MRI-negative Epilepsy: A Systematic Review & Meta-analysis

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RATIONALE

Patients with drug-resistant seizures are commonly dichotomized based on MRI lesion visibility into positive (MRI-pos) and negative (MRI-neg). Indeed, even though the characterization of the focus relies on multimodal convergence [1], a positive MRI is the strongest prognostic factor for postoperative seizure freedom [2]. Yet, this distinction creates biases, with many patients with histologically verified lesions being initially misclassified as MRI-neg [3]. While appropriate MRI protocol [4], reviewer's expertise [5] and post-processing [6]) may improve the detection of previously unseen lesions, the degree to which these criteria are applied remains unknown. We used a systematic review and meta-analyses in compliance with **PRISMA** guidelines to synthesize evidence for ambiguity in defining MRI-neg.

METHODS

The systematic review (1990–2021) across the *Embase*, *Cochrane*, *Medline* databases identified cohorts with MRI-neg drug-resistant focal epilepsy. Unsupervised clustering stratified studies based on co-occurrence of imaging modalities. Within identified clusters, we assessed the consistency of diagnostic reporting for MRI contrasts/parameters, post-processing, expertise and SEEG. In a subset of studies, meta-analyses evaluated the effect of MRI-neg status on postsurgical outcome and MRI post-processing on diagnostic yield.

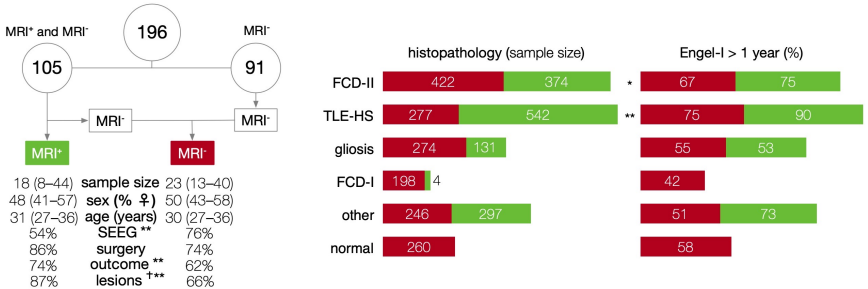

Figure 1. **Clinical and demographic information across 196 records**. Results are reported separately for MRI-positive (MRI+; green) and MRI-negative (MRI-; red) patients. Sample size, gender and age are reported as median (interquartile range), prevalence of SEEG, surgery, and postsurgical seizure outcome are expressed as mean. Plots on the right report seizure outcome stratified by histopathology (other refers to benign tumors, including DNET, hamartoma, and cortical malformations other than FCD type I and II; normal refers to normal or negative histopathological findings). **/*: significant difference (p<0.05) / trend (p<0.1). †: Lesions are represented as a percentage of patients that underwent surgery.

RESULTS

SCREENING & ELIGIBILITY of 196 studies were included in the systematic review: 91 (46%) provided data exclusively on MRI-neg patients and 105 (54%) on mixed cohorts, for a total of 7,436 MRI-neg and 4,585 MRI-pos. Compared to MRI-pos, MRI-neg patients underwent more often SEEG (76% *vs.* 54%; $p<0.05$), were less frequently operated (74% *vs.* 86%) and had a less favourable seizure outcome (62% vs. 74%; $p_{Bonf}<0.05$; **Fig. 1**).

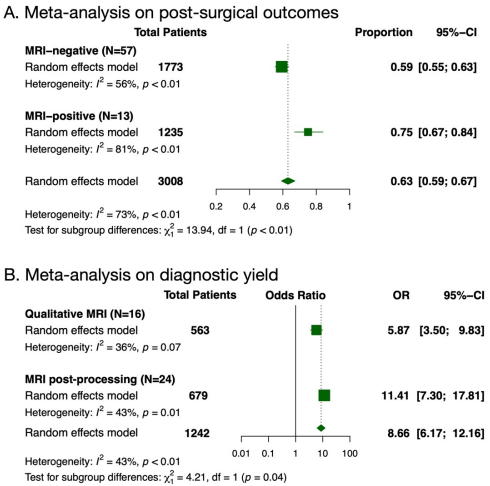

Figure 2. Meta-analyses with forest plots depicting effect estimates for the association between A) Post-surgical seizure freedom [Engel-I outcome (> 1-year follow-up)] and MRI-diagnostic status [MRI-neg (n=1773) vs. MRI-pos (n=1235)]; B) Diagnostic yield and MRI analysis procedures [post-processing (n=679) vs. qualitative (n=563)].

CLUSTERING identified three distinct groups: Consistency of MRI parameters reporting (*OR*s>5.3; $p<0.001$) and conducting post-processing typified the MRI-dominant, as opposed to the limited-MRI group ($\chi^2=37.5$, $p<0.001$). The latter was also less likely to report rater expertise (*OR*s>15.6, $p<0.001$). SEEG was mostly performed in the nuclear-imaging group (*OR*s>3.7, $p<0.02$).

META-ANALYSIS of 61 studies reporting *postsurgical outcome* (**Fig. 2A**) showed higher proportion of favorable outcome in MRI-pos compared to MRI-neg (75% *vs.* 59%; $\chi^2=13.9$, $p<0.01$). In addition, 50 studies reporting *diagnostic yield* (**Fig. 2B**) showed a two-fold gain (11.4 *vs.* 5.9, $p=0.04$) when using MRI post-processing over qualitative review.

CONCLUSIONS

There is a high degree of ambiguity in the definition of the MRI-negative status. Our findings reiterate that postsurgical outcome is poorer in MRI-neg epilepsy and provide the first meta-analytic evidence reinforcing the utility of MRI post-processing in reverting negative to positive.

REFERENCES

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