-eight
Thordstein et al[40]	Seizure focus	0.5 Hz	NR	3600 s	1	14 d	Figure-of-eight
	Seizure foci	0.5 Hz	NR	3600 s	1	14 d	Figure-of-eight
Liu et al[41]	R centrotemporal region (C4/T4)	1 Hz	70% MSO	1200 s	1	1 d	Figure-of-eight
	L sensorimotor cortex	1 Hz	100% rMT	1800 s	1	1 d	Figure-of-eight
VanHaerents et al[42]	Seizure focus	1 Hz	95%–100% rMT	600 s	D 1 Session 1: 3 with ISI 1 min Session 2: 3 with ISI 1 min D 2–10 3 with ISI 1 min	10 d	Figure-of-eight

(Continues)

Table 4. *Continued*

Author	Coil placement	Frequency	Percentage of rMT/MSO	Train duration	Number of sessions/d	Total treatment period	Type of coil
Mahajan et al[43]	L occipital lobe	1 Hz	NR	1800 s	1	18 d with 13 d divided into 3 periods	NR
Guzmán García et al[44]	Seizure focus	1 Hz	50%–65% MSO	1600 s	1	10 d	Figure-of-eight
Starnes et al[45]	Seizure focus	NR	NR	NR	NR	5 d	NR
Agac et al[46]	NR	NR	NR	NR	NR	7 d	NR
Yang et al[47]	R parietal and occipital regions	1 Hz	80% MSO	1800 s	2 with ISI NR	5 d	NR
Chang et al[48]	R hand motor cortex	10 Hz	50% MSO	1 s	120 with ISI 9s	1 d	Figure-of-eight
Rodríguez-Irausquin et al[49]	R centrotemporal region (C4/T4)	1 Hz	NR	NR	NR	10 sessions	NR
Lettieri et al[50]	NR	NR	NR	NR	NR	10 sessions	NR
	NR	NR	NR	NR	NR	10 sessions	NR
	NR	NR	NR	NR	NR	10 sessions	NR
Rhys Potter et al[51]	L central frontoparietal region	0.5 Hz	120%	3000 s	1d	1d	Figure-of-eight
Rodriguez-Villar et al[52]	NR	NR	NR	NR	NR	NR	NR

C4, C4 electrode; Cz, Cz electrode; ISI, interstimulus interval; L, left; R, right; MSO, maximal stimulator output; NR, not reported; rMT, resting motor threshold; T4, T4 electrode.

and NMDA-R2B, modulates neuroinflammatory pathways, and downregulates the activity of microglia and astrocytes.[58] Recent studies support this hypothesis by showing significant reductions in IL-6, IL-8, and tumor necrosis factor α after LF-rTMS targeting the dorsolateral prefrontal cortex in patients with stroke.[21] In summary, rTMS holds promise for effectively controlling NORSE without the long-term implications of an implanted device, thereby minimizing the impact on patients' quality of life (QoL) after treatment.

We systematically evaluated several variables as potential predictors of treatment efficacy but did not identify any significant correlations with patients' age, (S)RSE etiology, prior duration of (S)RSE, rTMS parameters, or prior treatment for (S)RSE with IVIG, KD, or steroid therapies. Nevertheless, our subgroup analyses indicated that an extended duration of the rTMS protocol is correlated with reduced recurrence rates and prolonged aftereffects. Literature supports this observation, indicating that longer multiday protocols produce more sustained therapeutic effects.[59]

Research also suggests that the common Val66Met polymorphism of the *BDNF* gene may significantly influence treatment outcomes in response to similar therapeutic paradigms.[60] This genetic variant has been associated with decreased hippocampal synaptic plasticity, including reduced dendritic spine density and increased synaptic elimination in hippocampal neurons, which may contribute to variability in individual responses to treatment.[61,62] Although the presence or absence of this polymorphism was not reported in the reviewed studies, screening for the Val66Met variant may serve as a valuable predictive biomarker for identifying optimal candidates for rTMS therapy in future research and clinical practice.

