# QEEG phenotypes, depression and TMS

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**In 2017, depression became recognised as the leading cause of ill health and disability worldwide.[1] In England, 1 in 6 people experience mental health problems every week,[2] 75%[3] of whom may not be able to access the treatment they need. There is a growing interest in electroencephalogram (EEG) analysis to identify anomalous patterns of electrical activity in the brains of depressed patients. These patterns are known as EEG phenotypes.**

Recommended treatment for depression, according to NHS Choices, includes a range of interventions, from 'watchful waiting' through self-help and exercise, to antidepressant medication and more formal psychological interventions. Nevertheless, according to both DSM-5 and ICD-10 diagnostic systems, there are several disorders presenting with depression, whose associations with optimal treatment remain unclear. For instance, the DSM-5 includes, as well as major depressive disorder with its numerous 'specifiers' (code 296), persistent depressive disorder (300.4), adjustment disorder with depression (309.0) and a number of 'other' and 'unspecified' depressive disorders, depression secondary to or comorbid with physical illness, substance use, medication, *etc.* Similarly, ICD-10 includes as well as various depressive episodes (F33), bipolar depression (F31.3-5), mixed anxiety and depression (F41.2) alongside other, unspecified, and secondary or comorbid depressive disorders. Given a lack of access to treatment,[3] low success rates and uncertain outcomes,[4] such as medication side-effects, the need for a more personalised method of diagnosing and treating depression more effectively has never been greater. EEG phenotypes offer clinical associations, particularly regarding treatment with medication. More recently, qEEG phenotypes have been utilised to direct the parameters of both neurofeedback therapy and transcranial magnetic stimulation treatment. These 'bespoke' approaches attuned to each individual patient may prove more

Table 1. An overview of candidate qEEG phenotypes[7]

| Candidate phenotype | EEG findings | Associated neurofeedback approach |
|---|---|---|
| Low-voltage fast | Low-voltage EEG overall | Reward alpha activity posteriorly |
| Epileptiform | Transient spike/wave, sharp waves, paroxysmal EEG | Inhibit low and high frequencies; sensorimotor rhythm training; also consider slow cortical potential control |
| Diffuse slow activity (with or without lower alpha) | Increased delta and theta (1–7Hz) with or without slower posterior alpha | Inhibit midline fronto-central activity slower than 10Hz, add reward for anterior beta for increased stimulating effect |
| Focal abnormalities (not epileptiform) | Focal slow activity or focal lack of activity | Inhibit slower activity and reward higher frequencies (consider medical referral) |
| Mixed fast and slow | Increased slower activity, lack of organized alpha, increased beta | Inhibit slow frequencies, reward alpha and SMR, inhibit faster beta |
| Frontal lobe hypoperfusion disturbances | Frontally dominant excess theta or alpha frequency activity | Inhibit midline fronto-central activity below 10Hz, reward anterior beta for increased effect |
| Frontal asymmetries | Frontal asymmetry primarily measured at F3, F4 | Adjust frontal symmetry with alpha, theta, and beta |
| Excess temporal lobe alpha | Increased alpha activity generated in temporal lobe | Inhibit alpha over affected temporal region(s),and inhibit frontal slow activity |
| Faster alpha variants, not low voltage | Alpha peak frequency greater than 12 Hz over posterior and parietal cortex | Reward 8-10 Hz alpha at Pz, shift alpha frequency slower with alpha/theta protocol |
| Spindling excessive beta | Rhythmic beta with a spindle morphology, often with an anterior prominence | Inhibit beta's spindle frequencies, wide band inhibit; alpha-theta training may help |
| Persistent eyes-open alpha | Alpha doesn't attenuate by at least 50% with eyes open; it is generally slower alpha | Reward beta frequencies, inhibit alpha; reward higher frequency alpha |

effective than 'blanket' approaches, such as left frontal rapid TMS for all patients with depression.

## EEG phenotypes and their associations

Raw EEG waveforms can be digitalised by computer, producing a map based on these measurements, alongside quantitative comparison with normative samples, resulting in a quantitative EEG (qEEG) for interpretation by a clinician. EEG recording is non-invasive and safe.[5] Recognisable patterns of EEG appearances in patients with psychological disorders are classified as specific qEEG phenotypes. These anomalous phenotypes mediate between an indvidual's genetics and neurophysiology, and their cognition, emotion and behaviour. An advantage of the phenotypic approach is that it transcends categorical diagnoses based on symptom criteria: beyond symptoms, it provides a reliable measure of brain functioning, information potentially valuable in treatment planning.[6] qEEG phenotypes do not require a diagnosis to suggest an effective treatment: it has become clear that patients, despite similar symptoms, may manifest different phenotypes underpinning those symptoms, which in turn require a variety of treatment approaches. A particular phenotype may be present in several DSM categories. One example is an excess frontal theta phenotype, seen in, but not limited to, ADHD patients: excess frontal theta occurs in other disorders, notably major depression.[7] This commonality may indicate that such depressed patients may require an antidepressant with stimulant-like properties, such as reboxetine, which is closely related to atomoxetine.

