

CRITICAL REVIEW – INVITED COMMENTARY

Comparison of minimally invasive and traditional surgical approaches for refractory mesial temporal lobe epilepsy: A systematic review and meta-analysis of outcomes

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Abstract

Magnetic resonance-guided laser interstitial laser therapy (MRgLITT) and radiofrequency ablation (RFA) represent two minimally invasive methods for the treatment of drug-refractory mesial temporal lobe epilepsy (mTLE). We performed a systematic review and a meta-analysis to compare outcomes and complications between MRgLITT, RFA, and conventional surgical approaches to the temporal lobe (i.e., anterior temporal lobe resection [ATL] or selective amygdalohippocampectomy [sAHE]). Forty-three studies (13 MRgLITT, 6 RFA, and 24 surgery studies) involved 554, 123, 1504, and 1326 patients treated by MRgLITT, RFA, ATL, or sAHE, respectively. Engel Class I (Engel-I) outcomes were achieved after MRgLITT in 57% (315/554, range = 33.3%–67.4%), RFA in 44% (54/123, range = 0%–67.2%), ATL in 69% (1032/1504, range = 40%–92.9%), and sAHE in 66% (887/1326, range = 21.4%–93.3%). Meta-analysis revealed no significant difference in seizure outcome between MRgLITT and RFA ($Q = 2.74$, $p = .098$), whereas ATL and sAHE were both superior to MRgLITT (ATL: $Q = 8.92$, $p = .002$; sAHE: $Q = 4.33$, $p = .037$) and RFA (ATL: $Q = 6.42$, $p = .0113$; sAHE: $Q = 5.04$, $p = .0247$), with better outcome in patients at follow-up of 60 months or more. Mesial hippocampal sclerosis (mTLE + hippocampal sclerosis) was associated with significantly better outcome after MRgLITT (Engel-I outcome in 64%; $Q = 8.55$, $p = .0035$). The rate of major complications was 3.8% for MRgLITT, 3.7% for RFA, 10.9% for ATL, and 7.4% for sAHE; the differences did not show statistical significance. Neuropsychological deficits occurred after all procedures, with left-sided surgeries having a higher rate of verbal memory impairment. Lateral functions such as naming or object recognition may be more preserved in MRgLITT. Thermal therapies are effective techniques but show a significantly lower rate of Engel-I outcome in comparison to ATL and sAHE. Between MRgLITT and RFA there were no significant differences in Engel-I outcome, whereby the success of treatment seems to depend on the approach used (e.g., occipital approach). MRgLITT shows a similar rate of complications compared to

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RFA, whereas patients undergoing MRgLITT may experience fewer major complications compared to ATL or sAHE and might have a more beneficial neuropsychological outcome.

KEY WORDS

mesial temporal lobe epilepsy, minimally invasive therapy, thermal ablation

1 | INTRODUCTION

Epilepsy is a common disorder, with mean prevalence rates of .55 % in high income countries; thus, it can be considered one of the most common neurological diseases worldwide with major impact on patients and the health care system.^{1,2} Among focal epilepsies, temporal lobe epilepsy is the most common cause of medically refractory epilepsy, related, in about 70% of cases, to mesial temporal lobe epilepsy (mTLE) with hippocampal sclerosis (HS).³ In such cases, anterior temporal lobe resection (ATL) and selective amygdalohippocampectomy (sAHE) are the principal, evidence-based treatment options.⁴ The success rate of these surgical approaches is significantly superior to drug therapy alone in refractory temporal lobe epilepsy, ranging from 34% to 74% depending upon the presence of extratemporal lesions, history of febrile seizures, and the presence of HS.⁵

Although surgical therapy is the favored therapeutic option for temporal lobe epilepsies refractory to medical therapy, treatment-related adverse effects such as cognitive dysfunction, visual field defects (VFDs), intracranial bleeding, and inadvertent neurological damage are possible.⁶ As such, newer minimally invasive therapies such as magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) or radiofrequency ablation (RFA) represent promising alternatives to conventional surgery.⁷ Both MRgLITT and RFA are thermoablative procedures that facilitate the destruction of the epileptogenic zone due to local heat development induced by a probe or electrode inserted through a burr hole.⁸ Whereas MRgLITT uses the radiation of a neodymium-doped yttrium aluminum garnet laser, which is transported via optical fibers and generates heat by the absorption of photons in the tissue, RFA establishes a current flow between two electrodes for heat induction.^{9,10} Both methods have already been successfully used in the treatment of refractory mTLE, making them attractive alternatives for patients with contraindications or in those who refuse to undergo open surgical treatment, and both may better spare cognitive functions as compared with conventional open surgery.^{11,12} Among existing thermal ablative techniques, MRgLITT offers the advantage of magnetic resonance imaging (MRI) thermometry, which enables the direct measurement of the temperature in the area of the probe and the surrounding tissue, resulting in nearly real-time monitoring and optimization of the ablation zone.¹¹ As

Key Points

- There was no significant difference in seizure outcome (Engel Class I) or complication rate between MRgLITT and RFA
- MRgLITT and RFA were both inferior relative to conventional surgical approaches (ATL and sAHE) in terms of seizure outcome (Engel Class I)
- The most frequent complications following MRgLITT and RFA were visual field deficits and cranial nerve palsies, with patients showing a high probability of recovering within months
- MRgLITT and RFA seem to be more favorable in terms of complications compared to ATL or sAHE
- The presence of mTLE + HS as shown by magnetic resonance imaging predicted an Engel Class I outcome
- Cognitive outcome might be more favorable after MRgLITT compared to ATL and sAHE

a result, MRgLITT has recently garnered increasing attention for the treatment of drug-refractory mTLEs.

Because the available data on the safety and efficacy of MRgLITT and RFA have been derived to date from single-arm retrospective studies, a direct comparison between the two thermoablative procedures and with conventional surgery is limited. Therefore, we sought to summarize the results of MRgLITT (outcomes and complications) via a systematic review and then compare them with those of similar thermoablative procedures such as RFA and conventional “gold-standard” surgical approaches (ATL and sAHE) in a meta-analysis.

2 | MATERIALS AND METHODS

This systematic review was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and recommendations.¹³ The PICO model (i.e., population, intervention, comparison, outcome) was adopted to determine the parameters of a search

strategy, and the following question was formulated: (population) how do patients with therapy-refractory mTLE (intervention) treated with MRgLITT (comparison) differ from patients who were treated with alternative thermal ablation (RFA) or via existing gold-standard epilepsy surgical approaches (outcome) in terms of seizure freedom and the rate of adverse effects?

A systematic search of the following databases was performed: MEDLINE, including published articles, electronic publications ahead of print, and in-process and other nonindexed citations; Embase; and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. The organization of the detailed search strategy including the keywords used for MRgLITT and RFA is presented in Figure S1. Identified studies were subsequently analyzed by two independent reviewers (K.K. and J.P.Z.) according to the defined inclusion and exclusion criteria and their reference lists were reviewed to identify further relevant studies.

