Journal of Affective Disorders 308 (2022) 322–327

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Quantitative EEG (qEEG) guided transcranial magnetic stimulation (TMS) treatment for depression and anxiety disorders: An open, observational cohort study of 210 patients

C. Robertson [a], A. Mortimer [b,*]

[a] Tranquality Solutions Limited, UK
[b] NAViGO, University of Hull, UK

ARTICLE INFO

Keywords:
TMS
TBS
qEEG
Depression
Real world study
Patients

ABSTRACT

Background: Major depression and anxiety disorders represent a substantial burden of morbidity. Neither antidepressant medication nor psychological interventions are fully effective, the former beset with side effects, interactions and compliance issues, and the latter requiring patient engagement, effort and a degree of psychological mindedness. Both treatments are lengthy. TMS by contrast is virtually free of side effects and compliance issues, relatively brief, and requires no patient effort. Nevertheless, remission rates are only about 1 in 3 with standard left frontal rapid (rTMS) stimulation, and up to 30 treatment sessions may be required. Our aim was to improve the effectiveness of TMS treatment using bespoke as opposed to standard left frontal rTMS, including theta burst stimulation (TBS).

Methods: 210 male and female patients were treated: regions and frequencies of TMS were guided by quantitative EEG analysis (qEEG) to elicit recognisable phenotypes, neuromarkers integral to the genesis of major depression and anxiety disorder, dictating treatment parameters.

Results: 98 patients (47%) achieved at least 50% reduction in Hamilton depression rating scale scores, while a further 60 (29%) patients achieved a 30–50% reduction, over a mean of 7.03 ± 0.3 treatment sessions. Theta burst stimulation (TBS) almost halved treatment time within session compared to rTMS. The effect size (Cohen's d) for both treatments was large (>0.8) with rTMS at 1.43 (1.16–1.70) and TBS at 1.87 (1.48–2.25).

Conclusions: qEEG guided TMS treatment is a safe and effective treatment in depression and anxiety disorders.

1. Introduction

1.1. Depression: a global disease burden

Depression is a common mental disorder. Globally, more than 264 million people of all ages suffer from depression (Anon, 2020). Depression is a leading cause of disability worldwide, and is a major contributor to the overall global burden of disease: the most serious consequence of depression is completed suicide, with at least 800,000 cases per year. It is believed that incidence and prevalence are both increasing (Hidaka, 2011). More recently, the number of adults experiencing some form of depression in Great Britain has doubled during the COVID-19 pandemic, according to figures from the Office of National Statistics (ONS). A nationally representative survey of 3527 adults in Great Britain reported that the proportion of people reporting moderate to severe depressive symptoms increased from 9.7% between July 2019 and March 2020, to 19.2% in June 2020 (The Pharmaceutical Journal, 2020).

It is remarkable that such apparent overall global worsening of the problem of depression (however acknowledging the possibility of better recognition, as opposed to a genuine increase) has taken place alongside a substantial expansion in both pharmacotherapeutic and psychological intervention options over the last three decades. Following the success of SSRIs, numerous other antidepressants with a wide range of mechanisms of action have been introduced. Some of these, such as ketamine and agomelatine, offer completely novel mechanisms. Moreover, antidepressants are now fairly commonly used in combination, or with adjuncts such as mood stabilisers co-prescribed.

Regarding psychological interventions, cognitive behaviour therapy and interpersonal therapy are well established and supported by

* Corresponding author at: 3–7 Brighowgate, Grimsby DN32 0QE, UK.
E-mail addresses: colin.robertson@tranquality.com (C. Robertson), ann.mortimer@nhs.net (A. Mortimer).

https://doi.org/10.1016/j.jad.2022.04.076
Received 17 January 2022; Received in revised form 9 April 2022; Accepted 12 April 2022
Available online 16 April 2022

evidence. Combining psychological and antidepressant treatment is recognised as affording the best outcomes (Pampallona et al., 2004). In the UK, psychological interventions are now readily available from 'Increasing Access to Psychological Therapies' services (IAPT) alongside GP prescription of first-line antidepressant medication.