Currently, 11 qEEG phenotypes have been identified (see Table 1); each indicates a specific neurofeedback intervention, where patients learn to modify their own EEG for therapeutic purposes.

Furthermore, qEEG phenotypes have been utilised to predict treatment outcome, and guide treatment planning. Results from a retrospective qEEG study of patients with DSM categorised attentional and mood disorders suggested that adopting a phenotypic perspective may enhance efficacy.[8] Following pre-treatment EEG and qEEG analysis, similar EEG pattern subgroups were identified: relative alpha frequency excess, relative theta frequency excess, and/or inter-hemispheric hypercoherence. Ignoring the DSM diagnosis, certain classes of drugs elicited similar responses amongst patients with EEG features in common and therefore in the same subgroup. For example, the frontal alpha excess subgroup was 87% responsive to antidepressants, whilst the frontal theta excess subgroup was 100% responsive to stimulants.[8]

Confirmation was achieved by Wright and Gunkelman[9] who demonstrated that an improved outcome was seen using qEEG to guide neurofeedback. Following the retrospective study, Suffin *et al.*[10] conducted a randomised controlled trial involving patients with chronic treatment-resistant depression. Half were given medication based on standard practice, the other half prescribed for based on the results of qEEG analysis. Clinicians were blind to treatment. Significant improvements were seen amongst the group treated according to qEEG, whereas the group treated according to standard practice saw little to no improvement.

## TMS treatment in depression

Since TMS was proposed as an important tool for therapy in psychiatric disorders, many studies have taken place. A number of reviews of the treatment applications of TMS, most notably those by George and Belmaker, 2006[11] and Wassermann *et al.* 2008,[12] are now available.

TMS has mostly focused on the treatment of depression, by applying rapid rTMS over the left prefrontal cortex. A recent review concluded that 'the antidepressive properties of rTMS now appear obvious'.[13] A 2002 study[14] showed that rTMS to the left frontal cortex led to 50% of patients with major depression having a sustained antidepressant response at two months follow up. A further study[15] reported a 22% reduction in symptoms, compared with a 9% reduction in a sham TMS treatment group. However, a 50% reduction in symptoms is by convention required to classify patients as treatment responsive in depression interventions: across studies, the traditional left frontal TMS response rate for depression is about 1 in 3 (Mortimer A, personal communication 2018). Even so, NICE guidelines[16] approve the use of TMS, and describe the efficacy and safety outcomes that are available from published literature. There are, however, unanswered questions regarding how TMS compares with other treatments across the spectrum of presentations of depression, because TMS has been largely considered for patients resistant to first-line therapies. TMS does, however, afford some distinct advantages compared with the alternatives. It is a good choice for patients unable to tolerate the side-effects

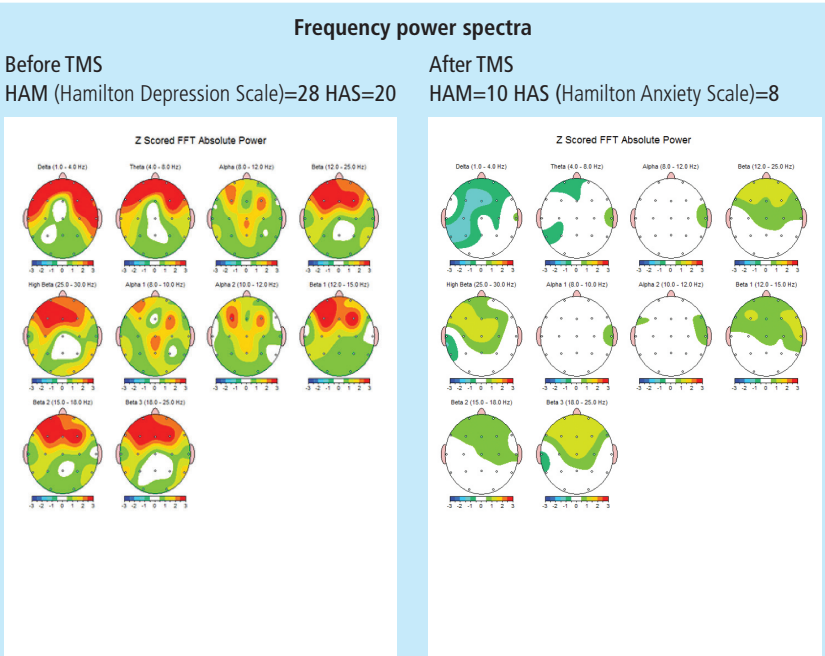
and interactions associated with many drugs used to treat depression: TMS works without side-effects, being non-invasive and non-systemic. Adherence to treatment is not in question: the treatment is observed by those delivering it. Furthermore, no effort on the part of the patient, as opposed to their contribution to psychological interventions, is required. Indeed, a recent study appraised the cost effectiveness of TMS as opposed to antidepressant medication over a lifetime. It was concluded that the probability of rTMS being cost-effective vs medication exceeded 70%.[17]