Because ATL and sAHE are already established procedures and have been performed nearly for decades, the literature contains multiple single-arm observational studies, comparative studies, and randomized controlled trials that have already been analyzed in systemic reviews by high-quality institutes such as Cochrane.¹⁴ A complete reanalysis of these studies is therefore not, in itself, of great value. For this reason, the search strategy for ATL and sAHE was adapted so that only randomized controlled trials (RCTs) and (retrospective/prospective) comparative studies between ATL and sAHE were included. The comparative studies were extracted from two recent high-quality comprehensive systematic reviews.^{15,16} Among the various classifications established for the outcome after epilepsy surgery or intervention, the Engel Epilepsy Surgery Outcome Scale was used most frequently among the studies examined so that only studies that included this classification were selected for the final analysis.¹⁷

Eligible studies were required to meet the following criteria:

- Established a diagnosis of mTLE based on seizure semiology, electroencephalographic (EEG) recordings (surface or invasive), or morphological findings due to MRI
- Involved MRgLITT, RFA, ATL, or sAHE as the treatment technique
- Incorporated at least 6 months for follow-up
- Used the Engel classification¹⁷ as the primary outcome

Meanwhile, studies that were excluded included the following:

- Studies with five or fewer patients, case reports, conference abstracts, and nonhuman studies

- Those that established a diagnosis of generalized/focal epilepsy other than mTLE with incomplete patient data
- Repeat publications of the same patient cohort

In cases where a study was a follow-up to or an expansion of an already published cohort, the paper reporting on the more detailed and comprehensive dataset was included. If other epilepsy syndromes were included in addition to mTLE in a single study, patients were only included if patient data and seizure outcome were provided separately.

2.1 | Outcomes and data extraction

For this study, the primary outcome was complete freedom from disabling seizures indicated by an Engel Class I (Engel-I) outcome during a follow-up period of at least 6 months.¹⁷ The secondary outcome was peri- or postinterventional morbidity, complications, and cognitive outcome (as discussed further below). In addition, multivariable logistic regression analysis was performed to determine the relationship between specific patient characteristics - specifically, gender, age at surgery, hemisphere of surgery, or mTLE + HS on MRI - and Engel-I outcome at 6 months or later.

2.2 | Assessment of complications

All complications and neurological deficits directly related to the intervention including intracranial hemorrhage (i.e., intracerebral, subarachnoid, sub-/epidural), infarction, infection (e.g., meningitis, wound infections), thrombosis, nerve injury (e.g., cranial nerve deficits), technical complications (dislocation, probe damage), and VFDs were compiled. The complications were subdivided into minor and major complications according to the SIR (Society of Interventional Radiology) grading system. According to the guidelines, a complication was considered to be major if it "...leads to substantial morbidity and disability [...] that increases the level of care, or results in hospital admission, or substantially lengthens the hospital stay [...]. All other complications are considered minor...."¹⁸ As a standardized severity assessment was limited by the retrospective design of the included studies, complications with permanent and relevant neurological deficits (such as homonymous hemianopsia), bleeding (clinical or subclinical with need of intervention), infections, or infarctions were classified as major complications. In addition, complications not solely attributable to the therapy but that may have been exacerbated by it were considered; these included psychiatric complications such as psychosis, depression, anxiety disorders, or suicide. However, as there was a high degree of heterogeneity between the studies regarding the reporting

or measuring of psychiatric symptoms, these were ultimately not included in the final assessment.

In addition, the neuropsychological outcome regarding verbal and figural memory as well as naming ability was assessed. Based on the provided data, the outcome was classified as improvement or deterioration of function depending on the procedure (MRgLITT, RFA, ATL, or sAHE) and surgical side (left or right); where possible, comparable data were summarized. Due to different statistical methods (individual or group level) between the studies and different neuropsychological test batteries that limit the outcome assessment, an adequate meta-analysis of cognitive outcome was not suitable and was therefore excluded.

2.3 | Quality assessment

The quality of the included studies was analyzed using the Newcastle Ottawa Scale (NOS) for cohort studies.¹⁹ However, the corresponding section of the NOS for comparability was not included, as the selected MRgLITT and RFA studies were all single-arm observational studies (Table S1).

2.4 | Statistics and meta-analysis

For the meta-analysis, a random-effects model was chosen. The individual proportions and effect strengths of binary data were calculated using the inverse-variance model. Each individual study was assigned a proportion and weighted relatively to the other studies. The Clopper–Pearson approach was used to estimate a confidence interval for each individual study. For between-study variance, τ^2 as a measure of heterogeneity was estimated using the DerSimonian and Laird approach.²⁰ Based on the assigned single proportion, overall proportions of Engel-I outcome were calculated for MRgLITT, RFA, ATL, and sAHE individually as well as for all four therapies together. The heterogeneity was reported as I^2 (0%–100%) with a 95% confidence interval, where a value of 0% explained differences between the studies on random fluctuations and a value of 100% assumed the study population itself. Thresholds for none, low, medium, and high heterogeneity were less than 25%, 25%–50%, 50%–75%, and greater than 75%, respectively. For the determination of differences between the subgroups, Cochrane Q was calculated with the level of significance set at $p < .05$. This meta-analysis was carried out using the RStudio version 1.1.463 software program.

Multivariable logistic regression analysis was performed using the SPSS Statistics for Windows version 26.0 software program (IBM). A regression coefficient was calculated and thereafter checked for significance by using the Wald test with the level of significance set as $p < .05$. Furthermore,

odd ratios with 95% confidence intervals were reported. The Engel-I outcome after 6 months was set as the dependent variable and compared with selected patient characteristics (e.g., age at surgery, gender, unilateral HS, epilepsy side) as the independent variable.

3 | RESULTS

Of the 373 reviewed abstracts and studies, a total of 37 studies dealing with thermal ablation (18 MRgLITT studies and 19 RFA studies) were closely analyzed. Finally, 13 studies dealing with MRgLITT^{21–31} and six dealing with RFA^{32–36} were included (Figure 1). For ATL and sAHE, four RCTs^{4,37–39} and 20 comparative studies^{40–59} were included.

3.1 | Patient characteristics

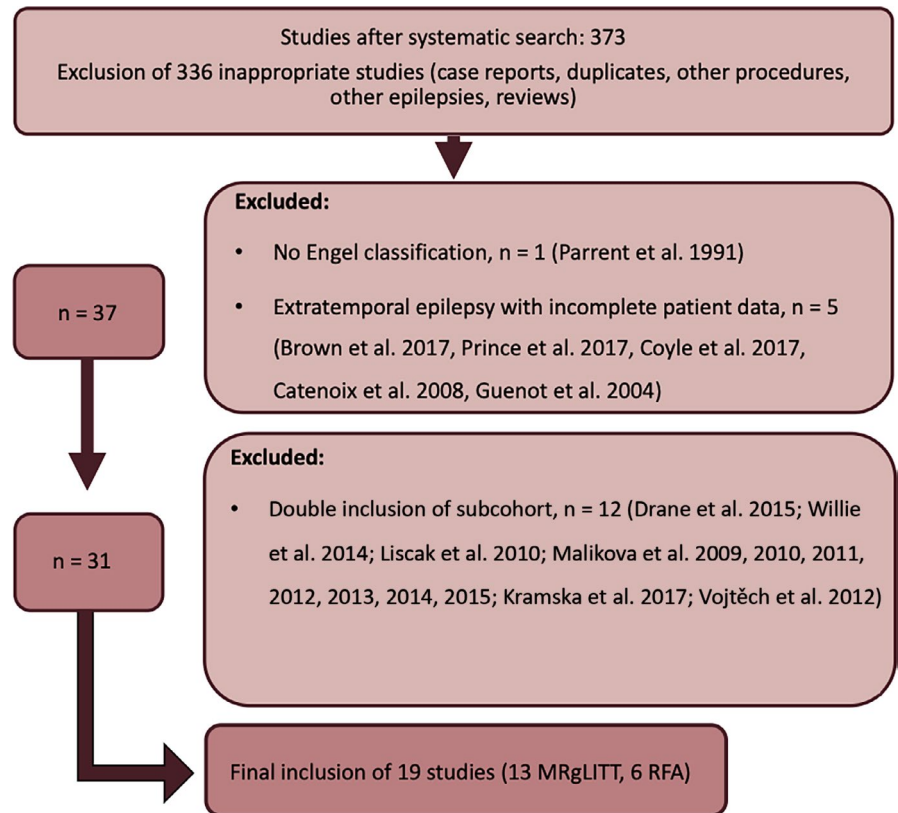
Among the included thermal ablation studies, a total of 667 patients were enrolled, including 554 who were treated by MRgLITT and 123 who were treated by RFA. The mean patient age was 43.1 ± 5.9 years and 35.4 ± 6.1 years for the MRgLITT and RFA populations, respectively. Gender data were available for 668 patients in total; 263 male (47%) and 297 female (53%) patients were treated by MRgLITT, and 57 male (53%) and 51 female (47%) patients were treated by RFA. The left side was targeted by MRgLITT and RFA in 57% and 69% of cases, respectively. Radiologically detectable HS was present in 414 patients (414/554, 74.7%) in the MRgLITT group and 78 patients (78/123, 63.4%) in the RFA group. The follow-up period among patients treated by MRgLITT ranged from 6 to 70 months, whereas the follow-up period in the RFA group ranged from 12 to 62 months.

