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Non-linear EEG analyses predict non-response to rTMS treatment in major depressive disorder

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HIGHLIGHTS

- There is no difference between MDD and HC in non-linear EEG measures.
- The change in LZC across time was significantly different for non-responders as compared to responders to rTMS treatment and HC.
- Non-linear EEG measures have added value over linear EEG measures in predicting treatment outcome.

ABSTRACT

Objective: Several linear electroencephalographic (EEG) measures at baseline have been demonstrated to be associated with treatment outcome after antidepressant treatment. In this study we investigated the added value of non-linear EEG metrics in the alpha band in predicting treatment outcome to repetitive transcranial magnetic stimulation (rTMS).
Methods: Subjects were 90 patients with major depressive disorder (MDD) and a group of 17 healthy controls (HC). MDD patients were treated with rTMS and psychotherapy for on average 21 sessions. Three non-linear EEG metrics (Lempel–Ziv Complexity (LZC); False Nearest Neighbors and Largest Lyapunov Exponent) were applied to the alpha band (7–13 Hz) for two 1-min epochs EEG and the association with treatment outcome was investigated.
Results: No differences were found between a subgroup of unmedicated MDD patients and the HC. Non-responders showed a significant decrease in LZC from minute 1 to minute 2, whereas the responders and HC showed an increase in LZC.
Conclusions: There is no difference in EEG complexity between MDD and HC and the change in LZC across time demonstrated value in predicting outcome to rTMS.
Significance: This is the first study demonstrating utility of non-linear EEG metrics in predicting treatment outcome in MDD.

1. Introduction

The application of repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder (MDD) has been investigated intensively over the last 15 years. Several meta-analyses have demonstrated that compared to placebo, the effects of rTMS applied to the left or right dorsolateral prefrontal cortex (DLPFC) have antidepressant effects (Berlim et al., 2013; Schutter, 2009; Schutter, 2010). With the establishment of the efficacy of rTMS, there has been increased interest in finding predictors of clinical response. The value of clinical features in predicting treatment outcome in MDD is very limited (Bagby et al., 2002; Simon and Perlis,

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2010) and a shift towards biomarkers is evident, evidenced by new initiatives such as the NIMH research domain criteria (RDoC) and precision medicine.

Since the first description by Lemere in 1936 who described that the capability to '*...produce "good" alpha waves...*' was associated with the '*...affective capacity of the individual...*" (Lemere, 1936), increased EEG alpha power is an often replicated finding in MDD (Olbrich and Arns, 2013). Recent studies further suggest that alpha power can be considered an endophenotype, mediating the pathway between the Brain Derived Neurotrophic Factor (BDNF) Val66Met polymorphism and depressive mood (Gatt et al., 2008; Zoon et al., 2013). Increased alpha power has also been associated with a favourable treatment outcome to antidepressant drug-treatments (Bruder et al., 2008; Bruder et al., 2001; Tenke et al., 2011; Ulrich et al., 1986), and a slow alpha peak frequency (APF) has been associated with less favourable treatment response to rTMS and antidepressants (Arns et al., 2012; Arns et al., 2010; Conca et al., 2000). Conceptually, the increased posterior alpha power can be regarded as a hyperstable vigilance regulation resulting in MDD behaviour, and it is known that treatments that destabilize vigilance (e.g., sleep deprivation) have strong antidepressant effects (Hegerl and Hensch, 2012). Given this supposed effect of destabilization, we hypothesised whether nonlinear measures would be more appropriate to assess the predictive power of these two dimensions of alpha (its amplitude fluctuations and frequency domain).

Nonlinear measures such as global and local scaling exponents and quantification of phase space dynamics have been successfully used to distinguish between healthy and pathological time series of human physiology and performance (e.g., Attention deficit disorders Gilden and Hancock, 2007; Ageing and disease Goldberger et al., 2002; Little et al., 2006; Developmental dyslexia Wijnants et al., 2012).

Fitting within a more general framework of health, wellbeing and complexity (Stam, 2010; Van Orden et al., 2009), analyses of neurophysiological time series and functional and structural networks of the brain also reveal dynamics such as long-range temporal correlations (LRTC) and topological structure associated with self-organised critical states of complex systems (Berthouze et al., 2010; Freeman et al., 2009; Orlandi et al., 2013; Palva et al., 2013; Rubinov and Sporns, 2010; Tagliazucchi et al., 2012; Yu et al., 2013). Nonlinear analyses of neurophysiological data have been used to characterize sleep, coma, anaesthesia, epilepsy, drug effects, schizophrenia, Alzheimer's disease and dementia as deviations from such optimal critical states or "small-world" network topology (Stam, 2005 for a review).