1.2. Drawbacks of current approaches to treatment: comparison with TMS

Both antidepressant and psychological therapies are associated with a number of important drawbacks. These include inadequate adherence to medication for a variety of reasons, such as patient attitudes, drug side effects and interactions, discontinuation symptoms, and, last but not least, poor efficacy. The drawbacks of psychological interventions are similarly consequential, including but not limited to a need for commitment and co-operation, investment of personal time in attending sessions and completing homework, unimpaired cognition, a degree of psychological mindedness, and a willingness to tolerate initial worsening. Severely depressed patients may prove incapable of engaging with such therapy, and see it as another failure. A disadvantage which both forms of therapy share is a lengthy time course, particularly for effortful psychological interventions, which may prove far from ideal.

In this scenario, what is lacking is a brief, effective therapy, which does not rely upon patient effort, which affords few if any side effects, where there are no compliance issues, and which works. Transcranial magnetic stimulation (TMS) is a potential solution: rapid stimulation of the left frontal lobe is in routine use in the USA, where the FDA approved it in 2008. A seminal meta-analysis in 2013, including data from 29 RCTs totalling 1371 subjects with major depression, reported that following approximately 13 TMS sessions, 29.3% and 18.6% of subjects were classified as responders and remitters respectively, compared with 10.4% and 5% of those receiving sham TMS, across a wide spectrum of clinical scenarios. Baseline depression severity and drop-out rates at study end were comparable between the real TMS and sham groups (Berlim et al., 2014).

2. Methods and materials

2.1. Preliminary remarks

The authors set up a limited NHS TMS service in the early years of this millennium, using standard left frontal stimulation to treat patients with depression and anxiety disorders. Our effectiveness results mirrored those reported above: approximately one in three patients responded satisfactorily. In this context it is worth pointing out that, although NICE approved TMS in 2015, national take-up by the NHS has proved virtually zero, possibly because, apart from the need for new equipment and training, TMS is not viewed as affording much benefit, given the rest of what is available.

Therefore, we sought to improve our response rates by abandoning the 'blanket approach' of rapid left frontal stimulation for all patients, instead identifying biomarkers which could inform 'bespoke' treatment parameters for each individual patient. We developed a system of quantitative EEG analysis (qEEG) which delivers, for each patient, a recognisable EEG phenotype, a biomarker associated with their depression or anxiety. This approach of utilising qEEG to guide TMS treatment did not exist, as far as we were aware, in the clinical literature. With the development of LORETA (Low Resolution Brain Electromagnetic Tomography) which solved the 'inverse problem', by Pascual-Marqui et al. (1994), we were enabled to identify, informed by the patient's EEG phenotype, appropriate frequencies and locations for TMS treatment, which we then utilised to correct the anomalous pattern of electrical activity in the brain, returning the patient's EEG phenotype to within the normal range.

We also wished to shorten the duration of treatment sessions as far as possible. Theta burst stimulation (TBS) a relatively recent development, has been particularly helpful in this regard (Huang et al., 2011).

We report here our open study of qEEG guided 'bespoke' TMS. Ethical approval for the study was granted in in 2012. Our study was funded and facilitated by NAViGO, a community interest company (CIC) NHS mental health service provider, covering North East Lincolnshire, in the U.K.

2.2. Ethics and consent statements

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by NAViGO Health and Social Care CIC, approval number 12/YH/0292, 2012.

Written informed consent was obtained from all patients. Written consent was witnessed and formally recorded. Capacity to consent was, as is legally appropriate, presumed, reinforced by documentation of patient capacity to determine health and welfare decisions routinely recorded in previous clinical correspondence.