Separately, a total of 2830 patients who underwent open surgery were enrolled, of whom 1504 (139 of RCTs) and 1326 (140 of RCTs) were treated via ATL or sAHE, respectively. Mean age was 29.9 ± 8.5 years for patients undergoing ATL and 31.1 ± 9.1 years for patients undergoing sAHE. Gender distribution was 50% male in patients treated by ATL and 48% male in patients treated by sAHE. The left side was targeted in 48% and 55% in ATL and sAHE, respectively. The follow-up period was 36.3 ± 29.0 (range = 12–116.4) months after ATL and 36.4 ± 25.6 (range = 12–104.4) months after sAHE.

3.2 | Outcomes

An Engel-I outcome was achieved using RFA in 44% (54/123, range = 0%–67.2%), MRgLITT in 57% (315/554, range = 33.3%–67.4%), sAHE in 66% (887/1326, range = 21.4%–93.3%), and ATL in 69% (1032/1504, range = 40%–92.9%) of patients, respectively. In the meta-analysis,

FIGURE 1 Selection of studies for inclusion. MRgLITT, magnetic resonance-guided laser interstitial thermal therapy; RFA, radiofrequency ablation



the proportions were .34 (.15–.61), .57 (.53–.61), .65 (.58–.72), and .69 (.62–.75) for RFA, MRgLITT, sAHE, and ATL, respectively. Heterogeneity (I^2 with 95% confidence interval) within the subgroups was 76% (47, 89%, $p < .001$), 0% (0, 45%, $p = .66$), 81% (71, 87%, $p < .001$), and 84% (78, 89%, $p < .001$) for RFA, MRgLITT, sAHE, and ATL, respectively. The subgroup analysis between MRgLITT and RFA revealed no significant differences ($Q = 2.74$, $p = .098$), whereas the analysis between MRgLITT and ATL as well as that between MRgLITT and sAHE revealed a significantly better outcome following conventional surgical therapy (MRgLITT vs. ATL: $Q = 8.92$, $p = .0028$; MRgLITT vs. sAHE: $Q = 4.33$, $p = .0374$; Figures 2–4). Meta-analysis between RFA and conventional surgery showed a significant difference between RFA and ATL ($Q = 6.42$, $p = .0113$) and sAHE ($Q = 5.04$, $p = .0247$). Because of the large range of follow-up in the surgery group, a subgroup analysis was carried out for patients with a follow-up of <60 months and ≥ 60 months. In the ≥ 60 -month group, mean Engel-I outcome was 72.7% after ATL (474/652, range = 46.3–89.3) and 68.5% after sAHE (376/549, range = 44.4%–81.5%), while ATL and sAHE reached a mean Engel-I outcome of 65.5% (558/852, range = 40%–92.9%) and 65.8% (511/777, range = 21.4%–93.3%) at a follow-up <60 months, respectively. Subgroup analysis revealed a significantly better Engel-I outcome between ATL (≥ 60 months) and MRgLITT ($Q = 6.68$, $p = .009$) or RFA ($Q = 7.4$, $p = .006$), respectively. Furthermore,

sAHE (≥ 60 months) resulted in a significantly higher rate of Engel-I outcome compared to MRgLITT ($Q = 4.09$, $p = .043$) or RFA ($Q = 5.8$, $p = .016$). In comparison between ATL (<60 months) and MRgLITT, the difference was marginally nonsignificant ($Q = 3.6$, $p = .057$), whereas ATL (<60 months) still revealed a better Engel-I outcome than RFA ($Q = 5.06$, $p = .024$). For sAHE (<60 months), similar results were obtained, with nonsignificant differences between sAHE (<60 months) and MRgLITT ($Q = 1.15$, $p = .28$) but a significantly better outcome compared to RFA ($Q = 3.89$, $p = .048$).

The rate of Engel-I outcome in patients with mTLE + HS treated by MRgLITT was 64% (123/192). Meta-analysis of this MRgLITT subgroup in comparison with non-mTLE + HS patients revealed significantly better outcomes in patients with proven mTLE + HS ($Q = 8.55$, $p = .0035$; Figure 5).

3.3 | Metaregression

A total of 180 patients were included in the multivariable logistic regression analysis. Gender, age at surgery, epilepsy side, and the detection of unilateral mTLE + HS were compared with Engel-I outcomes, which indicated a significant correlation between the presence of unilateral mTLE + HS and the chance of an Engel-I outcome ($p = .007$, odds ratio = 2.360, 95% confidence interval = 1.27–4.39; Table S2).

