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Efficacy of repetitive transcranial magnetic stimulation on refractory epilepsy in Malaysia

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Abstract

Background & Objective: Modulation of cortical excitability by low frequency repetitive transcranial magnetic stimulation (rTMS) has demonstrated therapeutic use in epilepsy. This study aimed to evaluate the efficacy of low-frequency rTMS on refractory epilepsy in a group of Malaysian subjects. *Methods:* Nine patients with refractory epilepsy completed the study. All patients received 10 sessions of 1Hz rTMS (1000 pulses per session) at 90% of resting motor threshold. Outcome measures included seizure frequency, Symptom Checklist-90 (SCL-90), Beck Depression Inventory II (BDI II) and Quality of Life in Epilepsy-31 (QOLIE-31). Responders were defined as having ≥ 50% seizure reduction. *Results:* The mean age was 33.8 years (SD 11.7), with 4 male. Three patients had mesial temporal sclerosis (MTS); 4 with focal cortical dysplasia (FCD) and two lesion-negative. Three patients achieved >50% seizure reduction at 8 weeks post-treatment, with 2 of them had improvement in the number of IED. All of the responders had FCD. The responders were younger (mean 24.7 vs. 38.3 years old), had shorter duration of illness (mean 15.7 vs. 30.5 years) and had less frequent seizure frequency prior to treatment (mean 5.5 vs. 10.8 attacks per week), as compared to the non-responders. Six patients had improvement in BDI-II scores, two in QOLIE-31 and four in SCL-90 post treatment, irrespective of seizure control. The mean scores in BDI-II improved significantly with treatment ($p<0.01$).
Conclusion: rTMS is a potentially promising treatment for epilepsy, especially in those with FCD, younger age, shorter duration of illness and lower seizure frequency.

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a noninvasive, generally well-tolerated method for cortical stimulation that is based on principles of electromagnetic induction, where small intracranial electric currents are generated by a strong fluctuating extracranial magnetic field.[1] Low frequency stimulation (≤ 1 Hz) results in reduction of cortical excitability and hence its role in treating epilepsy was explored in 1994.[2] Subsequently, repetitive TMS (rTMS) is emerging as a new therapeutic tool, especially for refractory focal epilepsy, with 38% of the treated patients achieving more than 50% seizure frequency reduction.[3] Treatment comprising of one to two-week daily 15-30 minutes of rTMS resulted in seizure control for at least 8 weeks.[3,4] Review on the safety and tolerability of this treatment showed that it is safe and well tolerated with only about 1% of the patients developed seizures during the procedure especially those on higher frequency of stimulation (> 1 Hz).[3]

rTMS is more widely used for stroke rehabilitation but not in epilepsy. It has advantages of being non-invasive, and relatively cheap compared with other palliative epilepsy therapies such as vagal nerve stimulation and trigeminal nerve stimulation. rTMS has been reported to be efficacious in epilepsy treatment[5], but most were based on small sample size. This study aimed to assess the efficacy of repetitive rTMS in patients with refractory focal epilepsy in University Malaya Medical Centre (UMMC), Malaysia.

METHODS

Patient recruitment

A total of 9 patients from UMMC with at least 2-year history of refractory epilepsy were recruited from neurology clinic and assessed according to UMMC comprehensive epilepsy program. Refractoriness was defined as failure of seizure control despite being on two or more maximally

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tolerated doses of antiepileptic drugs (AEDs). All patients were on steady dose for at least four weeks prior to recruitment. AEDs changes were avoided during study period, unless there was a strong clinical indication. All patients had to have at least four or more seizure attacks per month and had no evidence of progressive neurological disorders, major psychiatric disorder or any systemic disease. All were capable to keep a reliable seizure diary, charting their daily seizure attacks throughout the study period. Patients younger than 18 years old or had a cardiac pacemaker, vagus nerve stimulator or intracranial metal objects were excluded from the study. This study was approved by UMMC ethics committee (reference number: 1016.9). Written consents were obtained from all participants.