2.3. Patients and their clinical evaluation for TMS

Patients were most frequently referred by NAViGO mental health professionals, some by their GPs: a small number referred themselves through the NAViGO website. Information and referral forms clearly stated that patients must have a clinical diagnosis of primary depression or anxiety disorder. Patients with a history of epilepsy, a cardiac pacemaker or orthopaedic metal near the head could not be treated. Patients with comorbid neuropsychiatric disorder, alcohol or substance abuse, or a primary diagnosis of personality disorder, were not eligible for TMS. Antidepressant medication was required to be stable for six weeks prior to TMS treatment.

All patients were screened by AM, who scrutinised their mental health records to check their eligibility in terms of inclusion and exclusion criteria. AM then undertook to create a complete clinical summary of each patient's records, in order to fully understand their treatment history prior to a clinic appointment for baseline evaluation. At this initial appointment any gaps in history were explored, and eligibility confirmed in terms of a clinical diagnosis of primary depression or anxiety disorder. All patients met ICD-10 criteria for depressive or anxiety disorders: F31.3–5, F32, F33, F40 and F41.

The Hamilton depression rating scale was completed: a score of 15 was required for TMS treatment. Patients then gave informed consent, having received an approved information sheet with their appointment letter, and been invited to discuss their questions or concerns at the baseline evaluation.

As this was a naturalistic sample, degrees of dysfunctional personality traits, adverse personal circumstances or both attached to most of the patients: their significance in admitting the patient to the TMS service, or otherwise, proving a matter of clinical judgement. Because of the screening process, very few patients were excluded at baseline evaluation. Routine clinical correspondence to the patient was copied to the referrer and the GP.

Almost all patients were taking antidepressant medication at baseline, and this was not varied during TMS treatment. Psychological interventions, if any, either continued, or were put 'on hold' during TMS, as agreed between patients and their therapists.

Approximately four weeks after TMS was completed, patients were recalled for a follow-up evaluation with AM. CR provided an illustrated treatment report, with details of qEEG phenotype, TMS treatment parameters and changes to the qEEG measurements following treatment. Patients gave their account of their progress, and the Hamilton scale was repeated. AM discussed potential further antidepressant interventions if appropriate, particularly if there remained significant room for improvement. Clinical correspondence to the patient was copied to the

GP, and the relevant mental health professionals if appropriate, in order to implement this advice.

Clinical and demographic variables utilised are listed in Table 1. Onset age was determined from medical records and the patients' accounts. Chronic status was allocated if there had been no discernible return to previous function and wellbeing following the treatment of depression, unless duration since onset was less than two years. Treatment resistance was defined as the failure to respond to two or more courses of antidepressant treatment, psychological interventions, or both.

2.4. EEG recording, QEEG analysis and TMS/TBS treatment

EEGs were recorded by CR using a MITSAR 201 amplifier (Mitsar Co. Ltd., St Petersburg, Russia) a PC controlled, 19 channel EEG system, using WINEEG software. The EEG input signals were linked to referenced ear electrodes and were filtered between 0.5 Hz and 50 Hz and digitised at a sampling rate of 250 Hz. The recording speed was set at 30 mm/s, a gain of 100uV, low cut filter of 0.3 (0.53 Hz), high cut filter of 50 Hz, notch at 45-55 Hz and impedance was below 5KOhms for all electrodes. We used a Waveguard electrocap with 19 tin electrodes with the standard 10–20 International system.

All patients' EEGs were recorded in two conditions, eyes closed and eyes open. The raw EEG data were visually inspected for any artefacts such as paroxysms that could compromise the validity of the recording. The raw EEG data were converted to edf format and then processed by NeuroGuide analysis software (www.anineuroguide.com) to de-artefact the recording for any extraneous features such as eye blinks and muscle artefact. The recording was then analysed using NeuroGuide to produce a frequency graph, power maps, connectivity maps and 3-D whole brain images.