Nonlinear measures have been used to study MDD, Linkenkaer-Hansen et al. (2005) found a breakdown of LRTCs in the theta band (3–7 Hz) range in MDD patients during eyes-closed wakeful rest. The theta band LRCT magnitude over the left temporocentral region was negatively associated with severity of depression ($r = -0.79$), whereas the LRCT magnitude in the alpha band over the occipitoparietal region was positively correlated with severity ($r = 0.59$). These results seem to be in line with the reported increased alpha in MDD mentioned earlier, however, Linkenkaer-Hansen et al. (2005) did not find any correlations between amplitude and severity in different frequency bands which warrants further study of the relationship between these measures in MDD. In addition, few studies exist where nonlinear analyses have been applied to investigate efficacy of intervention in general and to the best of the authors knowledge, no studies exist where they have been used to predict treatment outcome in MDD to rTMS or antidepressant medication. Two studies have investigated non-linear measures and their association to treatment outcome to Electroconvulsive Treatment (ECT), in which a smaller post-seizure fractal dimension (Gangadhar et al., 1999) or smaller Largest Lyapunov Exponent (LLE) were interpreted to indicate a more predictable pattern of EEG seizure activity (Krystal et al., 1997) that was associated with a more favourable treatment outcomes.

The goal of many intervention studies using nonlinear analyses is to evaluate the added value of these methods above more traditional linear methods (Granic and Hollenstein, 2003; Hayes et al., 2007; Lichtwarck-Aschoff et al., 2012). Especially in the context of physiological measurements, the potential for clinical applications of these techniques receives much attention (Bravi et al., 2011; Harbourne and Stergiou, 2009; Huikuri and Stein, 2012). Although the potential of nonlinear tools is widely recognised, Bravi et al. (2011) note in their evaluation of 70 different variability analyses that the challenges for the field are to develop a shared vocabulary and increase coherence between results of different studies and the techniques that were used. With these challenges in mind and given the results described earlier, in this study we compared three non-linear EEG metrics and their added value to linear metrics to predict treatment outcomes. For this study the dataset from Arns and colleagues (2012) was used which consisted of 90 MDD patients, all treated with rTMS and psychotherapy. In this previous study the slow alpha peak frequency (APF) was the strongest measure in the discriminant analysis, hence in the present study we investigated the non-linear dynamics of the alpha band, and evaluated whether such measures would add to the prediction of treatment outcome, using exactly the same EEG channels and frequency bands as reported in the previous study. The alpha band employed by Arns et al. (2012) was 7–13 Hz for posterior APF and 6–13 Hz for anterior APF. These bandwidths differ from traditionally used frequencies that have studied alpha power. However, it is well known that the APF can range from 4–6 Hz in very young children (Niedermeyer and Da Silva, 1999), to 10 Hz in adults and 7–9 Hz in chronic pain patients (Boord et al., 2008) and Alzheimer patients (Rodriguez et al., 1999). Given that specifically the slow APF values have yielded predictive power (for overview see Arns and Olbrich, 2013) and LRCTs indicate power laws in which slow frequencies dominate the signal (Babloyantz, 1991; Linkenkaer-Hansen et al., 2005; Linkenkaer-Hansen et al., 2001), we used the above frequency band. A second reason was to keep the results comparable to the previous report and contribute to improve coherence between different studies and their interpretation and evaluation of these nonlinear measures (cf. Bravi et al., 2011). Furthermore, in previous analyses as well as in the present study, the focus will be on predicting non-response to treatment. This excludes the effects of placebo response and differential effects of rTMS and psychotherapy. Characterizing non-response to treatment is not only clinically meaningful, but could potentially also result in the development of new treatments based on such biomarkers.

2. Methods

2.1. Design

This study was a multi-site open-label study and inclusion criteria were: (1) a primary diagnosis of Depression or Dysthymic disorder according to DSM-IV criteria rated using the MINI (MINI Plus Dutch version 5.0.0) and (2) a Becks Depression Inventory (BDI) score of 14 or higher at enrolment. Exclusion criteria were: previously treated with ECT, epilepsy, wearing a cardiac pacemaker, metal parts in the head, pregnancy and the presence of paroxysmal EEG. All patients signed an informed consent form before treatment was initiated. All participants were asked to refrain from caffeine or nicotine intake for at least 2 h prior to testing. Data from healthy controls were drawn from a previous IRB approved study

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(also see: Kleinnijenhuis et al., 2008; Spronk et al., 2010) which employed identical EEG assessments in the same lab. These healthy controls only served as a baseline comparison group and did not undergo rTMS. A total of 20 non-responders (MDD-NR), 70 responders (MDD-R) and 17 healthy controls (HC) were included in the study.

