Appraisal of Sessional EEG Features as a Correlate of Clinical Changes in an rTMS Treatment of Depression

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Key Words
Alpha Activity
Asymmetry Index
Clinical Prediction
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Major Depressive Disorder
Transcranail Magnetic Stimulation

ABSTRACT

Previous findings on electrophysiological features related to depression predict that these correlate with clinical assessment, and potentially act as proxy measures of state changes. We investigated selected electrophysiological features to evaluate their utility as proxies for clinical ratings and in prediction of treatment outcome.

Using typical EEG data from an repetitive transcranial magnetic stimulation (rTMS) treatment regime, we analyzed individual alpha power and frequency, and asymmetry index from 39 patients with treatment resistant depression. The prognostic utility of these features was assessed in terms of group identification, correlation with clinical rating, or association with the time course of treatment.

There was no significant group difference in asymmetry between depression patients and normal and clinical controls. Background alpha was significantly less in depression patients than controls, with the schizophrenia group midway between. There was no significant group change in asymmetry index or background alpha activity with treatment. There was a weak effect of rTMS over each session on alpha power and on asymmetry, but in the opposite direction to predictions. There was weak evidence of predicted correlation between asymmetry index change and clinical rating change, as well as in final scores that was opposite to predictions. Finally there was no strong evidence that either feature fitted a linear or more complex model of daily treatment.

In conclusion, the findings are not sufficient, under our current clinical treatment regime, to support the use of background alpha activity or frontal asymmetry as proxies for clinical assessment. Several findings, however, provide support for further research in this direction.

INTRODUCTION

EEG features, in various forms, have long been associated with depression,[1] and have obvious relevance and potential in predicting treatment outcome.[2]

EEG and Depression

Standard QEEG analysis in depression has shown a decrease in slow (delta-theta bands) activity,[3,4] although not with magnetoencephalography,[5] and increases in the beta range.[6,7] Alpha activity, the most popular spectrum investigated, is less clear. A review of the alpha findings[8] found an increase in absolute power in clinical depression, consistent with a hypoactivation hypothesis, but also addressed the difficulties in varying approaches to this hypothesis. Roemer et al.[9] and Debener et al.[10] show a group based increase in absolute spectral power in the alpha band with depression, as well as asymmetry differences, but not all studies were consistent.[6] Trait based differences have thus been demonstrated with various techniques at several frequencies and regions.

More commonly than absolute power group differences, however, brain asymmetry (typically indexed by alpha band power) has been considered as a trait marker for the vulnerability to depression, with left anterior hypoactivation (higher alpha power) hypothesized to reflect cerebral hypoactivity.[11,12] This electrophysiological approach is thus consistent with associated hypoactivation evidence from stroke,[13,14] metabolic[15-18] and activity imaging studies.[19-21] In a nonclinical population, Schaffer et al.[22] supported the hypothesis of right hemisphere hyperactivation with high scoring participants (depressed) showing greater relative right frontal activation compared with low scoring (nondepressed) subjects. Similar studies have identified hypoactivation in clinical populations,[17,23] and in a similar clinical population that had been free of depressive symptoms for 1 year,[24] both compared with normal controls. Negative findings were reported by Reid et al.[25] (although that interpretation was disputed by the original authors[26]), but also by Bruder et al.[27] and Kentgen et al.[28] In sum, this research strongly indicates that electrophysiological asymmetry reflects some emotional state that may be associated with depression.

EEG changes correlated with state changes

In studying frontal EEG asymmetry in terms of emotional stimuli[26] the assumption is made that the feature is at least partially state related.[29] That assumption also applies to our study of asymmetry (and power) in a treatment setting. Evidence is cited primarily from emotional state based stimuli,[30-33] but also from biofeedback studies[34] and sleep[35] and attentional states,[36] but these are mainly from nonclinical populations. Similar studies have been conducted in depression prone individuals,[37] and the state based assumption has been imputed to the illness,[38] but direct evidence is still equivocal. No evidence was found of state based improvement in the QEEGs of depressed patients after clinical improvement resulting from 6 weeks of antidepressant treatment,[39] although only absolute amplitudes were analyzed. More recently, medication response has been predicted using asymmetry analysis,[40] although no absolute amplitude differences were evident. No asymmetry link was shown following light-induced remission[41] in a seasonal affective disorder (SAD) population, although in another EEG index, coherence was linked. A later study in

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the same form,[42] however, did find remitted SAD subjects showed normalization of inter-hemispheric asymmetry in lateral frontal areas. Finally, the results of task performance in a clinical group (depressed) suggest that trait affect actually combines with and moderates the effects of state affect on brain activation.[43]