We adopted the visual method to determine resting motor threshold (RMT) at 120% stimulation intensity, in accordance with conventional clinical practice. We used two types of brain stimulation, transcranial magnetic stimulation (rTMS) and theta burst stimulation (TBS). TMS was delivered in the form of repetitive stimulation for the purpose of activation (rTMS) and single pulse stimulation to reduce activation. Theta burst stimulation was similarly delivered using intermittent theta burst stimulation (iTBS) for the purpose of activation, or continuous theta burst stimulation (cTBS) to reduce activation. For rTMS we used trains of 10 Hz frequency with 1 s duration and a 4 s interval, with 50 repeated trains to give a set of 500 pulses. Each set was repeated 12 times to deliver 6000 pulses, comprising one 'session' of treatment, with a run time of approximately 50 min. Sessions took place daily, 5 per week, delivering a total of 30,000 pulses.

When NICE (National Institute for Health and Care Excellence, UK) published their recommendation in December 2015 for the clinical treatment of depression using TMS, this also included TBS. We then adopted both iTBS and cTBS as our preferred choice of treatment. For iTBS this comprised a triplet 50 Hz burst given at 5 Hz for 2 s with a wait time of 8 s to deliver 600 pulses, taking 3 min and 9 s. cTBS delivered 200 bursts uninterrupted for 40 s to give 600 pulses. Thus, TBS provided significant gains in efficiency, with the treatment time per session reduced by almost half in comparison to TMS treatments.

CR aimed to deliver 50,000 pulses to complete treatment, however the number of treatment sessions was determined jointly between CR and the patient: patients who felt they had responded partially and wished to continue after 50,000 pulses had further treatment.

Table 1
Clinical and demographic variables distributed between rTMS and TBS treated patients.

Variable	Treatment: rTMS (n = 134; 63.81%)	Treatment: TBS (n = 76; 36.19%)	Total (n = 210)	Missing values	p-Value
HAM-D before	21.57±0.51; 21 (10–35)	21.39±0.6; 21 (11–41)	21.51 ±0.39; 21 (10–41)	0	0.98
HAM-D after	12.04±0.64; 12 (0−33)	10.5±0.73; 10 (1−30)	11.49 ±0.49; 11 (0–33)	0	0.15
Reduction in HAM-D	9.53±0.55; 9 (−12–29)	10.89±0.61; 10.5 (−2–28)	10.02 ±0.41; 10 (−12–29)	0	0.12
Phenotype: Excess beta	5 (14.7%)	29 (85.3%)	34	0	<0.01
Phenotype: Excess theta	15 (38.5%)	24 (61.5%)	39	0	<0.01
Phenotype: Low alpha	114 (83.2%)	23 (16.8%)	137	0	<0.01
Gender: Female	52 (54.2%)	44 (45.8%)	96	0	0.01
Gender: Male	82 (71.9%)	32 (28.1%)	114	0	0.01
Treatment start age	49.68±1.24; 50 (19–82)	46.86±1.82; 48.5 (18–81)	48.66 ±1.03; 50 (18–82)	0	0.27
Onset age	33.15±1.21; 31 (12–77)	32.68±1.74; 30 (14–65)	32.98 ±0.99; 31 (12–77)	5	0.62
Treatment age-onset age	16.68±1.16; 14 (0–59)	14.26±1.28; 11 (0–50)	15.8 ±0.88; 13 (0–59)	5	0.37
Type: Chronic	52 (66.7%)	26 (33.3%)	78	4	0.65
Type: Episodic	80 (62.5%)	48 (37.5%)	128	4	0.65
Resistance: No	40 (59.7%)	27 (40.3%)	67	4	0.45
Resistance: Yes	92 (66.2%)	47 (33.8%)	139	4	0.45
Number of sessions	6.96±0.32; 5.5 (2–24)	7.18±0.62; 5 (2–29)	7.04±0.3; 5 (2–29)	0	0.42

2.5. Statistical analysis

We utilised 30% and 50% reduction in HAM scores as cut-off points to examine response rates. While a 50% reduction in HAM score is generally considered 'the industry standard' we argued that for patients with a substantial volume of depressive symptoms, even a 30% reduction could prove clinically worthwhile. We then compared effect sizes between rTMS and TBS treatments, and between the three phenotypes. We examined our data for potential confounders: independent variables which may prove predictive of treatment outcome, unintentionally associated with each other, or treatment type.