Repetitive transcranial magnetic stimulation (rTMS) protocol

rTMS intervention was done daily for two weeks using a commercially available 'figure-of-eight' coil at a frequency of 1Hz and an intensity of 90% of resting motor threshold (MT). The resting MT was determined using single pulse TMS prior to intervention on the first dorsal interosseous muscle of the dominant hand. During rTMS session, the coil was positioned over the cortical epileptogenic lesion or ictal onset zone, or over the vertex in those with deep epileptogenic lesion, lesion negative or bilateral ictal onset zone. Each session consisted of 2 blocks of 500 stimuli at 1Hz with a 10 minutes break between blocks. All patients received a total of 1000 stimuli a day, 5 days a week for a total of 2 weeks (10 days of treatment phase). Neurologist was readily available in time of seizures occurred. The session would be aborted if seizure occurred. Short-acting benzodiazepine would be given if seizure lasted for > 5 minutes.

Clinical outcome: Seizure response, interictal discharges and qualitative outcome

Our study was divided into three phases: pre-treatment phase (week -4 to -1), treatment phase (week 1-2 whilst receiving rTMS) and post treatment phase (week 3-10 i.e. total of eight weeks post treatment phase). The primary outcome of the study was a mean seizure reduction of at least 50% 8 weeks post-treatment, as compared to the baseline. Baseline seizure frequency was counted as average weekly seizure frequency for the last 4 weeks prior to treatment. Secondary outcome measures included the number of interictal epileptiform discharges (IEDs) within 30-minute recording, Beck Depression Inventory II (BDI II), Symptom Checklist 90 (SCL-90) and Quality of Life in Epilepsy (QOLIE-31), measured at 4 weeks pre and 8 weeks post treatment. Demographic and clinical variables were also recorded.

BDI II is a 21-item self-reported instrument intended to assess the existence and severity of symptoms of depression within a 2-week time period, with good internal consistency, validity and reliability.[6] It is a four-point Likert scale for each item ranging from 0 to 3. A total score of 0-10 is considered as normal, 11-16 as mild depression, 17-20 as borderline clinical depression, 21-30 as moderate depression, 31-40 as severe depression and >40 as extreme depression.

QOLIE-31 is a 31-item self-administered questionnaire clustered in seven multi-items scales in the following domains: Overall quality of life, Emotional well-being, Energy-fatigue, Cognitive functioning, Medication effects, Seizure worry and Social functioning. An overall score is calculated using a weighted average of the multi-item scale scores and the questionnaire also includes a single item that assesses overall health.[7]

SCL-90 is a 90 items self-report questionnaire with five-point Likert scale. It is intended to measure symptom severity in patients with psychiatric symptoms on nine different subscales: Somatisation, Obsessive-compulsive, Interpersonal sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation, Psychoticism.[8] The Global severity index (GSI), measured as the mean value of all the items, is used as the global of index measurement.

Statistical analysis

All data analysis was performed using SPSS software version 22. Due to small sample size, results for seizure frequencies, number of IEDs, BDI II, QOLIE-31 and SCL-90 scores pre and post treatment were compared using non-parametric Wilcoxon signed rank test. Mann-Whitney U Test was used to compare the relationships of continuous variables between responders and non-responders. Correlations between variables were calculated using Spearman's non-parametric correlations for continuous variables and Fisher's exact test for categorical variables

RESULTS

Demographic details and epilepsy profile

A total of 9 patients were recruited in the study. Patients' demographic details, seizure aetiologies

and treatment profiles are summarised in Table 1. Seizure semiology, EEG changes and MRI findings are summarized in Table 2. Four of our patients were male and the mean age was 33.8 years old (SD 11.7). Mean age of seizure onset was 8.2 years old (SD 4.7) and the mean duration of illness was 25.6 years (SD 14.7, range 8-50 years).