Comparing clinical state, Allen et al.[44] found "no robust relationship" between asymmetry and depressive severity, although the time frame, treatment, and ratings were different from our study, and the results were somewhat equivocal. In a general analysis of the effects of rTMS on EEG, Griskova et al.[45] found 10Hz rTMS of the LDPFC lead to an increase in delta power, but the effects on the alpha band were highly variable. The same group had previously found no frontal asymmetry in alpha power of depressive patients at baseline.[46] In the studies most similar to ours, Loo et al[47] found no EEG changes over a 2 week period although only qualitative assessment was reported, while Hoppner[48] found similar results over a 4 week period although asymmetry was not examined. These studies, therefore, support the contention that electrophysiological features reflecting emotional states may be expected to vary with those states. Similar group analyses before and after rTMS treatment are presented in our study.

If a feature is state related, however, then a series of measurements (either as individuals or with time) also allows for correlational analysis. Depression scale scores have been negatively correlated with frontal EEG alpha asymmetry scores,[49] and incidental negative correlations were reported with emotional states,[22,50,51] although not under rTMS treatment. A significant positive correlation between a relatively increased right frontal brain activity and depression was found,[52] with repeated measures over a 6 week period. This form of analysis, over a 4 week period of treatment, is also reported in the present study.

The time course for medication response and also spontaneous remission has been modelled as a sigmoidal function of time for clinical ratings.[53] In a meta analysis (older patients), Whyte et al.[54] report a similar plot for combined rating scales up to 13 weeks. The same form of relationship is shown, although the time of response onset appears to vary, and the authors propose implications for predicting relapse rates. While several potential risk factors affecting the time course were discussed, analogous to electrophysiological features, we are unaware of any specific modelling of such factors as proxy measures. Nor are we aware of such modelling in rTMS treatment, and report such analysis in the present study.

Intro summary

There is thus strong evidence that EEG asymmetry and power features may be linked to depression, that clinical state may be similarly evidenced, and there are preliminary data that a similar effect can be detected in rTMS based state changes. There is also a strong rationale for investigating such a physiological index of clinical effect for its utility in assessing treatment outcome. While there have been previous findings in this respect, the results are equivocal, do not derive from rTMS treatment, or do not address the compatibility with a routine EEG monitoring paradigm. In this study we investigate selected electrophysiological features, obtained from routine EEG monitoring during an rTMS treatment, to evaluate their utility as a proxy for clinical assessment.

We briefly replicate trait based investigations of EEG features of a treatment resistant depression population, in comparison with normal and schizophrenia control groups. The study focus, however, is on state-based activity in relation to depression rating scores throughout a course of rTMS treatment. Proposed indices of hypoactivity may reflect activity changes, which associate with clinical response. We, therefore, analyse correlation between electrophysiological features and clinical ratings, as well as the variation of such features with a course of rTMS treatment.

Specifically we test the hypothesis that EEG features of alpha power and asymmetry have prognostic value for the response to rTMS treatment. Prognostic value being in the form of group identification, of correlation with clinical rating, or of association with the time course of treatment.

METHODS AND MATERIALS

Participants

Participants comprised 39 patients with a DSM-IV diagnosis of major depression, with clinician's report of treatment resistance, who had taken part in a 4 week trial of rTMS adjunctive to their medication regime. While not an exclusion criterion, no patients were receiving lithium, during the treatment period. The study was approved by the Human Research Ethics Committee of the North Metropolitan Area Health Service-Mental Health, and written informed consent was obtained from all patients. The clinical trial was centrally registered at www.actr.org.au (ACTRN012605000145606).

A baseline clinical assessment was conducted in the week prior to commencement by the project psychiatrist (JL), using the 21 Item Hamilton Depression Rating Scale (HamD, 0,2,4 weeks) and Beck's Depression Inventory (BDI, 0,4 weeks). Comparison baseline data for normal controls[15] and a psychiatric control group (schizophrenia,[16]), who received no subsequent rTMS treatment, were selected from an archival database of the Western Australian Family Study of Schizophrenia. Although control participants were not recruited to match the patients in gender, age, education and handedness, sample characteristics were similar.[55]

EEG

Both EEG recording and analysis of power and asymmetry have been reviewed in detail elsewhere,[26,56,57] and our treatment follows these as much as permitted by our rTMS treatment protocol.