3. Results

No patient reported any significant adverse event associated with TMS treatment.

We note parenthetically that most patients were both relieved and gratified to be shown their EEG analysis graphics, commenting that these results verified that they had a genuine disorder, rather than weakness of character, or similar.

A total of 298 patients were referred for consideration of TMS. 88 patients did not complete treatment. 32 patients failed screening: 14 with personality disorder, 9 with alcohol abuse, 5 with organic disorder and 4 with a history of epilepsy. A further 31 patients, although accepted for an initial appointment for baseline evaluation, were not seen. There included 17 who defaulted their appointment, 9 who decided against pursuing TMS after referral, 2 who recovered while waiting for their appointment, 2 who deteriorated and had to be admitted for inpatient

treatment, and 1 patient who devolved to an alternative TMS clinic.

At baseline evaluation, 10 patients left the study: 3 had recovered but still attended their appointment, while 7 agreed alternative treatment recommendations made by AM. Of those accepted for treatment at baseline evaluation, 9 did not proceed: 4 patients changed their mind about going ahead, 3 were discovered to have subclinical seizure activity upon recording their first EEG, and 2 patients worsened and were admitted for inpatient treatment. Of the remaining 6 of 88 patients, 3 recovered while waiting for TMS, while a further 2 patients, both referred as inpatients, proved so agitated that it was not possible to apply TMS. One patient defaulted without notice, mid-treatment.

Table 1 is a summary of the distribution of the independent variables for the total cohort of treated patients, and separately for those patients who received rTMS or TBS, together with the *p*-value from a test of association between each independent variable and treatment type. Values for the continuous variables are presented as means ± SE, median and range.

Table 1 demonstrates some potential confounding factors: low alpha phenotype patients were more likely to receive rTMS than TBS, while the other two phenotypes were more likely to receive TBS.

Table 2 shows the before and after HAM-D scores for 98 of 210 patients whose scores were reduced by 50% or less than 50%. Of note is that the 50% responder mean post-treatment score was within the subclinical range.

Table 3 demonstrates that 48% (98 of 210 patients) achieved an improvement in their pre-treatment HAM-D scores of above 50%. A further 60 patients were 30% responders: only 52 patients did not achieve a 30% response.

Table 4 shows the mean reduction in HAM-D scores post treatment: the effect size is large (greater than 0.8) for both treatment types. There is no statistically significant difference between treatment types applying a Mann-Whitney *U* test with a *p*-value of 0.12, although the effect for TBS (1.87) is slightly larger than rTMS of 1.43.

Table 5 shows the mean reduction in HAM-D scores for the separate phenotypes, with large effect sizes for all three types, there is no statistically difference between them.

3.1. Statistical modelling: 30% responders

Table 6 shows the model of best fit for 30% responders. This table provides details of the coefficients, their standard errors, the odds ratio, the 95% c interval for the odds ratio, the test statistic associated with the coefficient and its *p*-value. The odds ratio provides the odds of an event occurring given an independent variable when the values of the remaining variables are fixed. For example, the odds of a patient with episodic depression having a 30% reduction in their Ham-D score post treatment is 2.24 times greater than a patient with chronic depression. The model of best fit contains 4 variables: phenotype, onset age, episodic versus chronic depression, and number of treatment sessions.

Since there are three possible phenotypes, we also provide the pairwise contrasts for each phenotype in Table 7.