Four patients had temporal lobe epilepsy (TLE), two with frontal (FLE), one with parietal (PLE), one with occipital lobe epilepsy (OLE) and one with Lennox-Gastaut Syndrome. Out of the eight patients with focal epilepsy, four patients were found to have focal cortical dysplasia (FCD) and three patients had mesial temporal sclerosis (MTS). One patient (Patient 7) had lesion negative MRI brain.

Table 1: Summary of the demographic details, seizure and treatment profiles for individual patient in the study

	Epilepsy Syndrome	Age (year)	Gender	Age of seizure onset	Aetiology	Duration of illness (years)	Site of lesion	Current AEDs and daily dose	Previous failed AED
1	LGS	31	F	11	Unknown	20	Unknown	CBZ 300mg, ZNS 100mg, CLZ 0.25mg	VPA, PHT, LVT, LTG
2.	OLE	23	M	14	FCD	9	Deep, medial occipital lobe	LTG 200mg, VPA 400mg, TPX 200mg	PHT, LVT, CBZ, ZNS
3	FLE	25	M	10	FCD	15	Deep, frontal and para-sagittal (SMA)	LTG 200mg, VPA 800mg, LVT 1000mg CLZ 0.25mg	GBP, CBZ, TPX
4	TLE	33	M	3	MTS	30	Deep, mesio-temporal	CBZ 1000mg, LVT 3000mg, CLZ 0.25mg	PB, VPA, TPX
5	FLE	26	M	3	FCD	23	Deep, basal frontal	PHT 360mg, VPA 1200mg, ZNS 200mg, CLZ 0.25mg	LTG, CBZ, RTG
6	TLE	24	F	16	MTS	8	Deep, mesio-temporal	LVT 3000mg, TPX 200mg, CLP 0.5mg	VPA, LTG, CBZ
7	TLE	37	F	6	Unknown	31	Unknown	LTG 500mg, PHT 300mg	CBZ, RTG
8	TLE	56	F	6	MTS	50	Deep, mesio-temporal	LVT 3000mg, LTG 200mg, VPA 400mg	CBZ, CLZ
9	PLE	49	F	5	FCD	44	Deep, frontal-parietal operculum	CBZ 800mg, ZNS 100mg LVT 3000mg	LTG, VPA

*LGS = Lennox-Gastaut Syndrome, OLE = occipital lobe epilepsy, FLE = frontal lobe epilepsy, TLE = temporal lobe epilepsy, PLE = parietal lobe epilepsy, FCD = focal cortical dysplasia, MTS = mesio-temporal sclerosis, F = female, M = Male, SMA = supplementary motor area, CBZ = carbamazepine, ZNS = zonisamide, CLZ = clonazepam, LTG = lamotrigine, VPA = sodium valproate, TPX = topiramate, LVT = levetiracetam, PHT = phenytoin, GBP = gabapentin, PB = phenobarbitone, RTG = ratigabine

Table 2: Summary of the seizure semiology, EEG changes 4 weeks pre and 8 weeks post-rTMS, and MRI brain findings of all 9 patients in the study