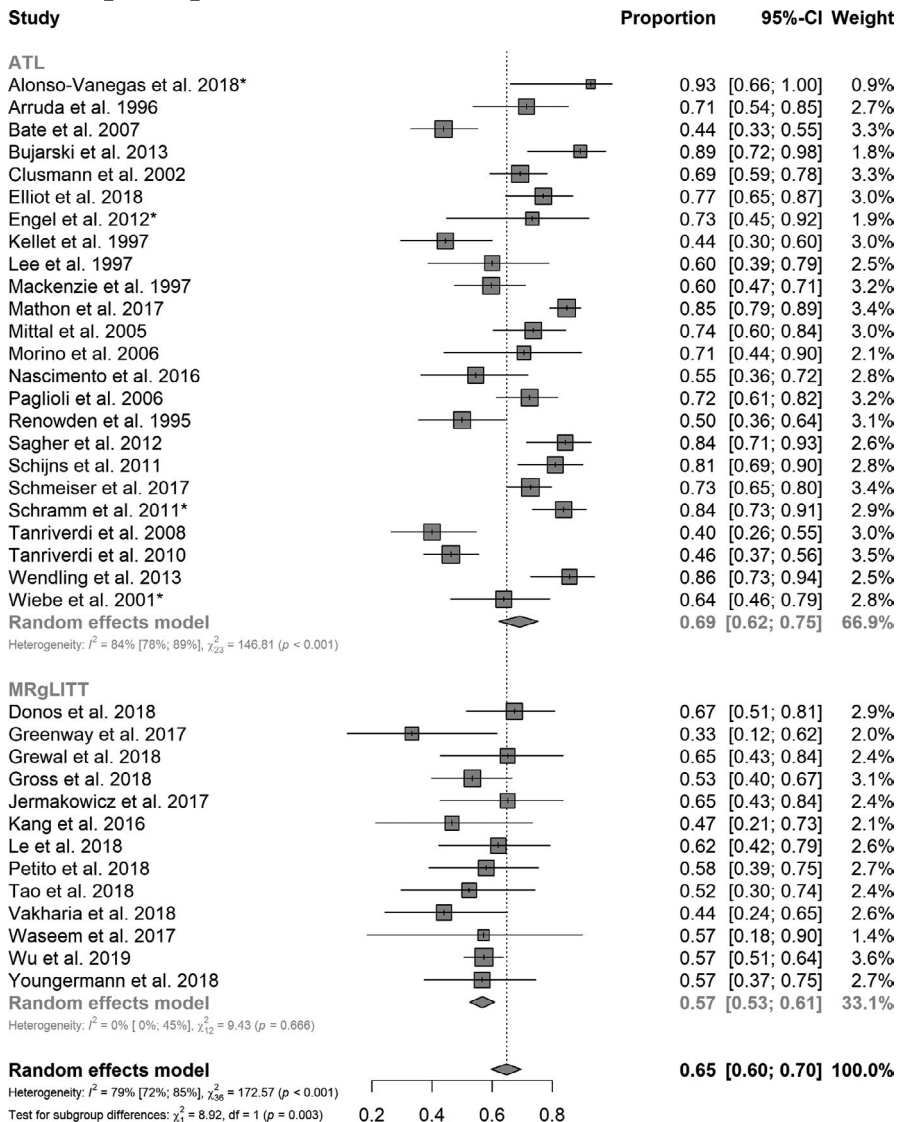


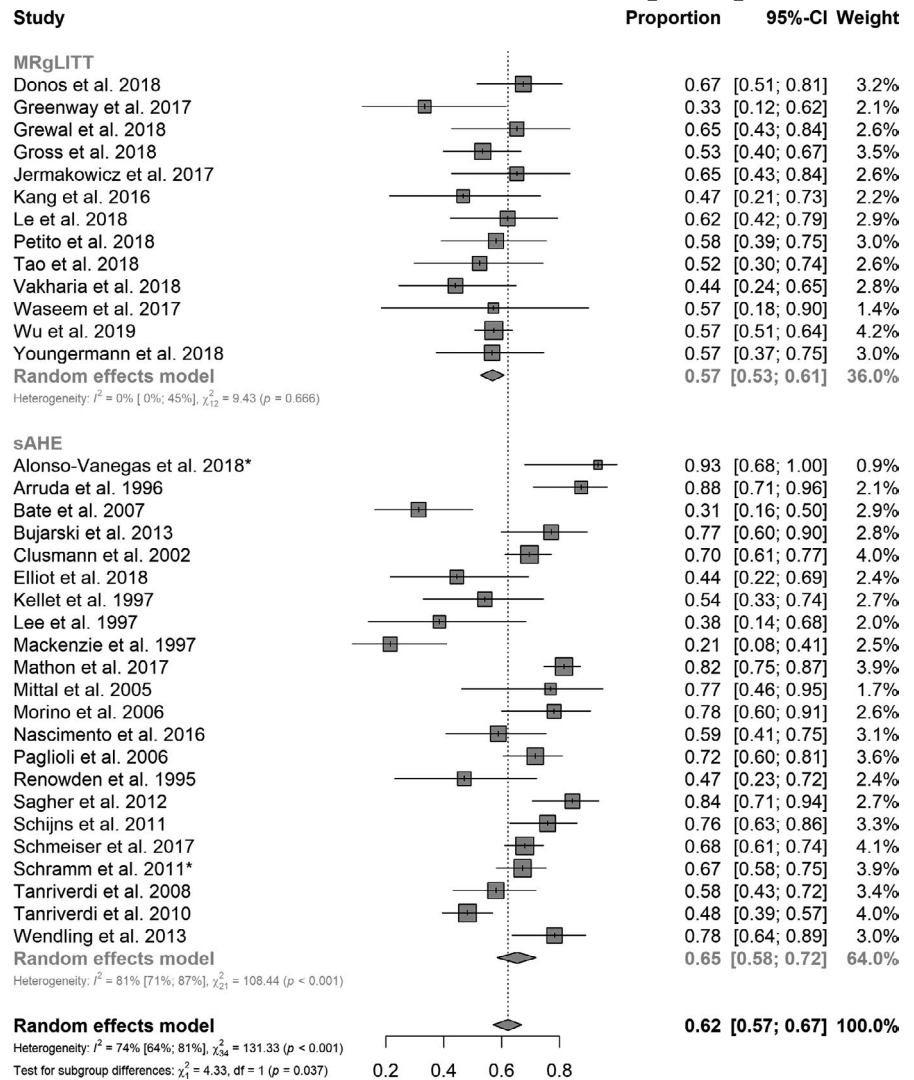
FIGURE 2 Statistical evaluation of the effect strengths with respect to Engel Class I outcomes achieved in a pairwise comparison between magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) and anterior temporal lobe resection (ATL). Heterogeneity is stated as I^2 with 95% confidence interval (CI) in brackets for the subgroups and all groups together as well as Cochrane Q (χ^2_{df} ; df , degrees of freedom) for subgroup differences with the level of significance set at $p < .05$ and * = randomized controlled trial.

3.4 | Complications

Overall complication rates were 14.1% (37/262), 17.5% (19/108), 31.3% (72/230), and 18.2% (27/148) for MRgLITT, RFA, ATL, and sAHE, respectively. The rates of major complications were 3.8% (10/262) for MRgLITT, 3.7% (4/108) for RFA, 10.9% (25/230) for ATL, and 7.4% (11/148) for sAHE. Meta-analysis revealed no significant differences concerning overall complication rate or major complications between the respective procedures (Figure 6). The tests for subgroup differences in overall complications for MRgLITT in comparison to RFA, ATL, or sAHE given as Cochrane Q (p -value) were .14 ($p = .71$), 3.19 ($p = .07$), and .21 ($p = .64$), respectively. For RFA in comparison to ATL or sAHE, the tests of subgroup differences in overall complications were 2.73 ($p = .09$) and .39 ($p = .53$), respectively. For ATL and sAHE, the test was .9 ($p = .34$). In the analysis of major complications of MRgLITT compared to RFA, ATL, or sAHE, the tests of subgroup differences given as Cochrane Q (p -value) were .12 ($p = .73$),

2.47 ($p = .12$), and .47 ($p = .49$), respectively. Comparing RFA with ATL or sAHE concerning major complications, the values were 1.4 ($p = .24$) and .19 ($p = .67$), whereas between the open surgical procedures it was .27 ($p = .6$). In MRgLITT, the group of major complications consisted of five homonymous hemianopsia, three intracranial hemorrhages (clinical), one subdural hematoma (subclinical with operative treatment), and one aseptic meningitis. In RFA, the major complications consisted of one aphasia/anomia, one intracerebral hemorrhage (clinical), and two infections. In the MRgLITT group, VFDs were recorded in 8.8% (23/262); in 1.9% (5/262), the defects were complete homonymous hemianopsias, whereas in 6.9% (18/262), the defects were homonymous quadrantanopsias. Among the reported cases, homonymous quadrantanopsias became asymptomatic or resolved completely in five patients, whereas homonymous hemianopsias persisted in all patients. Other cranial nerve lesions were reported in 3.1% (8/262) of cases and were transient in all cases. Furthermore, clinically overt intracranial hemorrhage occurred in 1.5% (4/262; three