EEG data were collected from 9 scalp positions (F3/4, F7/8, T3/4, Fz, FCz, Pz) for 2 minute periods before and immediately after each treatment with eyes closed. A Neuroscan system with signal gain of 75K (150x at the headbox) was used, with a vertex reference (Cz), hardware band-pass (0.1-30 Hz) and 200Hz sampling. Each record was visually screened to remove eye movement or muscle artifact as well as other recording artifacts. This paradigm, together with the question of segment length (infra), represent a compromise between the ideal methodology[57] and the clinical requirements of speed and patient comfort. An FFT was applied (4 second, Hamming window, 10% taper), and power averaged over the alpha band (8-13 Hz), then log transformed (asymmetry) to normalize data.[58] Individual alpha frequency[59] (iafreq) and power (iafamp) were from Pz, while asymmetry (assind) was computed by subtraction (ln[F4]-ln[F3]). While spectral estimates can be reliably obtained from 20-30 second segments[60], longer segments are preferred.[61] In an effort to increase reliability,[51] an additional analysis was also conducted on alpha power averaged over four consecutive recordings (assind4).

rTMS

Repetitive TMS was administered using a Magstim Super Rapid magnetic stimulator (Magstim, Sheffield, England) and handheld 70-mm figure-8 coil. Prior to the commencement of the first rTMS treatment session, single-pulse TMS was used to measure the resting motor threshold (RMT) for the abductor pollicis brevis muscle based on visualization of movement.[62] However, the initial value could be lowered to 90% of RMT to alleviate discomfort (as recorded in four

Table 1

Group comparison contrasting depression features at baseline with controls, and with a schizophrenia group; comparing features before and after each treatment session; comparing features before and after the 4 week course of treatment, and comparing features based on whether each participant had responded to treatment. The features examined were: asymmetry index based on a single session (assind), asymmetry index averaged over first or last four sessions (assind4), individual alpha power (iafamp) and frequency (iaffreq). Two df values in each comparison relate to the different numbers for asymmetry and alpha power calculations.

Comparison	df	assind(ln) {t}[p]	assind4(ln) {t}[p]	iafamp(μV) {t}[p]	iaffreq(Hz) {t}[p]
Depression vs	50[a]	.076±.26 {.39}	.11±.18 {1.20}	15.0±.19.5{-2.93}	9.4±1.3 {.62}
Controls	51	.048±.11 [.70]	.048±.11 [.23]	37.3±35.5 [.01]*	9.1±1.1 [.54]
Depression vs	51[a]	.076±.26 {.12}	.076±.26 {.81}	15.0±.19.5{-1.30}	9.4±1.3 {1.62}
Schizophrenia	52	.068±.13 [.91]	.068±.13 [.42]	23.5±27.8 [.20]	8.8±1.2 [.11]
Schizophrenia vs	29	.068±.13 {.46}	.068±.13 {.46}	23.5±27.8 {1.20}	8.8±1.2 {-.93}
Controls	29	.048±.11 [.65]	.048±.11 [.65]	37.3±35.5 [.24]	9.1±1.1 [.36]
Pre Session vs	32[c]	.003±.23[d]	.003±.14[d]	.03±.18[d]	.06±.87[d]
Post session[h] (Baseline only)	37[a]	{.08} [.93]	{.13} [.90]	{.01} [.99]	{.45} [.66]
Pre Session vs	560[a]	-.02±.23[d]	[e]	.82±10.8[d]	.13±.83[d]
Post session (All recordings)	678[b]	{.46} [.05]*		{1.98} [.05]*	{4.14} [.00]*
Baseline vs	34[a]	.098±.25{.61}	.105±.18{.65}	15.74±19.8{1.81}	9.37±1.3{.01}
Final Treatment	36[b]	.076±.19 [.55]	.087±.19 [.55]	12.17±12.4 [.08]	9.37±1.1 [.99]
Responders vs	34[a]	.14±.24 {1.89}	.13±.19 {1.60}	18.9±22.2{1.60}	9.40±1.45 {.16}
NonResponders (Absolute Baseline)	36[b]	-.03±.25 [.07]	.02±.14 [.12]	7.3±6.05 [.11]	1.32±0.88 [.87]
Responders vs	34[a]	.04±.21 {-.66}	.02±.17 {-.16}	-4.78±13.5{-1.01}	-.15±1.16 {-1.27}
NonResponders (Change value)	36[b]	.02±.24 [.52]	.01±.11 [.88]	-.29±5.76 [.32]	.39±1.11 [.21]

* Significant at α=.05 level

[a] For assind and assind4, one recording did not allow calculation of asymmetry.