Other neuromodulation techniques also have indicated varying efficacy in treating (S)RSE. Invasive VNS (iVNS) is an invasive neuromodulation technique, in which two helical electrodes wrapped around the cervical part of the left vagus nerve are connected to a subclavicularly implanted pulse generator through a subcutaneously funneled lead.[63,64] The latest comprehensive review on iVNS reported a cessation rate of 35 of 45 (77.8%) in (S)RSE cases after implantation, with a median latency to cessation of eight days (range: three–84 days) and recurrence in four of 25 (16%) (Table 5).[64] In the pediatric population, rapid titration of iVNS (up to 1 mA in the first 24–36 hours) caused an SRSE cessation rate of 12 of 15 (80%), with no reported recurrences.[65] Transcutaneous auricular nerve stimulation (tVNS) offers a less invasive alternative to iVNS and has shown efficacy in refractory epilepsy.[66] Sarma et al conducted the sole study on tVNS in patients with (S)RSE, observing a significant reduction or resolution of ongoing electroencephalography (EEG) patterns in all three patients with coma during stimulation, with abnormal patterns reemerging approximately 20 minutes after treatment cessation.[66]

Deep brain stimulation (DBS) is a neurostimulation technique characterized by the surgical implantation of electrodes into deep brain structures.[4] The most comprehensive literature review on DBS for (S)RSE reported a cessation rate of five of eight (62.5%), targeting the caudal zona incerta, centromedian nucleus of the thalamus (CMN), or anterior nucleus of the thalamus (Table 5).[67] The median latency to cessation was within 24 hours after DBS treatment, with no recurrences (Table 5).[67] A recent case report targeting the sensorimotor territory of the internal globus pallidus in refractory EPC showed favorable outcomes in interrupting seizure propagation.[70] Moreover, a systematic review in four pediatric patients with NORSE showed a three of four cessation rate (75%) with CMN stimulation, with a median latency of 29 days

Table 5. Cessation Rate, Median Latency to Cessation, Recurrence Rate, and Mortality of Patients Treated With Different Neuromodulation Techniques.

Parameter	rTMS	iVNS[64]	DBS[67]	ECT	
				RSE[68]	SRSE[69]
Cessation rate	25/33 (75.8%)	35/45 (77.8%)	5/8 (62.5%)	11/19 (57.9%)	5/8 (62.5%)
Median latency to cessation	<24 h	8 d	<24 h	2–8 d	<24 h
Recurrence rate	8/17 (47%)	4/25 (16%)	0%	2/11 (18.2%)	NR
Mortality	3/33 (9%)	4/32 (12.5%)	0%	5/19 (26.3%)	5/8 (62.5%)

NR, not reported.

(range: 20–33 days). Data on recurrence in these patients were unavailable.[71]

ECT is a noninvasive technique performed under sedation, aiming to elicit a seizure through transcutaneous electrical stimulation of the cerebral cortex.[4,72] A 2019 review reported a cessation rate of 16 of 27 (59%) in patients with (S)RSE who underwent ECT, with a median latency to cessation of two to eight days for RSE and within 24 hours for SRSE (Table 5).[5,68,69] RSE recurred in two of 11 (18.2%), with no recurrence data available for SRSE (Table 5).[68,69] More recent case series and reports suggest higher cessation rates; however, evidence is limited, and potential publication bias must be considered.