Holding all other variables constant:

- The odds of a patient with phenotype Excess Beta and Excess Theta being a 30% responder is 5.8 and 2.9 times (respectively) greater than a patient with phenotype Low Alpha (although we note the uncertainty associated with these estimates as evident in their wide c intervals). There is less evidence of a difference in the odds between Excess Beta and Excess Theta phenotypes.
- For every additional year of onset age, the odds of a patient being a 30% responder are reduced by 3%.
- The odds of a patient whose depression is episodic being a 30% responder is 2.2 greater than a patient whose depression is chronic.
- For every additional treatment, the odds of a patient being a 30% responder are reduced by 4.4%.

Table 2
"Headline" results: Change in HAM-D scores using 50% cut-off.

Number of patients	Before treatment HAM-D score		After treatment HAM-D score		Effect size
	Mean	SD	Mean	SD	
98	20.45	5.32	6.03	3.69	d = 3.151 *r* = 0.844

Table 3
Breakdown of patients by 30% and 50% responders.

	50% responder: yes	50% responder: no	Total
30% responder: yes	98	60	158
30% responder: no	0	52	52
Total	98	112	210

Table 4
Differences in Hamilton scores between rTMS and TBS treatments.

	Mean Ham-D difference	Cohen's d effect size	Effect-size correlation
rTMS	9.53 [8.45, 10.61]	1.43 [1.16, 1.70]	0.58
TBS	10.89 [9.67, 12.12]	1.87 [1.48, 2.25]	0.68

Table 5
Differences in Hamilton scores before and after treatment between phenotypes.

Low alpha	9.90 [8.80, 11.00]	1.44 [1.18, 1.71]	0.58
Excess theta	9.97 [8.35, 11.59]	1.83 [1.30, 2.37]	0.68
Excess beta	10.51 [8.81, 12.21]	2.25 [1.63, 2.87]	0.75

3.2. Statistical modelling: 50% responders

The model of best fit for 50% responders is given in Table 8, for which two variables remain: treatment type and initial Ham-D. The model results highlight that, holding all other variables constant:

- The odds of a patient who has received TBS treatment being a 50% responder is 1.8 times greater than a patient who has received rTMS.
- For every additional Ham-D score point pre-treatment, the odds of a patient being a 50% responder are reduced by 6.1%.

3.3. Exploration of interactions

We carried out a simple exploration of two interactions, focusing on 30% and 50% responders, of clinical interest: between phenotype and treatment type, and between number of treatments and treatment type.

Table 9 highlights that there is a reasonably equal split of patients with each phenotype who have been treated with TBS, but most patients treated with rTMS had Low Alpha phenotype (85.1%).

Comparing the 30% response rates across phenotype and treatment (Table 10) the response rates do not differ greatly, suggesting that an interaction between the two may not exist for 30% responders.

The 50% response rates (Table 11) do suggest a potential difference, patients with Excess Beta and Excess Theta phenotypes treated with TBS had a higher proportion of 50% responders than those with the same phenotypes treated with rTMS, for which response rates did not differ between phenotypes. There were insufficient data to explore this potential interaction, however a re-run of the model with Low Alpha phenotype found no evidence of a treatment effect. This suggests that the effect suggested in Table 11, that TBS may deliver better efficacy than rTMS, is likely to be driven by those patients with Excess Theta and Excess Beta phenotypes, for which we have less data.

Table 6
The final model of best fit for 30% responders.

	Coefficient	Standard error	Odds ratio	OR 95% CI	Test statistic	p-Value	Significance
(Intercept)	3.614	0.926	37.098	(7.261, 305.775)	3.904	0	***
Phenotype: Excess theta	−0.688	0.888	0.503	(0.067, 2.591)	−0.774	0.439	
Phenotype: Low alpha	−1.759	0.769	0.172	(0.027, 0.631)	−2.287	0.022	*
Onset age	−0.024	0.013	0.976	(0.952, 1)	−1.946	0.052	.
Type: Episodic	0.807	0.353	2.241	(1.123, 4.513)	2.284	0.022	*
Number of treatments	−0.045	0.021	0.956	(0.917, 0.994)	−2.193	0.028	*

Table 7
Model contrasts for all levels of phenotypes.