FIGURE 3 Statistical evaluation of the effect strengths with respect to Engel Class I outcomes achieved in a pairwise comparison between magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) and selective amygdalohippocampectomy (sAHE). Heterogeneity is stated as I^2 with 95% confidence interval (CI) in brackets for the subgroups and all groups together as well as Cochrane Q (χ^2_{df} ; df , degrees of freedom) for subgroup differences with the level of significance set at $p < .05$ and * = randomized controlled trial.



intracranial hemorrhages [ICH] and one subdural hemorrhage [SDH]). Aseptic meningitis was reported in .4% (1/262), probe displacement in .4% (1/262), and other neurological deficits in .4% (1/262) of cases. In the RFA studies, the rate of reported VFDs was .9% (one case of homonymous quadrantanopsia; 1/116) and no cranial nerve lesions were observed. Additionally, intracranial bleeding occurred in 4.3% (5/116), consisting of one clinically overt ICH, one subclinical SDH, one subarachnoid hemorrhage, and two subclinical intracerebral hemorrhages along the trajectory. Infections were reported in 1.7% (2/116), aseptic meningitis in 6.9% (8/116), damage to the electrode during surgery in 1.7% (2/116), and other neurological deficits in .9% (1/116) of cases (Table S3). Major complications in ATL were four homonymous hemianopsias (1.7%), four hemorrhages (1.7%; one epidural hematoma, one subdural hematoma, one intracranial hemorrhage, and one subarachnoid bleeding), 10 infections (4.3%; four meningitis, two abscesses, one empyema + osteomyelitis, two mastoidites, two operation side infections), and seven vascular events (3.0%; two subclinical, one sensory deficit of the thigh, one mild aphasia, one transitory hemiparesis, one permanent hemiparesis, and one permanent hemiplegia).

In sAHE, major complications comprised six homonymous hemianopsias (4.1%), one intracerebral hemorrhage (.7%), two infections (1.3%; one abscess, one operation side infection), and two vascular events (1.4%; two with permanent hemiparesis). Furthermore, homonymous quadrantanopsias were described in 13.9% (32/230) and 7.4% (11/148) for ATL and sAHE, respectively. Cranial nerve lesions were described in 3.0% (7/230) after ATL and in 2.0% (3/148) after sAHE. Spinal fluid fistula and subdural cerebrospinal fluid accumulation were reported in 3.0% (7/230) and .7% (1/148) after ATL and sAHE, respectively. Further complications were reported by Clusmann et al.,⁴⁰ Mittal et al.,⁴¹ Schmeiser et al.,⁴² Tanriverdi et al.,⁵¹ and Wendling et al.⁴³ As they were given as total complications for sAHE and ATL, a differentiation was not possible; thus, the studies were excluded from the meta-analysis of complications.

3.5 | Neuropsychological outcome

For MRgLITT, a total of six of the included studies used a reliable change index or a standard deviation greater than 1

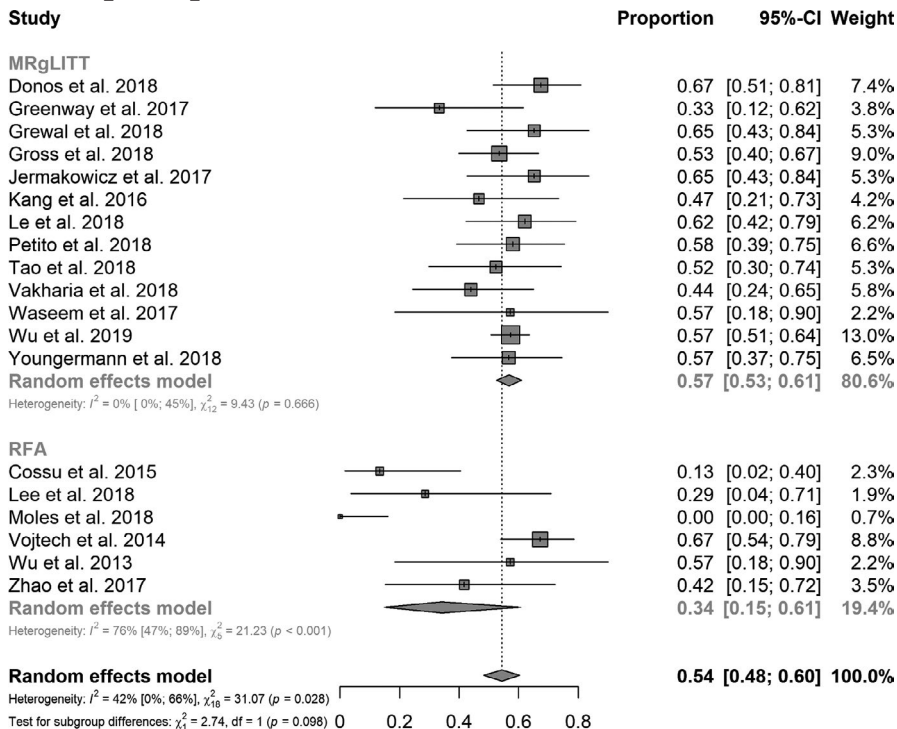


FIGURE 4 Statistical evaluation of the effect strengths with respect to Engel Class I outcomes achieved in a pairwise comparison between magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) and radiofrequency ablation (RFA). Heterogeneity is stated as I^2 with 95% confidence interval (CI) in brackets for the subgroups and all groups together as well as Cochrane Q (χ^2_{df} ; df , degrees of freedom) for subgroup differences with the level of significance set at $p < .05$

