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MEG and navigated TMS jointly enable spatially accurate application of TMS therapy at the epileptic focus in pharmacoresistant epilepsy

Dear Editor

Pharmacoresistant epilepsy is associated with increased morbidity, mortality and a reduced quality of life for patients [1]. Several neurostimulation techniques have been evaluated for pharmacoresistant epilepsy including repetitive transcranial magnetic stimulation (rTMS). At present, the efficacy of rTMS as a therapeutic alternative remains uncertain [2]. We studied three patients with refractory focal epilepsy. The seizure onset zone (SOZ) was estimated using a combination of seizure semiology, electroclinical findings, MRI imaging and magnetoencephalography (MEG). The MEG measurements were performed using an Elekta TRIUX system (102 magnetometers and 204 gradiometers). Interictal MEG was visually analysed using *Curry 7.0*®. All 306 channels were visually investigated and spikes or sharp waves were manually marked by a specialist (GC). The averaged spikes or sharp waves were localised using an equivalent current dipole. A boundary element model was used for the forward model and was constructed using patient specific MRI. An average of the upstroke of the spike/sharp wave was used in the localisation. The centre for the rTMS stimulation, marked by the orange sphere (Fig. 1 A, B and C), was centred within the 95% uncertainty ellipsoid of the localised dipole. The exact position depended on practical issues, mainly the placing and angle of the rTMS coil. As there is local spread of the induced rTMS current it was assumed that centering the rTMS stimulation within the uncertainty ellipsoid would keep stimulation within the possible spatial accuracy of the estimated SOZ. Baseline seizure frequency was estimated using a seizure diary during an initial 4-week period followed by 2 weeks of rTMS treatment and 6 weeks following treatment. There were no changes in medication during this period. Motor mapping of the hand (case A, B & C) and foot (case A) regions were done using MRI navigated TMS (nTMS) in the affected hemisphere before starting the rTMS treatment [3].

The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki and approved by the regional ethics committee (Dnr. 2018/641-32).

Patient A was a 15 year-old boy with normal development and neurological status who started having left sided short focal motor seizures without dyscognitive symptoms from the age of 1 year. MRI brain images were examined without any abnormalities. However, prolonged video EEG monitoring indicated seizure onset with tonic motor symptoms of the left leg as the initial manifestation of the seizure. This could indicate early involvement of the primary or premotor cortex in the right hemisphere. We mapped the interictal zone to gain further evidence in distinguishing between the probable sites of seizure onset. Patient A showed one type of spikes, Fig. 2 A, B in supplemental file. We found the interictal MEG zone just adjacent to the primary motor area of the left leg on the parasagittal surface of the frontal lobe, Fig. 2C. The rTMS pulses were centred to this region (orange ball, Fig. 1A).

Patient B was a 14 year-old boy with normal development and neurological status who presented with epilepsy at the age of 10 years. Prolonged video EEG monitoring showed that seizures started with tingling of the left hand over the 4th-5th finger with early clonic involvement of the hand and arm. This could indicate seizure initiation in proximity of the right primary somatosensory cortex with spread to the primary motor cortex. Patient B did not show any spikes or sharp waves although, there was a cortical lesion visible in the patients MRI brain in the postcentral gyrus in the right hemisphere. To functionally locate the right primary somatosensory cortex of the left hand a somatosensory evoked field (SEF) was triggered from the medial aspect of the left hand. The left ulnar nerve was electrically stimulated at the wrist at 3 Hz for 10 minutes (1800 stimuli) and a stimulus triggered SEF was measured, Fig. 3A & B. The upstroke of the peak field (20 ms post stimulus) was used to estimate the location of the sensory area of the medial aspect of the left hand, Fig. 3C supplemental file. This was done as before using an equivalent current dipole. The current dipole was located just adjacent to the area with the cortical lesion. The co-location of the somatosensory cortex of the medial aspect of the left hand and the MRI lesion together with the semiology was considered highly indicative of the seizure onset zone being located at or near the MRI lesion. The rTMS stimulation was centred in proximity to the left somatosensory cortex just adjacent to the structural lesion in the postcentral gyrus (orange ball in Fig. 1B).

Patient C was a 35 year-old woman with normal development and neurological status until viral encephalitis at the age of 6 years. She then developed refractory epilepsy together with mild cognitive dysfunction. The patient experienced several types of seizures but reported only one type of seizure during this study: focal seizures with diffuse sensory symptoms that sometimes progressed to dyscognitive seizures with rare generalisation. Recent prolonged video EEG monitoring was not performed and MR imaging did not show any clear cortical lesions. Patient C showed one type of spike over the right convexity in the right inferior parietal lobule which was determined to be epileptic by a specialist (GC), Fig. 4A, B and C in supplemental file. The rTMS was centred within the 95% uncertainty ellipsoid (orange ball Fig. 1C).