[b] For iafamp and iaffreq two subjects from baseline did not proceed to final.

[c] Not all baseline recordings had useable data Pre and Post for F3 and F4.

[d] Differences, as repeated measures.

[e] Four record average not defined for each recording.

[f] For assind and assind4, two recordings did not allow calculation of asymmetry at baseline and final.

[g] In Response comparisons, Participants were grouped as Responders if a >50% decrease in Hamilton rating was achieved. The difference in absolute scores at baseline, and the group difference in.change values, from baseline to final, are presented in the last two comparisons.

[h] In Session comparisons, the group differences before and after a session were compared, firstly for a single session (Baseline) representative of the participant, then for all completed sessions.

cases, one responder). At all times, the coil was held tangential to the scalp, with the handle pointing back and away from the midline at 45°. The site of stimulation during the TMS sessions was defined using electroencephalographic methods[63] as a point 1 cm anterolaterally from F3,[64] with 2000 stimuli (40trains x 50pulses) per session.

Analyses

Consistent with our literature review, two main features were analyzed; frontal asymmetry from a single recording and from a four recording average (assind and assind4) and individual alpha rhythm amplitude and frequency (iafamp and iaffreq). These four features were compared in various groups using t-tests, and collated. If EEG activity is to prove useful as a proxy for clinical change, however, we might anticipate a stronger association than simple group differences. Bivariate correlation between the four features and the raw scores from two clinical assessments (HamD, BDI) was analyzed before and after treatment. The change in rating as a percentage of the baseline rating is arguably the most accepted index of clinical change when there is variability in the baseline,[65] so correlation between change in the four features and the clinical variables was also analyzed.

The final method of assessment of each feature's association with clinical course was to measure how the feature varied over the course of treatment on a daily basis. While such assessment could not be linked to clinical ratings, it does give an indication of how the treatment may be affecting the EEG independent of clinical state. In day based analyses, any day when no TMS therapy was conducted, whether due to weekends, holidays, midweek starts or just missed days, is included as missing data. In this analysis, therefore, not all days have the same number of participants. In particular, error bars at the start and end of 4 week displays are less meaningful than at the midpoints. As well as a simple display of EEG features over treatment course, the features were regressed against time (day) and session to test for a possible causal model. A constant was included in the model, as residual background alpha activity is certain and residual asymmetry is likely. The regression value (reflecting the daily effect of treatment), and also the coefficient of determination (R^2: how well the model fits the data), are reported.

RESULTS

There was no significant group difference (F=2.58, df=2/67, p=.09) in age between depression (42.9±13.8; N=39; 20Male/19Female), schizophrenia (34.1±9.9; N=16; 14M/2F) and control groups (38.6±16.8; N=15; 7M/8F). Gender distribution is not independent of illness (Pearson chi-square = 7.25) most likely as the schizophrenia group had an overrepresentation of males.

Table 2

Correlations between clinical ratings and EEG features

Correlation of feature with: HamD (N) BDI (N)	Pearson correlation {r} [p] (N)[a] Raw score, numeric change or percentage as per comparison column				
Feature	Ratings	assind(ln)	assind4(ln)	iafamp(μV)	iaffreq(Hz)
Baseline: HamD	24.0±5.5(40)	{-.08}[.65](37)	{.12}[.48](37)	{.05}[.75](37)	{.01}[.98](37)
and BDI	33.3±9.8(40)	{-.09}[.58](37)	{-.05}[.75](37)	{-.09}[.60](37)	{-.11}[.50](37)
Final: HamD	16.6±7.9(38)	{.36}*[.03](35)	{.15}[.40](35)	{.38}[.02]*(37)	{-.02}[.92](37)
and BDI	26.5±12.9(36)	{.39}*[.02](33)	{.01}[.95](33)	{.25}[.15](35)	{-.09}[.62](35)
Change in HamD	7.6±6.5(38)	{.18}[.30](35)	{.12}[.49](37)	{.18}[.28](37)	{.06}[.49](37)
and BDI. (Numeric)	6.4±11.6(35)	{.24}[.18](32)	{.21}[.23](34)	{.16}[.36](34)	{.03}[.23](34)
Change in HamD	31.5±29.4(38)	{-.37}*[.03](35)	{-.12}[.50](36)	{-.20}[.23](37)	{.18}[.29](37)
and BDI (Percent)	17.7±41.1(35)	{-.34}[.06](32)	{.04}[.84](33)	{-.21}[.22](34)	{.13}[.45](34)

* Significant at α=.05 level

[a] Statistics in Table 1.