	Coefficient	Standard error	Odds ratio	OR 95% CI	Test statistic	p-Value	Significance
Excess beta – excess theta	0.688	0.888	1.989	(0.345, 11.468)	0.774	0.439	
Excess beta – low alpha	1.759	0.769	5.805	(1.274, 26.449)	2.287	0.022	*
Excess theta – low alpha	1.071	0.524	2.918	(1.039, 8.197)	2.040	0.042	*

Table 8
The final model of best fit for 50% responders.

	Coefficient	Standard error	Odds ratio	OR 95% CI	Test Statistic	p-Value	Significance
(Intercept)	1.023	0.588	2.782	(0.892, 9.004)	1.742	0.082	
Treatment: TBS	0.6	0.298	1.821	(1.019, 3.286)	2.011	0.044	*
Initial Ham-D	−0.063	0.026	0.939	(0.89, 0.988)	−2.385	0.017	*

Table 9
Breakdown of phenotype by treatment type.

	Excess beta	Excess theta	Low alpha	Total
rTMS	5 (3.7%)	15 (11.2%)	114 (85.1%)	134
TBS	29 (38.2%)	24 (31.6%)	23 (30.2%)	76

Table 10
Breakdown of phenotype by treatment type and 30% responder status.

Treatment type and responder status	Excess beta	Excess theta	Low alpha
rTMS			
30% responder: No	0 (0%)	3 (20%)	36 (32%)
30% responder: Yes	5 (100%)	12 (80%)	78 (68%)
TBS			
30% responder: No	3 (12%)	3 (13%)	7 (30%)
30% responder: Yes	26 (88%)	21 (88%)	16 (70%)

Table 11
Breakdown of phenotype by treatment type and 50% responder status.

Treatment type and responder status	Excess beta	Excess theta	Low alpha
rTMS			
50% responder: No	4 (80%)	11 (73%)	64 (56%)
50% responder: Yes	1 (20%)	4 (27%)	50 (44%)
TBS			
50% responder: No	12 (41%)	9 (38%)	12 (52%)
50% responder: Yes	17 (59%)	15 (63%)	11 (48%)

4. Discussion

qEEG-guided TMS treatment demonstrated >50% improvement in symptoms for 98, almost half, the patients (47%). Their reduction from a HAM-D score mean of 20.45, which may be classified as "severe depression", a score between 19 and 22, to a mean of 6.03, equating to the higher end of the "normal" non-case range, is impressive. Effect sizes are mostly large and significant, providing strong support for qEEG guided TMS as a treatment for depression. Only one quarter of patients failed to reduce their HAM-D scores by 30% or more: even those who did not reduce their HAM-D scores by 50% achieved a mean fall in HAM-D of 6 points.

Rating score decrements of approaching 50% have been reported, in up to half of patients treated with standard left frontal, non qEEG guided TMS (Perera et al., 2016) but this required at least 30 sessions of treatment. Our guided approach, especially with TBS, has brought this down to a mean of 7. These developments render TMS treatment a far more rapid and practicable option than previously, while maintaining its known effectiveness, alongside its lack of side effects, patient effort and adherence issues (Blumberger et al., 2018; Chen et al., 2019; Giam et al., 2021).

We have tried to go beyond the matter of qEEG enhancement of our TMS treatment by utilising TBS, which delivers equivalent stimulation in just over half the time taken by rTMS, alongside examining factors operating upon the outcomes. We found that both rTMS and TBS resulted in a reduction in Ham-D score post-treatment, with large effect sizes (Cohen's d effect sizes 1.43 and 1.87 respectively). While there is no evidence of a difference in mean reduction of Ham-D scores post-treatment between rTMS and TBS, we found that a higher percentage of patients who received TBS were 50% responders compared to rTMS, 1.8 times greater (95% CI [1.0, 3.3]). This better effectiveness appeared to arise from patients with the less common Excess Theta and Excess Beta phenotypes, which deserves further exploration.