2.2. rTMS Treatment

rTMS was administered using a Magstim Rapid^2 (Magstim Company, Spring Gardens, UK) stimulator with a figure-of-8 coil (70 mm diameter). Patients were treated with left DLPFC rTMS (10 Hz; 30 trains, 5s. duration, ITI: 30 s: 1500 pulses per session; $N = 57$) or with right DLPFC LF TMS (1 Hz; 120 trains; 10 s. duration; ITI: 1s: 1200 pulses per session; $N = 33$). The DLPFC was determined by placing the coil 5 cm anterior to the motor cortex area of the musculus abductor pollicis brevis and stimulation intensity was at 110% of the motor threshold (MT). In patients older than 55 yrs. of age the stimulation intensity was increased by 10% (in order to compensate for potential frontal atrophy, which seldom occurs before the age of 55). Furthermore, rTMS treatment was complemented by psychotherapy by a skilled psychologist for all patients, where psychotherapy was applied concurrent with the rTMS. BDI scores were assessed during intake, outtake and after every fifth session, to track progress of treatment. The total number of sessions was determined by the therapeutic response of the patient and this was on average 21 sessions.

2.3. Pre-treatment QEEG

EEG recordings were performed using a standardized methodology (Brain Resource Ltd., Australia) from 26 EEG locations, for 2 min Eyes Closed (EC) and 2 min Eyes Open (EO). Details of this procedure have been published elsewhere (Arns et al., 2012). In summary, patients were seated in a sound and light attenuated room, controlled at an ambient temperature of 22 °C. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (Quikcap; NuAmps; 10–20 electrode international system). Data were referenced to averaged mastoids with a ground at Fpz. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Skin resistance was <5 K Ohms for all electrodes. A continuous acquisition system was employed and EEG data were Electro-Oculogram (EOG) corrected offline (Gratton et al., 1983). The sampling rate of all channels was 500 Hz. A low pass filter with attenuation of 40 dB per decade above 100 Hz was employed prior to digitization.

2.4. Clinical outcome

The primary outcome measure is the response to treatment defined as reaching remission (BDI $\leqslant$ 12) or response (a more than 50% decrease in BDI) after treatment in agreement with the cut-offs as suggested by Riedel et al. (2010). Using this definition, patients were labelled as either a responder (MDD-R) or a non-responder (MDD-NR) to treatment. In order to investigate possible differential treatment effects between HF and LF rTMS one way ANOVA's were used to test for differences in age, education, number of sessions, BDI at intake, outtake and percentage improvement on BDI, as well as Chi-Square tests for differences in gender and percentage responders.

2.5. Linear EEG analyses: APF and alpha power

The APF values were taken from Arns et al. (2012) and consisted of: A linked ears montage, filtering (1–40 Hz), automatic artifact removal (threshold of 150 μV), segmentation in 8 s. segments, and an FFT power spectrum calculation. This pipeline was applied to both eyes open (EO) and eyes closed (EC) conditions. The power spectrum from EO was subtracted from the FFT from EC and within the range of 7–13 Hz the maximum alpha suppression was determined across P3, Pz, P4, O1, Oz and O2. The site where the maximum alpha suppression occurred was chosen as the site where the APF was scored by establishing the exact frequency at which the alpha suppression was maximal (posterior APF). The APF at frontal sites (F3, Fz and F4) was scored by determining the maximum alpha suppression across these 3 sites and scoring the peak frequency where the highest alpha suppression took place between 6 and 13 Hz (anterior APF).

EEG data at Fz and the posterior site established above were high-pass filtered at 7 Hz (8th order Butterworth) and low-pass-filtered at 13 Hz (8th order Butterworth filter) and power was extracted by trapezoidal numerical integration and segmented into 2 one minute epochs for further non-linear processing.

In this study 1-min epochs have been used to calculate the non-linear measures. Based on previous work by Tirsch et al. (Tirsch et al., 2000; Tirsch et al., 2004), who reported a periodicity in alpha with 50–60 s., 1-min epochs should allow us to capture the nested fractal dynamics of the alpha band.

2.6. Non-linear EEG analysis

The analysis was confined to the posterior site and Fz. Hereby results from non-linear analyses could be directly compared to results from linear analyses. Furthermore, this also served to increase the signal:noise ratio, by picking the site with maximum alpha.

Three nonlinear measures, that can be classified as belonging to the invariant domain (see Bravi et al., 2011) were applied on the two 1-min epochs for all EC EEG data, summarized below:

Lempel–Ziv Complexity (LZC): This measure is defined by:

$$\mathrm{LZC} = \frac{c(n)}{b(n)}$$

Where n is the number of data points of the EEG time series, $c(n)$ is the maximum possible value of $b(n)$ when n tends to infinity and $b(n)$ is the number of times that the operation insert has to be used to generate a string of n numbers, it is the number of times that the string cannot be extended by copying from the previous elements of the string. Therefore, $0 \leqslant \mathrm{LZC} \leqslant 1$, with the maximum complexity corresponding to 1 for a random string, because by definition no pattern or order or causality exists in such string that has to be extended by continuous insertions. A reduction of complexity means order or presence of determinism. Noise can be formally defined as infinite dimensional determinism thus, in this context, complexity may be related with dimensionality of a dynamical system generating the time series. However, LZC has nothing to do with dimension but to the characterization of the order retained in a one-dimensional temporal parameter, an EEG time series in this case (also see: Aboy et al., 2006).