Patient	Semiology	EEG pre rTMS	EEG post-rTMS	MRI brain
1	Obscuration of vision, generalized tonic, clonic myoclonic, absence and atonic.	Background 6-7Hz. Frequent episodes of generalized spikes and waves, and generalized paroxysmal fast activity. Frequent runs of slow-spike-and-wave activities.	Background 6-7Hz. Frequent runs of slow-spike-and-wave with one tonic seizure associated with generalized slow waves followed by decremental response	Left parietal encephalomalacia from previous left parietal DNET resection in 2009
2	Visual aura of flashing lights, déjà vu, absence, right hemianaesthesia and mild hemiparesis, GTC	Normal background. Frequent bilateral anterior temporal sharp waves (L> R)	Normal Background. Frequent bilateral anterior temporal sharp waves (L>R)	Left medial occipital FCD
3	Nocturnal hypermotor, left version, gelastic, GTC	Background 7Hz, infrequent right frontal sharp waves	Background 7Hz, infrequent right frontal sharp waves	Right fronto-parasagittal (SMA) FCD
4	Early left deviation, right dystonia, late oral automatism, GTC	Normal background. 2 sharp waves over both anterior temporal regions.	Normal background with infrequent left anterior temporal sharp waves	Left MTS
5	Hypermotor seizure, unilateral left tonic-clonic, GTC	Normal background. Frequent sharp waves over left mid and posterior temporal region, bilateral TIRDA	Normal background with frequent bilateral fronto-temporal sharp waves.	Left basal frontal FCD
6	Aura of epigastric rising, blank stare, oral automatism, GTC	Normal background. Frequent bilateral anterior temporal sharp waves.	Normal background. Very frequent bilateral anterior temporal sharp waves.	Right MTS
7	Oral and left upper limbs automatism, GTC	Normal background. Bilateral anterior temporal sharp waves.	Normal background. Bilateral anterior temporal sharp waves (L>R)	Normal
8	Oral automatism, left dystonia, peri-ictal water drinking, GTC	Normal background with frequent right anterior temporal sharp waves	Normal background with no epileptiform discharges seen	Right MTS
9	Left sided limbs sensory aura, left version, left dystonia, nocturnal ypermotor, left asymmetric tonic, GTC	Normal background with intermittent right sided predominant anterior temporal sharp waves.	Normal background with very frequent right sided predominant anterior temporal sharp waves	Right frontal opercular FCD

*GTC – generalized tonic-clonic, TIRDA – temporal intermittent rhythmic delta activity, EEG – electroencephalograph, MRI – magnetic resonance imaging, FCD – focal cortical dysplasia, rTMS – repetitive transcranial magnetic stimulation, L – left, R – right.

Seizure frequency and response to treatment

All of our patients had refractory epilepsy, in which all of them had previously failed at least two to four maximally tolerated doses of AEDs (mean = 3, SD 0.8). On average, our patients had about 9 seizure attacks per week (SD 12.3, range 0.25-34.8) despite being on at least two to four antiepileptic drugs (mean = 3, SD 0.6) prior to enrollment. The average daily seizure frequency in all patients was 1.6 per day (SD 2.2, range 0-6) (Table 3).

The average weekly seizure frequency 4 weeks post rTMS was 10.7 (SD 15.6, range 0.5-39). The frequency slightly improved 4 weeks later to 10 (SD 14.9, range 0.3-37.3). Figure 1 shows the mean weekly seizure frequency for individual patient during pre-treatment, treatment and post treatment phase. Our data showed an increased in the average daily seizure frequency during the treatment phase (mean 1.8 per day, SD 2.4, range 0.1-6.1). However, this increment in the seizure frequency did not reach statistical significance in all patients or in the non-responder group alone, and started to significantly improve during the last 4 weeks of post treatment phase i.e. week 7-10 ($p<0.05$) (Figure 2). This improvement in frequency however did not return to baseline.

Three patients had more than 50% improvement in weekly seizure frequency 8 weeks post-rTMS (Patients 2, 3 and 5) (Table 4). All responders had FCD, in which patient 2 had medial occipital FCD; patient 3 right frontal parasagittal FCD and patient 5 basal frontal FCD. There was a significant correlation between FCD with response to treatment ($p<0.05$). There was an improvement in the count of interictal discharges amongst 2 out of 3 responders. Based on our observation, the responders in this study were younger (mean 24.7 vs. 38.3 years old), had shorter duration of illness (mean 15.7 vs. 30.5 years) and had less frequent weekly seizure frequency prior to treatment (mean 5.5 vs. 10.8 attacks per week), as compared to the non-responders, although this was not statistically significant.