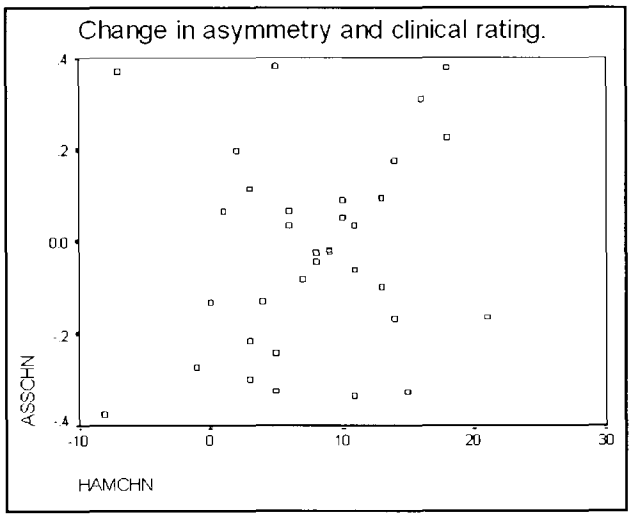

Figure 1.
Correlation between change in asymmetry index (ASSCHN) and change in Hamilton's clinical rating (HAMCHN), from baseline to final.

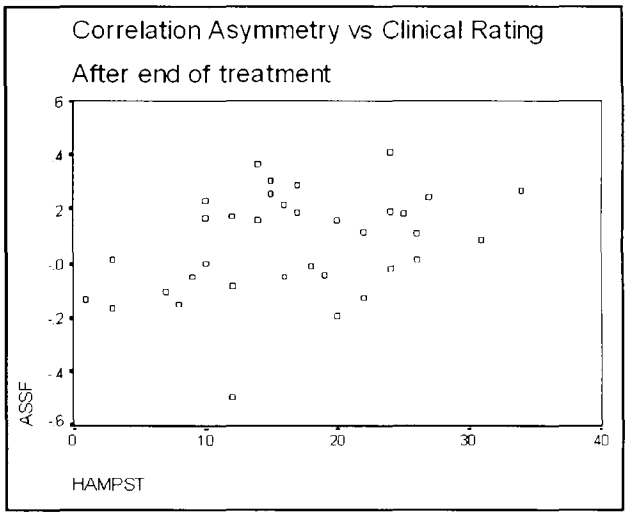

Figure 2.
Correlation between asymmetry (ASSF) and clinical rating (HAMPST) at end of treatment.

Group based comparisons, by illness, by session, by treatment, and by response, are accumulated in Table 1 for readability, as a series of two group t-test analyses. Two subjects from the depression group did not complete the treatment for reasons unrelated to their illness, and were included in baseline analyses only. Ten of the remainder showed a 50% decrease in HamD score (Responders). For completeness, a three group ANOVA by illness likewise showed a significant difference but only for individual alpha power (iafamp) (F= 4.13, df= 2,65, p= .02).

Correlation values for each of the four features with HamD and Beck depression scores are presented in Table 2. The correlations between values at baseline and at final assessment are presented, as well as correlation between the feature change and rating change over the course of the treatment. Nonparametric correlation (Kendall's Tau and Spearman's rho) were similar with one difference (the percentage change in assind was not correlated with either rating), that will be discussed. A representative plot of a significant correlation with raw asymmetry index at final assessment, is shown in Figure 2, and of asymmetry change in Figure 1.

There were several significant (α<.05) correlations not tabulated as they do not address the main hypothesis. As could be expected, the individual alpha characteristics (amplitude baseline-final: r=.82; frequency baseline-final: r=.54) were correlated over treatment, and the clinical assessment variables were correlated with each other (HamD-BDI baseline: r=.44; final: r=.80). Less predictably, some electrophysiological features were correlated across treatment (iafamp baseline – Hamd final: r=.45; individual alpha frequencies (iafreq) baseline – BDI final: r=.37).

Treatment course is illustrated for background alpha (Figure 3) and asymmetry (Figure 4) for the daily average of all participants and for responders only. The comparable ratings course is also shown (Figure 5). Of the 39 patients, only 4 showed a significant goodness of fit over the daily course of treatment (R^2 >0.1) and in each of these, the constant was the significant predictor rather than the day.