Transcranial direct current stimulation is a noninvasive neurostimulation technique that modulates neuronal excitability by delivering a constant transcranial current through electrodes placed on the skull.[63] Despite positive preclinical findings suggesting its potential for SE treatment, its efficacy in humans remains not known.[73]

The results of this systematic review should be interpreted with caution owing to several limitations. First, cessation of (S)RSE is defined differently by various authors, leading to potential inconsistencies in outcome reporting and making direct comparisons across studies challenging. Second, despite the inclusion of all reported studies with negative outcomes, there remains a substantial risk of publication bias, which may contribute to an overly optimistic cessation reported in both the review by Zeiler et al and the present review. Third, this review does not represent the entire (S)RSE population, potentially limiting the generalizability of the findings. Fourth, the retrospective uncontrolled design and small sample sizes of the included studies reduce the quality of evidence. Last, the high variability in outcome data and reported FU made a comprehensive analysis challenging. Although positive outcomes were observed shortly after rTMS administration, these cannot be unequivocally attributed to the rTMS neuromodulation technique alone; they also may have resulted from the combined effect of multiple ASMs and other treatments. Therefore, further studies are needed to provide valuable insights into the efficacy of rTMS in patients with (S)RSE and its potential as a neuromodulatory treatment strategy.

CONCLUSIONS

Although iVNS and DBS are viable options after standard treatments fail, rTMS emerges as a noninvasive, well-tolerated intervention suitable for intensive care unit settings. Our study reaffirms its potentially high efficaciousness in promptly terminating (S)RSE and indicates that prolonged treatment duration correlates with extended periods of seizure freedom. To our knowledge, this study is the first to describe the potential of rTMS in managing high-mortality (S)RSE types, including generalized and nonconvulsive (S)RSE with coma. Moreover, our findings indicate efficacy in NORSE cases, improving posttreatment QoL compared with other neuromodulatory techniques. The manuscripts included in this review showcased a wide variety of treatment protocols, highlighting the need for further research to identify the most effective approach. Although data regarding EEG changes in response to rTMS from the included cases were limited, continuous EEG could be used as an objective biomarker for assessing rTMS efficacy and warrants further exploration. On the basis of our review, a ten-to-14–day protocol for (S)RSE comprising daily LF-rTMS sessions targeting the epileptogenic focus or vertex could potentially produce favorable outcomes and merits investigation in future research.

MEETING PRESENTATIONS

This research was presented as a poster presentation at the 9th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures and at the 10th Congress of the European Academy of Neurology.

Authorship Statements

Chloé Algoet designed and conducted the study, including patient recruitment, data collection, and data analysis, and prepared the manuscript draft with important intellectual input from Kato Van Rooy, Paul Boon, Evelien Carrette, Sofie Carrette, Mathieu Sprengers, Robrecht Raedt, Ann Mertens, Alfred Meurs, and Kristl Vonck. Chloé Algoet and Kristl Vonck had complete access to the study data. All authors approved the final manuscript.

Conflicts of Interest

Paul Boon obtained a Bijzonder Onderzoeks Fonds (BOF) grant from Ghent University for the purchase of transcranial magnetic stimulation equipment, obtained consultancy fees from LivaNova, Medtronic, and Angelini Pharma, and participates in the advisory board of LivaNova, Synergia Medical, and Medtronic. Alfred Meurs reported a relationship with Union Chimique Belge that includes speaking and lecture fees, and travel reimbursement; and a relationship with Angelini Pharma that includes speaking and lecture fees, and travel reimbursement. Kristl Vonck obtained a BOF grant from Ghent University for the purchase of transcranial magnetic stimulation equipment, obtained consultancy fees from LivaNova,

Synergia Medical, All Man Foundation, Precisis, and Angelini Pharma, and participates in the advisory board of LivaNova, Synergia Medical, Precisis, and Angelini Pharma. The remaining authors reported no conflict of interest.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.com and at https://doi.org/10.1016/j.neurom.2025.02.001.

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COMMENT

This manuscript is well-prepared and provides a systematic and comprehensive review of the application of rTMS in managing refractory and superrefractory status epilepticus. It is clearly structured, with a detailed assessment of current literature that offers a solid basis for examining rTMS as a potential noninvasive neuromodulation treatment for this complex condition. Overall, the manuscript is of high quality and presents a meaningful contribution to the field, meeting high standards of clarity, rigor, and relevance.

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