Using non-parametric correlations, we found that certain variables correlated significantly with the average seizure frequency 8 weeks post treatment. These variables include age of seizure onset ($p < 0.01$, R= -0.83), number of IEDs on EEG prior to treatment ($p<0.05$, R= -0.70),

Table 3: Summary of average daily and weekly seizure frequency for individual patient pre- and post-repetitive transcranial magnetic stimulation (rTMS). Pre-treatment phase (week -4 to -1), treatment phase (week 1-2), post-treatment phase (week 3-10)

No	Average Daily Seizure Frequency			Average Weekly Seizure Frequency				
	Pre-Treatment Phase	Treatment Phase		Pre-Treatment Phase	Treatment Phase	Post-Treatment Phase		
	-7 days	7 days*	14 days*	Week -4 to -1	Week 1-2	Week 3-6†	Week 7-10†	Week 3-10
1	0.14	1.00	0.57	0.50	4.00	1.25	1.50	1.38
2	0.14	0.43	0.21	0.75	1.50	0.50	0.25	0.38
3	1.14	0.86	0.93	6.50	6.50	2.25	2.50	2.38
4	4.71	5.00	6.07	24.50	39.50	36.75	33.25	35.00
5	1.29	0.57	0.86	9.25	6.00	8.00	6.25	7.13
6	0.14	0.29	0.50	0.25	3.50	2.75	1.00	1.88
7	0.29	0.00	0.14	1.75	1.00	2.00	1.75	1.88
8	0.29	1.00	1.07	2.75	7.50	3.75	2.50	3.13
9	6.00	3.71	5.93	34.75	40.00	39.00	35.50	37.25

* Average daily seizure frequency during the first seven days and first two weeks of treatment phase
† Breakdown of average weekly seizure frequency during the first month (week 3-6) and second month (week 7-10) of post treatment phase

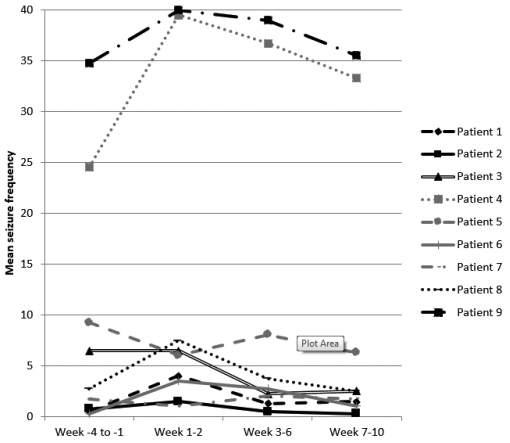

Figure 1. Mean seizure frequency for individual patients during pre-treatment (week -4 to -1), treatment (week 1-2) and post-treatment phase of rTMS. Post-treatment phase is further divided into the first month post rTMS (week 3-6) and the second month post-rTMS treatment (week 7-10).

the average weekly seizure frequency prior to treatment ($p<0.01$, $R= 0.90$) and during treatment ($p<0.01$, $R= 0.85$).

BDI II, QOLIE-31 and SCL-90 Scores

As a whole group, 6 patients had significant improvement in BDI-II scores ($p<0.05$), 2 had improvement in QOLIE-31 and 4 in SCL-90 8-week post treatment, despite not all of them belong to the responder group (Table 4). Greater percentage of seizure change was seen in those with higher BDI score pre-treatment ($p<0.05$, $R=0.78$). Of the responders, Patient 3 had improvement in all scales, Patient 5 in his BDI-II score, and Patient 2 with no improvement in all scales (Figure 3).

DISCUSSION

rTMS can be effective in selected patients with a 33% respondent rate in our cohort, compatible with previous studies.[9,10] In addition, there were significant improvements observed in depression (BDI-II) and psychological function (SCL-90), despite a small sample size, and some improvements were noticed in those without reduction in seizure frequency.

All our responders had FCD. Our result is consistent with a previous meta-analysis that showed >50% seizure reduction in patients with FCD[4] whilst mild and short-lived average seizure reduction were reported in patients with MTS or non-lesional neocortical epilepsy.[11] Epileptogenesis in patients with FCD might be the result of an imbalance between excitatory and inhibitory neurons.[12] As a result, rTMS in FCD and neocortical foci may be particularly effective because of their focus in the cortical convexity, which makes it easily accessible by rTMS. For those with MTS, stimulation was performed at vertex, not directly on the epileptogenic lesion. In addition, the location of the stimulation was not decided based on epilepsy network. With better understanding of epilepsy network in MTS, a study to determine the stimulation location and the strength of stimulation is needed to improve the effectiveness of rTMS in MTS.