DISCUSSION

Several measures of clinical association were investigated in electrophysiological data from an rTMS paradigm for the treatment of depression. None of the proposed measures, (group identification,

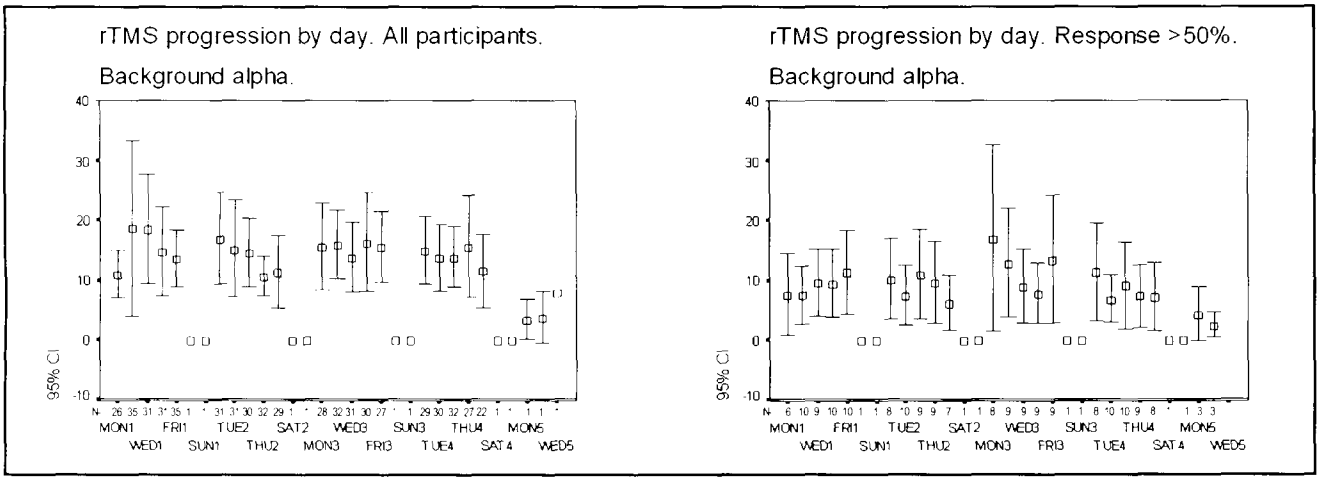

Figure 3A and B.
Background alpha power over daily course of rTMS treatment. All participants. Ten responders whose Hamilton rating reduced by >50%. Note: Data values on weekends are not real, but are used as space markers.

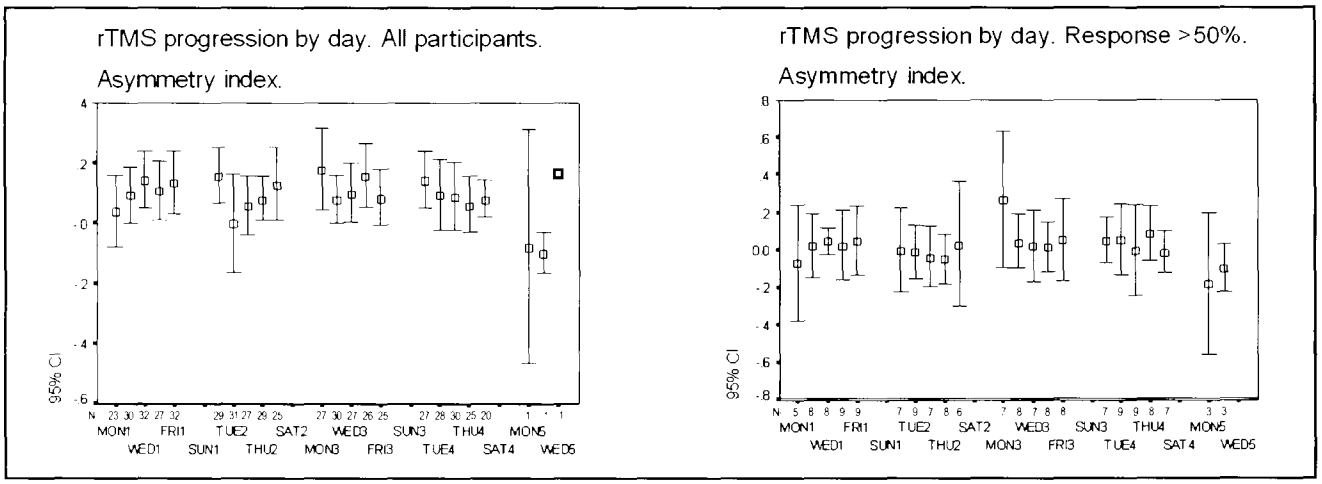

Figure 4A and B.
Asymmetry index over daily course of rTMS treatment. All participants. Ten responders whose Hamilton rating reduced by >50%.

correlation with clinical rating, or association with the time course of treatment), were sufficiently strong to indicate that power or asymmetry features could be used as a proxy for diagnostic ratings. Several previous findings were replicated, a weak correlation between asymmetry scores and clinical rating was detected, and new indicators of clinical effect were found, but in a clinical setting, the variability in these features appears to be greater than the putative state effect.