Clinical characteristics played out, for the most part, as expected: chronic versus episodic course, older age at treatment, treatment resistance and greater initial HAM-D scores all appeared to confer a degree of limitation to improvement, with a 'law of diminishing returns' applying to increasing numbers of treatment sessions. Antidepressant drug therapy is known to be similar in this regard, which argues, obviously, for earlier and more effective treatment whenever possible. We would consider that TMS may well have a part to play here.

The data has been collected as part of an open, uncontrolled naturalistic study, therefore we cannot make any conclusions about how rTMS and TBS would compare with alternative treatments, used alone. However, we see this as a strength, not a weakness, as our sample may be capable of generalisation to most NHS community mental health practices in relatively deprived urban areas. We would commend the advantages of qEEG guided TMS treatment to health commissioners, as a valuable addition to the therapeutic armamentarium.

Author statement

Prof A Mortimer and Dr. C Robertson.

Funding statement

This research received no specific grant from any funding agency, commercial or not-for profit sector.

Conflict of interest

Prof Mortimer and Dr. Robertson have no conflicts nor interest nor any declaration of interests to disclose regarding this submission. Please see our manuscript and our author statement.

Acknowledgements

The authors would like to thank the patients who made this work possible, and the NAViGO Board who facilitated it.

Author contribution

AM was personally responsible for patient screening, evaluation and post-treatment follow-up.

CR carried out all EEG procedures, qEEG analysis and TMS treatments.

CR and AM were responsible for statistical analysis.

Data availability

The data that support the findings of this study are available from CR upon reasonable request.

References

Anon, 2020. https://www.who.int/news-room/fact-sheets/detail/depression, 30TH January.

Berlim, M.T., van den Eynde, F., Tovar-Perdomo, S., Daskalakis, Z.J., 2014. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol. Med. 44 (2), 225–239.

Blumberger, D.M., Vila-Rodriguez, F., Thorpe, K.E., Yoshihiro, N., Giacobbe, P., Knyahnytska, Y., Kennedy, S.H., Lam, R.W., Daskalakis, Z., Downer, J., 2018. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet 391 (10131), 1683–1692.

Chen, L., Chung, S.W., Hoy, K.E., Fitzgerald, P.B., 2019. Is theta burst ready as a clinical treatment for depression? Expert Rev. Neurotherapeutics. https://doi.org/10.1080/14737175.2019.1641084.

Giam, A., Chen, L., Hahn, L., Gill, S., Clarke, P., Ng, F., Galletly, C., Fitzgerald, P., 2021. Comparing theta burst stimulation with standard left high frequency transcranial magnetic stimulation in the treatment of depression in a randomized controlled study. A preliminary comparison study. J. Affect. Disord. Rep. 5, 100162.

Hidaka, B.H., 2011. Depression as a disease of modernity: explanations for increasing prevalence. J. Affect. Disord. 140 (3), 205–214.

Huang, Y.-Z., Rothwell, J.C., Chen, R.S., Lu, C.S., Chuang, W.L., 2011. The theoretical model of theta burst form of repetitive transcranial magnetic stimulation. Clin Neurophysiology 122 (5), 1011–1018.

Pampallona, S., Bollini, P., Tibaldi, P., Kupelnick, B., Munizza, C., et al., 2004. Combined pharmacotherapy and psychological treatment for depression: a systematic review. Arch. Gen. Psychiatry 61 (7), 714–719.

Pascual-Marqui, R.D., Michel, C.M., Lehmann, D., 1994. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int. J. Psychophysiol. 18 (1994), 49–65.

Perera, T., George, M.S., Grammar, G., Janicak, P.G., Pascual-Leone, A., Wiercki, T.S., 2016. The clinical TMS Society consensus review and treatment recommendations for TMS therapy for major depressive disorder. Brain Stimul. 9 (3), 336–346.

The Pharmaceutical Journal, 2020. PJ August. https://doi.org/10.1211/PJ.2020.20208279.