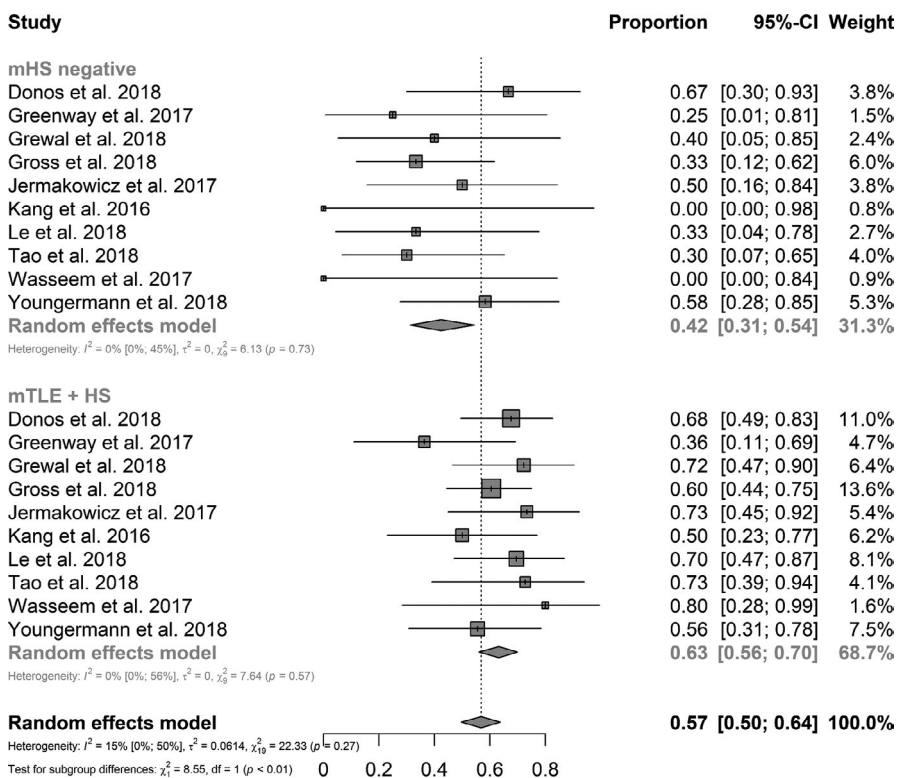
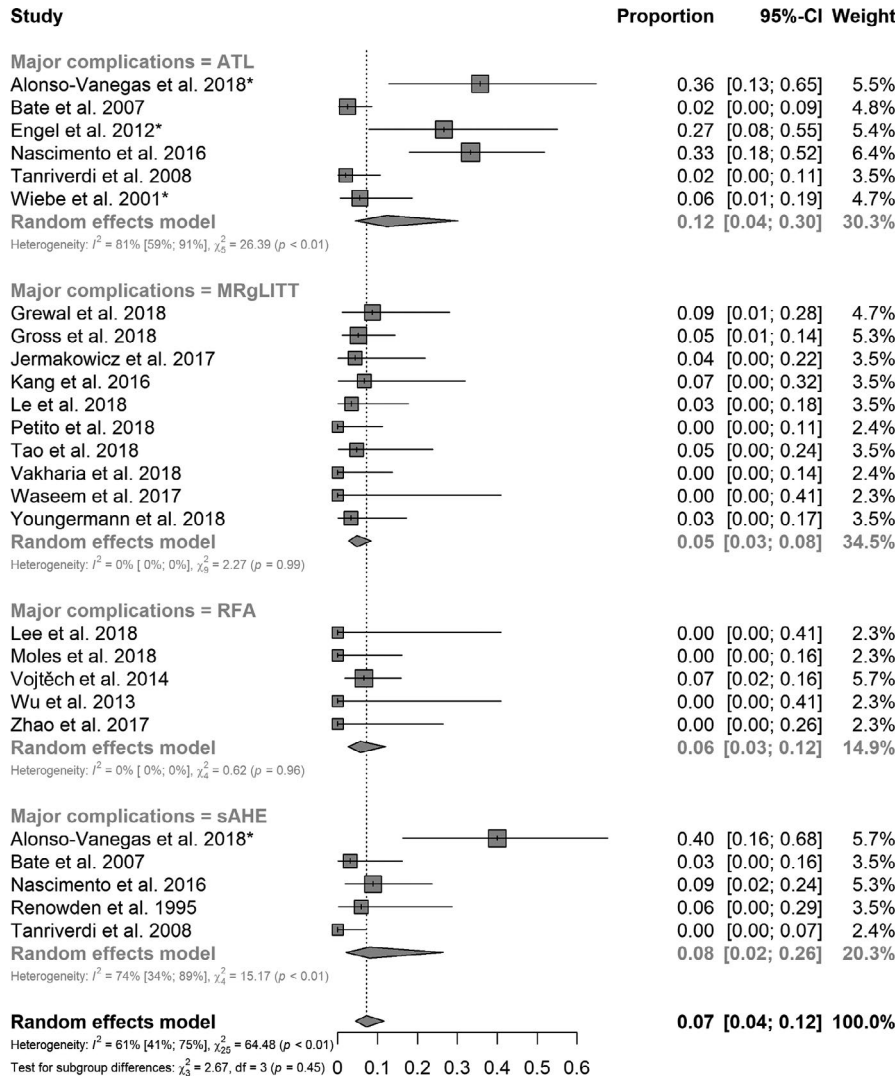


FIGURE 5 Statistical evaluation of the effect strength with respect to Engel Class I outcome in patients with and without mesial temporal lobe epilepsy (mTLE) + hippocampal sclerosis (HS) treated by magnetic resonance-guided laser interstitial thermal therapy. Heterogeneity is stated as I^2 with 95% confidence interval (CI) in brackets for the subgroups and all groups together as well as Cochrane Q (χ^2_{df} ; df , degrees of freedom) for subgroup differences with the level of significance set at $p < .05$. mHS, mesial HS

to evaluate the neuropsychological performance. Of these, verbal memory function was reported in five of the studies, figural/visual memory in two, and object/face recognition in four. Verbal skills in learning and delayed recall were reduced independently of the side in 26.0% (26/100), whereas a decline occurred in 35.3% (18/51) after interventions on the dominant and in 16.3% (8/49) on the nondominant side. An improvement of verbal memory was reported in 3.9% (2/51)

and 20.4% (10/49) after dominant- and nondominant-sided surgery, respectively. The risk for postoperative decline in figural memory was 28.6% (10/35) in total, 31.6% (6/19) for the dominant side and 25.0% (4/16) for the nondominant side. An improvement could be observed in 10.5% and 12.5% for the dominant and nondominant side, respectively. The recognition of objects or faces was reduced in 10.7% of all patients (6/56), in 12.1% with operations on the dominant

FIGURE 6 Statistical evaluation of the effect strength with respect to major complications in patients treated by magnetic resonance-guided laser interstitial thermal therapy (MRgLITT), radiofrequency ablation (RFA), anterior temporal lobe resection (ATL), and selective amygdalohippocampectomy (sAHE). Heterogeneity is stated as I^2 with 95% confidence interval (CI) in brackets for the subgroups and all groups together as well as Cochrane Q (χ^2_{df} ; df , degrees of freedom) for subgroup differences with the level of significance set at $p < .05$ and * = randomized controlled trial.



side (4/33), and in 8.7% with operations on the nondominant side (2/23). An improvement was reported in 6.1% (2/33) and 17.4% (4/23) for the dominant or nondominant side, respectively.

In the included RFA studies, either no data on neuropsychological outcome were stated or there was no standardized statistical analysis, so a summary of the results was not feasible. The neuropsychological outcome of the patients of Vojtěch et al. (2014)³³ was evaluated in the study by Vojtěch et al. (2012).⁶⁰ Zhao et al. reported on 12 patients with bilateral ablation of the temporal lobes and could demonstrate a significant improvement at the group level in all scales of the Wechsler Adult Intelligence Scale–Revised (WAIS-R) as well as the Wechsler Memory Scale–Revised, except the delayed recall.³² In contrast, Lee et al. could not detect a significant difference in WAIS-R at 6 months after RFA.⁶¹

Neuropsychological data at an individual level were found in six of the open surgery studies and were summarized.^{4,37,38,40,44,45} Postoperative visual memory decline was reported in 24.8% (35/141) and 25.7% (45/175) after ATL and sAHE, respectively, whereas an improvement in visual

memory function was found in 31.2% (44/141) after ATL and in 33.1% (58/175) after sAHE. A deterioration of verbal memory was reported in 24.7% (55/223) after ATL and in 24.0% (52/217) after sAHE, whereas an improvement of verbal memory performance was found in 11.7% (26/223) and 15.2% (33/217) after ATL and sAHE, respectively. Based on the provided data, a subdivision into treatment side (dominant/nondominant) was not possible. On a group level, surgery on the left (language dominant) side was associated with a significantly higher rate of verbal memory deterioration in eight studies.^{40,42-48} Concerning different procedures, a significantly higher rate of verbal memory impairment after ATL was described in four studies,^{40,44,46,49} although Lee et al. found that a better preoperative memory function was associated with a poorer outcome.⁴⁹ Morino et al. described a tendency toward a less favorable verbal memory outcome after ATL, which did not reach the level of significance.⁴⁷ In contrast, Sagher et al. reported stable verbal memory function after ATL but a significant decline after sAHE.⁵⁰ Concerning nonverbal memory, Schmeiser et al. reported a decline in 29.0% of patients; there were no significant

differences regarding operation side or procedure.⁴² In contrast, Wendling et al. reported a significantly higher rate of worse short-term visual memory and delayed reproduction after ATL irrespective of the operation side.⁴³ A nonsignificant tendency toward a worse visual memory outcome after ATL, especially after right-sided surgery, was reported by Tanriverdi et al. and Morino et al.^{47,51} In contrast, a significant improvement in figural memory performance was found in four studies with a tendency towards left-sided surgery.^{48,49,51,52} A decline in naming ability was reported by Engel et al. in 55% (6/11) of patients after ATL.³⁷ In contrast, Sagher et al. did not find significant changes in Boston Naming Test scores after either ATL or sAHE.⁵⁰