Our responders had shorter duration of illness and had less frequent weekly seizure frequency prior to treatment, as compared to the non-responders. This finding indicates that response rate might be affected by the refractoriness of the epilepsy, and thus suggests that rTMS should be considered earlier in the treatment course.

The transient increase of seizure frequency in five patients during rTMS treatment have been reported in other studies in about 1-2% of

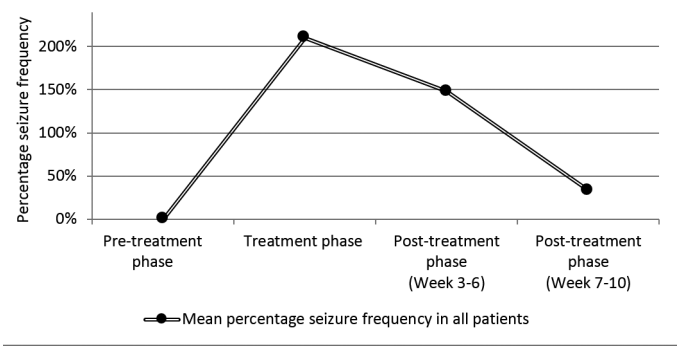

Figure 2. Graph showing mean percentage changed in seizure frequency weeks during pre-treatment, treatment and post-treatment phase.

Table 4: Summary of the mean weekly seizure frequency for each patient, their response to treatment, change in the interictal epileptic discharges (IED) counts post treatment and their total scores for Beck Depression Inventory II (BDI II), Quality of Life in Epilepsy 31 (QOLIE-31) and Symptom Checklist 90 (SCL-90) scales pre- and post-treatment

No	Mean Weekly Seizure Frequency			> 50% response	IED counts	Scores Pre- and Post-Treatment Phase of rTMS					
	Pre-rTMS	Post-rTMS				BDI II		QOLIE-31		SCL-90	
	Week -4 to -1	Week 3-6	Week 3-10			Pre	Post	Pre	Post	Pre	Post
1	0.50	1.25	1.38	No	↑	17	7	65	50	68	54
2	0.75	0.50	0.38	**Yes**	↓	12	20	40	31	151	197
3	6.50	2.25	2.38	**Yes**	↓	7	1	83	93	55	15
4	24.50	36.75	35.00	No	↑	13	1	76	73	41	20
5	9.25	8.00	7.13	**Yes**	↑	9	5	57	53	38	76
6	0.25	2.75	1.88	No	↑	37	32	44	37	166	170
7	1.75	2.00	1.88	No	↑	2	8	64	63	23	29
8	2.75	3.75	3.13	No	↓	18	11	71	50	48	82
9	34.75	39.00	37.25	No	↑	11	13	33	44	131	129

patients and the risk increases to approximately 0.5% per 1000 stimuli.[3] These seizures are thought to arise from excessive activation of pyramidal cell, spread of excitation to neighboring neurons or overwhelming of inhibitory mechanisms.[13] However, due to small percentage of reported cases in the literature and the naturally frequent seizures reported in all recruited subjects with refractory epilepsy, the attributing causality for this increment may prove difficult. It is possible that this transient increase in seizure frequency could be explained by (1) natural cyclical fluctuation of seizure frequency; (2) regression to the mean, particularly when our patients already had severe symptoms prior to enrolment.

More than half of our patients had significant clinical improvement in the depressive scale. Repetitive TMS was proven to be effective in treating treatment-resistant depression, using 10Hz stimulation frequency to the left dorsolateral prefrontal cortex[14], which is expected to increase cortical excitability. In our study, a low-frequency stimulation at 1Hz aiming to reduce cortical excitability might also be effective in reducing the depression score irrespective of seizure control.