Group differences in EEG

The background alpha activity in the control group was more than twice the power of the depression group. Moreover, 7 of 15 members of the control group but only 4 of 38 from the depression group had power >30μV^2 in recordings characterized by intermittent alpha activity. The lower averaged alpha activity in the depression group is therefore a genuine finding at odds with the previous reviews[8,66] reporting increased alpha power in depression groups. Within that review,[8,66] however, only two of the eight candidate findings were accepted as showing the reported effect. There was no difference, however, in the asymmetry index between any of the groups, either from a single baseline recording or from the four recording aggregate. The direction of change, moreover, with the depression group having higher positive values for asymmetry than either control group, is inconsistent with Henriques and Davidson,[17] but supports negative findings from Reid[25] and their reservations about methodological difficulties. Finally, while not significant, the peak frequency of the depression group was 0.6 Hz higher than in schizophrenia, being similar to the control group.[6,66] Comparison of clinical groups, in summary, is not consistent with several previous findings for asymmetry, but is probably a genuine reflection of methodological variability as consistently reported. We feel that the key aspect in this comparison, as with all our asymmetry findings, is the segment length being analysed. The reliability of short segments is recognised as low (parallel test correlations of about 0.50)[60] with good reliability requiring 8 minutes of data.[61] In routine QEEG analysis,[67] a 30 minute sample of eyes closed resting EEG is recorded to assemble a two minute segment to similarly improve reliability. Neither recording time is available in our rTMS paradigm, but if extra time were justified, then asymmetry features may well prove useful.

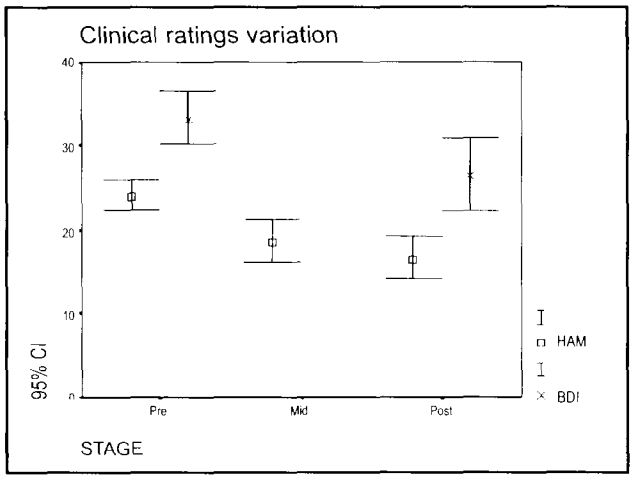

Figure 5.
Clinical ratings (Hamilton's [HAM] and Beck's [BDI]) variation over the course of rTMS treatment.

There was no significant change in an individual's features before and after a single session (Table1; Baseline Only). However, when all recordings were included for each individual, the asymmetry index became significant (Table1; All Recordings) more negative (effect size: Cohen's ◘ -0.07), and the background alpha amplitude (effect = 0.04) and frequency (effect = 0.08) both increased. It is possible these are real effects of 2000 TMS pulses, but the weakness of the effect means they are unlikely to prove useful for clinical prediction[2] on a daily basis. It is also possible these changes reflect non specific effects of the session on attention or alertness. As clinical ratings were only conducted over two week periods, it was not possible to similarly analyse sessional changes in state.

There was no significant difference between baseline and final treatment scores (Table1; Baseline vs Final) after 4 weeks, supporting the findings by Allen[44] that changes in asymmetry scores or background alpha over the treatment interval were not significantly related to changes in clinical state. The group average background alpha activity was slightly less after treatment, but the asymmetry index changed from a reasonably positive value to a lower positive value, with alpha activity at F3 increasing slightly (2.6μV to 2.8μV). There appears, therefore, to be less left-sided activation after treatment, the opposite of asymmetry predictions. While results are reported for the combined cohort, analysis of only responders (N=10) showed no more significant differences.