All three patients received 10 consecutive sessions of rTMS at 1 Hz for 30 minutes (i.e. a total of 1800 stimulations) at 90% of resting motor threshold (of the first Interosseal Dorsal muscle) over the estimated SOZ (orange ball, Fig. 1 A, B and C) [4]. Baseline

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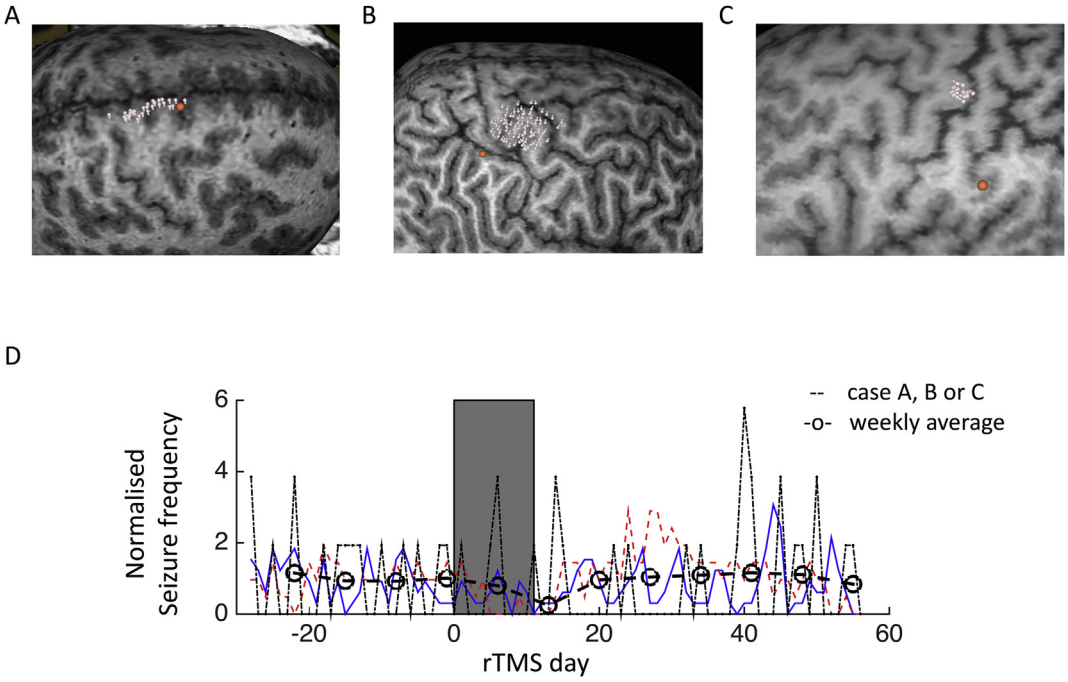

Fig. 1. A) The rTMS stimulation was centred at the orange point. Positive motor points marked in white for left leg (anterior tibial and abductor hallucis muscle). B) The rTMS stimulation was centred at the orange point adjacent to the MRI lesion in the postcentral gyrus. Positive motor points marked in white for left hand (short abductor pollicis, first dorsal interosseal and extensor digitorum muscle). C) The rTMS stimulation was centred at the orange point which was located in the inferior parietal lobule. Positive motor points marked in white for right hand (short abductor pollicis, first dorsal interosseal and extensor digitorum muscle). D) Change in seizure frequency during the study. Dotted lines show normalised seizure frequency for each day of the study for patient A (red), B (blue) and C (black). Circles show weekly averaged normalised seizure frequency (per day). Region with stimulus is marked in grey. Significant difference could be seen between stimulus and baseline periods ($p < 0.01$) and also between the three days following treatment and baseline ($p < 0.01$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

measurements of seizure frequency for patients A, B and C were 3.3, 2.1 and 0.6 seizures per day, respectively. During the rTMS treatment period, seizure rates dropped to 1.7, 0.84 and 0.4 seizures per day, respectively. During the post-treatment phase the rates were: 2.7, 2.5 and 0.5 seizures per day, respectively. The following changes (percentage and 95% confidence intervals) in seizure frequency were noted relative to pre-treatment: pre-treatment − 100% (92%–110%), treatment − 56% (0%–61%) and post-treatment − 99% (48%–105%). There was a significant difference in seizure rates between treatment and pre-treatment period ($p < 0.01$, Mann-Whitney *U* test) but no difference between the pre- and post-treatment periods (Fig. 1). Moreover, there was a significant difference between the 3 days (58%, 0%–68%) following treatment and the baseline rate ($p < 0.01$).

In contrast to previous studies investigating the effect of rTMS on refractory epilepsy we included interictal MEG recordings, which can localize interictal spikes with high spatial accuracy [5]. Furthermore, we used MRI navigated TMS to apply repeated stimulation over the predicted SOZ, also with high spatial accuracy. This combination has not, to our knowledge, been reported previously. The seizure onset zone was estimated using non-invasive methods and as such would not be as accurate as invasive estimation of the seizure onset zone using e.g. subdural or stereo-EEG electrodes. However, in the three presented cases semiology, MRI-findings and interictal findings were all concordant and as such provided, for non-invasive measurements, a highly probable seizure onset zone. This case series suggests rTMS applied with spatial precision to the SOZ transiently reduces seizure frequency. The duration of effect is at least 3 days following treatment. The relatively short-lived changes seen in this study are in contrast to some studies with seizure reduction over several weeks, although conclusions based on data from three patients are limited [6–8]. However, a shorter duration of effect following stimulation cessation is more in line with results from continuous invasive cortical stimulation of the SOZ [9,10].

Overall, results suggest difficulty in using rTMS for chronic seizure reduction; however, navigated rTMS could provide a non-invasive means of assessing treatment prognosis prior to permanent implantation for chronic invasive cortical stimulation.

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. MI, KW, AC and GC were funded by Stockholm City Council, Sweden (ALF: 20160096). BNL was funded by the Mayo Clinic Foundation as a Mayo Scholar, U.S.. DL and LMA were supported by the Knut and Alice Wallenberg foundation, Sweden (KAW: 2014.0102).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.06.026.

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