## Combining TMS with qEEG: a more tailored treatment?

To improve efficacy and therefore the clinical usefulness of TMS, qEEG guidance may afford potential. Two approaches are currently in development. The first, magno-EEG resonant therapy (MERT) uses the EEG to identify the magnetic resonance stimulus intensity, frequency, location and duration required to normalise anomalous qEEG activity, particularly the dominant alpha frequency, which is still considered a 'hallmark of depression'.[18] Here, instead of using the generic left frontal rapid TMS protocol, a tailored treatment is provided on the basis of the qEEG.

The second approach has been developed by NAViGO, a community interest company (CIC) commissioned by the NHS to provide mental health and social care in North East Lincolnshire. NAViGO is currently the only treatment facility worldwide that utilises qEEG to indicate a 'bespoke' TMS treatment for each patient.[19] Through a series of brain imaging and analysis techniques, anomalous qEEG phenotypes are identified. TMS treatment parameters involving application to specific brain regions, at stipulated frequencies, are then derived. These predictions appear to have met with some success: a response rate of 60%,[20] approximately 2 in 3 (twice that with traditional left frontal TMS) is claimed. This 'targeted treatment' also requires fewer applications – approximately 10, compared with the 20–30 treatments required with the left frontal approach. No clinical publications about this ongoing work are currently available, for commercial reasons: the information is derived from NAViGO's website. Figure 1 shows two maps for the frequency power spectra before and after treatment with TMS on a patient who suffered with depression and anxiety.

Figure 1. Maps for the frequency power spectra before and after treatment with TMS on a patient who suffered with depression and anxiety (Robertson C, personal communication)




The maps before treatment indicates significant over activation for alpha and beta frequencies, shown in red on the first row. The rating scale for depression (HAM) indicates severe depression and the anxiety scale (HAS) indicates moderate severity. The maps after treatment show that alpha and beta frequencies are no longer significantly elevated, appearing in white on the first row. The HAM score indicates mild depression and the anxiety scale is it within the normal range.

Recording the EEG concurrently to TMS is another potential option: the literature[21–2] provides a description of the challenges arising from TMS-induced electromagnetic and physiologic artefacts. By applying modifying strategies, such as using TMS-compatible EEG systems, filtering any remaining artefacts and conducting controlled experiments, interpretable data can be obtained.

## Discussion

Despite the reliable nature of anomalous neurophysiology captured by qEEG phenotype

analysis, direct correspondence between phenotypes and diagnosis remains lacking. It is widely acknowledged that although subjective aspects of mental function may be associated with objectively derived neuromarkers, these relationships are not simple.[23] Although qEEG analysis shows promise in treatment planning in depression[24] the identification of a qEEG phenotype is no substitute for clinical evaluation.[25] Clinical judgement, carefully utilising diagnostic criteria to formulate a patient's behavioural history and clinical presentation, is essential, prior to the application of qEEG phenotypes to guide treatment approaches. Nonetheless, the work of Suffin and Emory,[8] suggests that using qEEG phenotypes, as opposed to clinically-based stepwise trials of antidepressant medication, has the potential to improve outcomes in the treatment of depression.

NAViGO claims that by applying a new method of qEEG analysis to guide bespoke 'targeted TMS' better outcomes can be achieved and maintained, rapidly and with relatively little effort on the part of the patient.[19,20] These claims are based on an open treatment series, and thus await the establishment of a more rigorous evidence derived from trials that minimise bias and placebo effects. There are obvious reservations attaching to a lack of peer reviewed reporting of NAViGO's methodology, albeit for commercial reasons. In general, however, despite difficulties in researching TMS treatment for depression, such as blinding and sham TMS placebo control, there are many large published studies confirming consistent positive outcomes. Going forward, TMS and qEEG is a partnership poised to provide us with more detailed information on the workings of the brain, potentially allowing for personalised, more effective treatment, not only of depression and anxiety, but possibly of other disorders as well.

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## Declaration of interests

No conflicts of interest were declared.

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