In summary, all procedures carry a risk of postoperative cognitive deterioration. In particular, left-sided (language-dominant) treatments are associated with an increased risk for verbal memory impairment, whereas figural memory seems to be less lateralized. Although the associated severity of cognitive impairment was not evaluated in correlation with the treatment, it appears to increase with the invasiveness of the respective intervention. Negative predictive factors were shown to be a high preoperative cognitive level and resection of functionally intact areas. Detailed results are summarized in the supplements (Table S4).

4 | DISCUSSION

The analysis of the data showed that overall, patients treated by MRgLITT had a lower chance of achieving an Engel-I outcome (Figures 2–4) relative to those who were treated by sAHE or ATL. In the subgroup analysis (follow-up ≥ 6 months), long-term outcome of ATL was superior compared to MRgLITT, which might be a result of complete and permanent destruction of the epileptic network after ATL. Long-term data are available for ATL, which reported freedom from seizures in 41% (95% confidence interval = 36%–48%) after 10 years and in 36.8% (95% confidence interval = 30%–44%) even after 15 years.⁶² Comparable data on MRgLITT are not yet available. However, because the tissue is not completely removed in comparison with open surgery, insufficient destruction can lead to reorganization of epileptic networks and, thus, to a recurrence of seizures, which emphasizes the importance of good patient and surgical technique selection. Whereas data on conventional epilepsy surgery suggests that outcome after 1 year is already a good predictor for long-term seizure outcome, comparably robust data after MRgLITT or RFA is not yet available.^{63,64} To date, there is no RCT available that contrasts MRgLITT with more traditional surgical therapies such as sAHE or ATL. However, a retrospective comparison between open resection and MRgLITT found no significant difference in Engel-I outcomes at 6 months.^{65,66} Drane et al. stated that in

selected patients with a defined epileptogenic network in the mesial temporal lobe, thermoablation might be as effective as open surgery.⁶⁵ An important criterion for the selection of patients for MRgLITT is the detection of mesial HS (mTLE + HS). In the meta-analysis, MRgLITT achieved a significantly higher rate of Engel-I outcome (64%) in patients with mTLE + HS with a positive correlation in the logistic regression analysis (Table S2). However, a recent multicenter compilation by Wu et al. could not demonstrate a significant correlation between the outcome and evidence of mTLE + HS.²¹ Donos et al. showed similar results in that patients with morphological evidence of HS compared to MRI-negative patients with mesiotemporal seizure onset zone confirmed by intracranial EEG did not exhibit significant differences.⁶⁷

From these results, the authors concluded that, although HS may be an indication of a good outcome, patients without such evidence can achieve comparable results if they are carefully selected and diagnosed preoperatively.⁶⁷ With an Engel-I outcome of 79.5% after 6 months and 67.4% at the last follow-up (~20.3 months), their results were comparable to those of open surgery.⁶⁷

Another important consideration is that MRgLITT is a relatively novel procedure that will continue to benefit from the increasing learning curve of surgeons, adaptation of ablation techniques, and improvement of patient selection, whereas open surgery is a procedure that has been established for several decades with high standards and experience.

Among MRgLITT and RFA, the meta-analysis did not suggest that significantly different results existed with regard to the achievement of an Engel-I outcome, despite Figure 5 showing a clear tendency toward more favorable outcomes with MRgLITT than with RFA. A reason for this might be the small number of RFA studies and the high heterogeneity ($I^2 = 76\%$), which underestimates the difference between procedures. Separately, a reason for the high heterogeneity among the RFA studies is that various ablation approaches were used. Within the RFA group, Vojtěch et al. achieved results (67.2% after 12 months) that were closest to those of MRgLITT or common open surgery.³³ The main difference relative to other RFA studies was that Vojtěch et al. used an occipital approach (similar to the MRgLITT procedure), in which the probe or electrode was placed along the long axis of the hippocampus. In contrast, Moles et al. and Cossu et al. used a transtemporal/orthogonal approach, which may limit the amount of tissue that can be destroyed and may be the reason for a poorer outcome.^{34,35} It was shown that the ablation volume of the amygdala and the concentration of energy in a more mesial, anterior, and inferior ablation area including the amygdala, hippocampal head, parahippocampal gyrus, entorhinal cortex, and perirhinal cortex are associated with an increased chance of an Engel-I outcome.²¹ Cossu et al. and Moles et al. used a so-called stereo-EEG (sEEG)-guided RFA approach, in which sEEG electrodes were implanted

and could also be used as coagulation electrodes, which enables targeted ablation of the “hotspot” structures. However, an Engel-I outcome was achieved in only a low proportion of patients, which could be attributed to the failure of the individually placed lesions to completely destroy the usually robust epileptic network seen in mTLEs.^{34,35} The use of an occipital approach allows, as in open surgery, one to completely destroy the anterior–mesial structures of the hippocampus with the use of just one trajectory, which may be the optimal approach for MRgLITT and RFA. Although a more extensive resection may lead to a higher chance of seizure-free survival, it might also be associated with an increased risk of complications. Visual field deficits are among the most common complications to appear following surgical therapy including sAHE and ATL in up to 78% of cases.⁶⁸ In contrast, our systematic review found a markedly lower rate of homonymous hemi- or quadrantanopsias for both ATL and sAHE. Because visual field deficits might be subclinical, they will be detected only by a standardized visual field test. In a study that performed ophthalmologic testing during the follow-up, the rate of visual deficits—85.7% and 46.7% after ATL and sAHE, respectively—was more reliable.³⁸ In comparison, the overall rate of VFDs in patients treated by MRgLITT was 8.8% (23/262), which could be subdivided into 1.9% (5/262) and 6.9% (18/262) for homonymous hemi- and quadrantanopsias, respectively. Wu et al. noted similar results and suggested VFDs to be the most frequent complication of MRgLITT, affecting 5.1% of cases.²¹ However, most of the included studies were retrospective; thus, detailed information on all complications was not available. In particular, a standardized visual field test was only conducted in a few of the studies, so significantly higher numbers of unreported or unrecognized VFDs have to be assumed. In accordance to this, a recent study by Donos et al. reported a VFD, mostly an octanopsia, in 37.5% after MRgLITT.⁶⁹