The lack of a significant effect of seizure frequency and response to treatment on health-related quality of life (HRQOL) in our study is in agreement with previous other reports.[15,16] Nearly half of our patients showed improvement in SCL-90 with rTMS. Although this improvement did not reach statistical significance and not all of them correlated with treatment response, our study showed that rTMS may have a role in improving psychological function.

This study is limited by its small sample size but it provides a guide in rTMS treatment among those with refractory epilepsy. A bigger sample size, longer duration of follow-up and a case-control design may help to improve our understanding.

In conclusion, rTMS is a potentially promising treatment for focal epilepsy in younger patients with shorter duration of illness, FCD on MRI, and lower seizure frequency. Its antiepileptic efficacy and concurrent impact on psychological function need further exploration.

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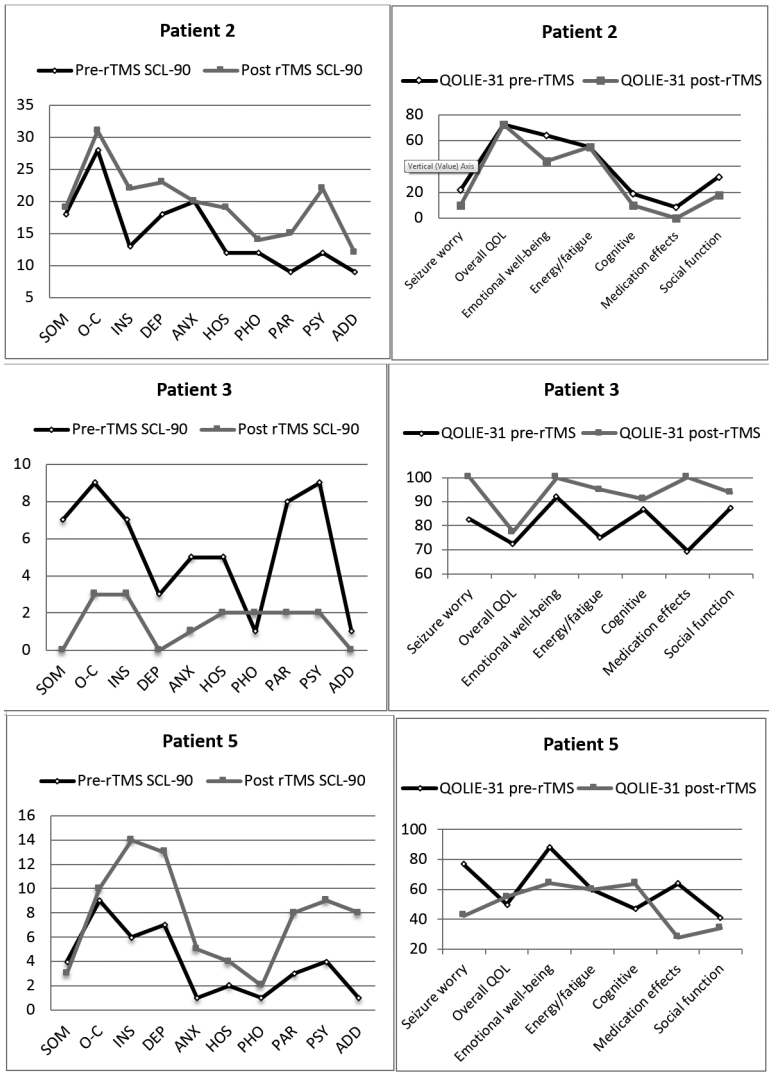

Figure 3. Pre- and post-rTMS breakdown of individual SCL-90 and QOLIE-31 domains for the three patients who responded to treatment. SOM: somatisation, O-C: obsessive compulsive, INS: interpersonal sensitivity, DEP: depression, ANX: anxiety, HOS: hostility, PHO: phobic anxiety, PAR: paranoid ideation, PSY: psychoticism, ADD: additional items (primarily covers symptoms of appetite and sleep disturbances)

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