Finally, there was no significant difference in patients who had responded (>50% reduction) to the treatment, either in baseline score or in change from baseline to final, in either asymmetry index or background alpha. Those who responded well showed a trend toward had a more positive asymmetry index, and more background alpha, consistent with a less severe illness[68,69] or with better prognosis[26,70] but this finding is too weak to serve as the basis of a group membership prediction.

In summary from group analysis, apart from a weak effect of session with a large number of sessions, neither electrophysiological feature showed a clear effect of clinical group, session, treatment, or treatment response.

State differences in EEG

Clinical ratings (Hamilton and Beck) at the end of treatment were correlated with higher asymmetry index at the same time (Table 2; Final). Since positive asymmetry implies a decrease in left side alpha power relative to the right, a putative improvement in clinical state, this is the opposite correlation to that predicted from clinical findings.[17,23] The change in Hamilton rating as a percentage of the baseline rating, was also significantly correlated with percentage change in asymmetry (Table 2; Change-Percent). Unfortunately the baseline asymmetry feature has a mean close to zero, whereby percentage treatment will be nonlinear. Nonparametric treatment showed no such correlation (Kendall's tau = -.02), so this measure was not considered valid.

Apart from these, there was no correlation between sessional EEG features and clinical ratings after treatment. In particular, the correlation between change in asymmetry index and change in clinical rating (Table 2; Change-Numeric), while positive as predicted, did not attain significance. The plot (Figure 1) shows a potential outlier (asschn=.37; hamchn= -7), and if this member is removed, there is a significant correlation as predicted (r=.37; p=.04). However, this member is not flagged as an outlier (SPSS) in either feature individually, and while this subject was elderly, there was no a priori reason to exclude the data. While this consideration of correlation is encouraging, it serves to reinforce the view that the feature is not a highly robust measure of clinical effect. As the overall treatment effect was not significantly (or at least robustly) correlated, it is unlikely that session based changes would be significantly correlated (Figures 3, 4) as would be necessary for the use of electrophysiological features as a clinical measure. Notwithstanding this fragility, we consider a correlation between asymmetry score and clinical rating to be encouraging for the development of EEG based clinical prediction.

Treatment course

There was no significant association between the averaged background alpha activity (β=-.17, R^2=.03) or averaged asymmetry index (β=-.28, R^2=.08) with the daily course of rTMS treatment, using a linear regression model. A display of averaged background alpha (Figure 3) shows a possible decrease over a weekly cycle, but asymmetry index (Figure 4) shows no evidence of time based changes. The display for responders (Figure 3b and 4b) shows that the time course does not appear to vary with clinical response, but does have a lower starting point (c.f. Baseline values in Table 1). This finding may indicate a potential line of future research by defining electrophysiological groupings that respond well to rTMS. Given that lower asymmetry values are linked with greater severity, unfortunately, this is opposite to the treatment refractoriness indicators in clinical prediction.[65,71]

Finally, the pattern itself of daily change may prove clinically useful. A pattern in electrophysiological features that was similar to that found from either medication or ECT treatment would support the hypothesis that EEG features reflect the clinical effect. While a linear model of how the electrophysiological features change with time did not fit the data well, the display likewise did not appear to suggest a sigmoidal model.[53] The ECT induced course of improvement[72] suggests "a rapid antidepressant action of ECT with substantial contribution of early treatments," a description (consistent with their display) consistent with an exponential model of response. Unfortunately, from a prediction perspective, none of these patterns appear to pertain to our daily data. The pattern is possibly linear, but validity of that model is confounded by continuing variability.

CONCLUSION

Previous findings on electrophysiological features related to depression give cause to predict that such features may correlate with

clinical assessment, and have the potential to act as proxy measures of trait changes. Using typical EEG data from an rTMS treatment regime, and commonly utilized features and analyses, we have collated a range of findings from a single cohort pertaining to that potential.

Apart from a weak effect of session on both background alpha power and asymmetry index, neither electrophysiological feature showed a clear effect of clinical group, session, treatment, or treatment response. There was some evidence of association between the asymmetry index and clinical rating in the predicted direction, but this was not robust, as well as correlation in final scores that was opposite to that predicted from the literature. Finally there was no strong evidence that either feature fitted a linear model of daily treatment, nor graphical indication for more complex models. In summary, the findings are not sufficient, under our current clinical treatment regime, to support the use of background alpha activity or frontal asymmetry as proxies for clinical assessment or in predicting treatment outcome. Several findings, however, provide support for further research in this direction.

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DISCLOSURE AND CONFLICT OF INTEREST

G. W. Price, J. W. Lee, C. Garvey and N. Gibson have no conflicts of interest in relation to this article.

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