Because those patients did not report a clinically overt visual deficit or suspicious clinical testing of vision, the study supports the thesis that clinically silent VFDs are caused by MRgLITT more often than expected, whereas the percentage and extent of VFDs are still less than those in patients who were treated by open surgery.⁶⁹ Besides thermal damage of the visual radiation, a cranial nerve lesion, especially of the third and fourth cranial nerves, was detected in 3.05% (8/262) of cases, presumably caused by heat propagation with subsequent damage of the cranial nerves in the area of the tentorium during ablation of the basal structures such as the uncus or the entorhinal cortex.⁷⁰ However, this thermal damage to the cranial nerves was transient in all cases and also recovered completely within months (Table S3). Intracranial hemorrhages in MRgLITT or RFA occurred in the area of the insertion point as a subdural hematoma or along the trajectory as an intracerebral hemorrhage. Gross et al. reported one

patient after MRgLITT who presented an acute subdural hematoma directly after intervention that was immediately surgically addressed and did not cause any permanent neurological deficit.⁷⁰ In RFA, Vojtěch et al. reported a total of four bleedings: two asymptomatic ICHs in the course of the trajectory, one asymptomatic subdural hematoma, and one clinically symptomatic ICH.⁴⁶ The latter was similarly in the course of the trajectory, with a rupture in the occipital horn of the lateral ventricle, which led to an acute occlusive hydrocephalus and temporary application of external ventricular drainage.³³ Despite those more complicative reports, most of the intracranial hemorrhages were accompanied by only mild neurological deficits and could be treated conservatively. The rate of intracranial hemorrhage after ATL or sAHE was relatively similar to what was found after MRgLITT or RFA and in accordance with previous reviews that reported intracranial hemorrhages in 1.4%.⁶ These were both intraparenchymal and sub-/epidural hemorrhages, which mostly had to be surgically addressed, but were usually without permanent deficits.⁷¹ It was noticeable that an increased amount of distant bleeding could be detected in the cerebellum (2.5%–4.9%), which was attributed to the high cerebrospinal fluid loss during surgery and fluid changes in the intracerebral compartments.^{72,73} With regard to complications, it was also noticeable that no infections after MRgLITT and two cases (1.7%) with meningitis requiring temporary antibiotics after RFA were reported.³³ On the other hand, a total of 12 infections were found in the surgical group, and they consisted not only of meningitis, but also of mastoiditis, abscesses, osteomyelitis, and wound infections. Another complication that appeared more often in ATL or sAHE was postoperative infarctions. Although no case was reported after MRgLITT or RFA, these occurred in a total of nine cases in the included surgical studies and were often associated with severe neurological deficits such as hemiplegia.^{4,37,44,53} A possible explanation for the occurrence of strokes can be vasospasms, which is a known problem after conventional surgery but has not been described for thermoablative procedures.⁷⁴ Furthermore, Bate et al. assumed a possible injury to the anterior choroidal artery during sAHE, which resulted in a stroke with consecutive hemiparesis.⁵³ Apart from that, the risk of neuropsychological constraints also represents a crucial factor. For thermal procedures as well as for open surgery, there was a risk of postoperative cognitive impairment. Whereas left-sided surgery was associated with an increased risk of verbal memory deterioration, there was a less clear lateralization for figural memory.⁴⁷ An important predictor for postoperative cognitive decline was, besides a high preoperative cognitive baseline level, the resection of functionally preserved brain areas.^{40,49} In mTLE, the parahippocampal structures, the temporal neocortex, and the white matter

tracts in the temporal stem such as the uncinatus fasciculus or inferior fronto-occipital fasciculus are important for learning and memory as well as for visual processing and recognition.⁷⁵ Although more selective procedures such as the sAHE, which do not remove the temporal neocortex, are considered to have a more favorable outcome, the approach used (transsylvian, transtemporal, subtemporal) and the dissection of white matter tracts can lead to relevant damage.⁷⁶ By using thermal procedures such as MRgLITT or RFA via an occipital access route, these areas are spared.⁶⁷ Correspondingly, Drane et al. were able to demonstrate no restriction of naming ability or object recognition in 19 patients when comparing MRgLITT with conventional epilepsy surgery, whereas in 21 of 22 patients with surgery on the left side there was a decline in naming ability or facial recognition, and in 11 of 17 patients with surgery on the right side there was a restriction in facial recognition; the authors attributed this to functional preservation of the abovementioned structures.⁶⁵ A recent review by Drane also suggested a significantly better outcome in terms of verbal memory compared to open surgery.¹² Although thermoablative procedures can also lead to verbal memory impairment, this was suggested to be less severe.⁶⁷ Overall, thermoablative procedures are thought to preserve cognitive function better than open surgery, although risk stratification always depends on individual patient characteristics (MRI-negative, broad epilepsy network, high baseline cognitive score, functionally intact tissue). Because the chance of seizure freedom is always compared to its possible risk (complications, neuropsychological outcome), the latter is essential for the final evaluation of the procedures. Although the chance of seizure freedom seems to be somewhat lower for thermoablative procedures than for open surgery, the data suggest that this disadvantage can be balanced by a more positive risk–benefit ratio, especially with regard to neuropsychological deficits. However, further studies using standardized neuropsychological tests that assess the wide range of cognitive functions are needed to address this question.

The major limitations of this review and our meta-analysis are that for MRgLITT and RFA, only single-arm retrospective studies without control groups are included, whereas the open surgery group consists of RCTs and comparative studies, thus resulting in studies of varying scientific quality and in a limitation of effect size calculation of the respective studies. Moreover, because Engel-I outcome was not assessed at similar follow-ups and the long-term outcome of MRgLITT and RFA is not yet completely evaluated, the different follow-ups need to be taken into account. Due to the significant differences in the quality of complication assessment between the studies, a general transferability of the stated complication rate is only possible to a limited extent.

4.1 | Conclusions

MRgLITT is an effective and safe thermoablative technique for the treatment of mTLE but shows a significantly lower rate of Engel-I outcomes in comparison with conventional surgical procedures (ATL and sAHE). For the selection of patients, mesial HS might be a prognostic factor for a more favorable outcome in patients treated by MRgLITT. MRgLITT and RFA did not present significantly different results from one another concerning Engel-I outcomes. The high heterogeneity in RFA suggests that some approaches such as the occipital approach may be similar to MRgLITT, whereas others are not. In terms of complications, there was no significant difference in major complications between the procedures, whereas MRgLITT and RFA showed a tendency to be more advantageous compared to ATL and sAHE. Cognitive function might be affected by all procedures, although lateral temporal functions such as naming or object recognition might be less affected by MRgLITT. However, sufficiently powered and standardized studies with comparative groups are still necessary to confirm these results.

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CONFLICT OF INTEREST

K.K. has no conflict of interest to disclose. J.P.Z. reports honoraria from Desitin Arzneimittel and Eisai. N.T. is involved in the Medtronic-sponsored SLATE trial; he is the site principal investigator for the trial at University of Texas Health Science Center at Houston and is on the surgical committee guiding the trial. A.S. reports personal fees and grants from Arvelle Therapeutics, Desitin Arzneimittel, Eisai, GW Pharmaceuticals, LivaNova, Marinus Pharmaceuticals, Medtronic, Sage Therapeutics, UCB Pharma, and Zogenix. F.R. reports personal fees from Arvelle Therapeutics, Eisai, GW Pharmaceuticals, Medtronic, Cerbomed, ViroPharma, Shire, and Sandoz; grants and personal fees from UCB and Desitin Arzneimittel; personal fees and other from Novartis; and grants from the European Union, the German Research Foundation, the Detlev-Wrobel Fund for Epilepsy Research, and the Landes-Offensive zur Entwicklung wissenschaftlich-ökonomischer Exzellenz program of the State of Hesse in Germany.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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