False Nearest Neighbours (FNN): This measure is defined by:

$$\frac{|x(n+d) - x'(n+d)|}{2R_d} \geq R_{tol}$$

Where $x(n+d)$ and $x'(n+d)$ are the $d+1$ components of the d-dimensional point $\boldsymbol{y}(n)$ and its Nearest Neighbor, NN. R_d is the distance between $\boldsymbol{y}(n)$ and its NN in d-dimensions, R_{tol} is some

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threshold value depending on the characteristics of the time series. The left hand side of the inequality measures the ratio of the distance between a point and its d-dimensional NN in $d + 1$ dimension to the distance between the same two points in d dimension. The inequality tells us that the distance between a point and its NN in $d + 1$ dimensions is more than R_{tol} times the distance between the same two points measured in d dimensions. When this happens, the NN is considered to become a false nearest neighbor, FNN. The dimension d when there is no more FNN, is an estimate of the minimum dimension to unfold the attractor represented by the time series. Again, we may use the FNN method to measure deterministic content in a time series without assuming a chaotic attractor underplaying the EEG. FNN is a simple and robust measure but it gives discrete values implying a potential low sensitivity to the small changes that we are looking for in EEGs (also see Kantz and Schreiber, 2004).

Largest Lyapunov Exponent (λ; LLE): This measure is defined by:

$$\lambda = \frac{1}{h} ln \frac{S_k}{S_0}$$

Where h is the step between consecutive data points in the EEG time series, s_k is the distance between neighbor trajectories at point k and s_0 is the initial distance between the two neighbor trajectories. λ is a measure of the divergence of nearby trajectories, more precisely, it is the parameter of an exponential divergence, therefore it has to be positive. In order to estimate λ, a scalar time series have to be reconstructed in a D-dimensional phase space which involves at least two parameters: the time delay and the embedding dimension. For a complexity or order measure application, these two parameters can be tuned to obtain the best results, e.g., a clear difference of the measure values of λ obtained for two EEGs. Again, we are not assuming that the EEG is a chaotic time series corresponding to a well-defined chaotic attractor; however, it may have order or deterministic content that may be measured (also see Kantz and Schreiber, 2004).

Surrogate data were generated by processing the original data such that it conserves its characteristics but it has lost most of its deterministic character. If the values of the measures are the same for the original time series and the corresponding surrogate data, a model of a purely stochastic processes will best represent the original time series. The results of this work show that it is not the case for the EEGs and detectable variations are observed for some patients in their EEGs for particular channels.

2.7. Data analysis

All statistical analyses were performed in SPSS 17.0. One-way and repeated measures Analyses of Variance (ANOVA's) were performed to investigate pre-treatment differences between: (1) responders (MDD-R) and non-responders (MDD-NR), (2) an unmedicated group of depressed patients (MDD) and an age and gender matched group of healthy controls (HC). For EEG measures repeated measures with factor site (OP vs. Fz) and time (1st vs 2nd minute) were performed, with responder status as between subject factor. Furthermore, a bivariate correlation was performed between the non-linear measures and the percentage improvement in depression severity (%BDI) and BDI at intake and outtake.

Using the significant biomarkers a discriminant analysis was performed and a Receiver Operator Characteristic (ROC) curve was plotted to investigate how well the non-linear and linear measures could be used to predict treatment outcome. An ROC curve is a graph displaying the true positive rate vs. the false positive rate for responder status.

3. Results

A total of 90 patients were enrolled (average age: 42.9 yrs, range 19–69 yrs; 49 females and 41 males). There were no differences in any of the clinical outcome measures and demographics between the HF and LF TMS groups nor between the MDD-R and MDD-NR groups.

From the 70 responders, 58 (83%) achieved remission and the remainder demonstrated a more than 50% improvement on the BDI, resulting in 20 MDD-NR and 70 MDD-R and 29 of the 90 patients were unmedicated. For the whole group, the average BDI at intake and outtake was 30.3 (9.35) and 12.3 (11.3) respectively, in on average 20.7 sessions.

There were no differences in LZC, FNN and LLE values for medicated vs. non-medicated subjects (all $p > .269$; 32% of the sample was unmedicated), in agreement with the previous findings from (Arns et al., 2012) regarding linear EEG measures. Therefore, the analyses were performed on the whole group. There were no differences between MDD-R and MDD-NR as well as between MDD and HC in age and gender. As reported in Arns et al. (2012) there was no difference between MDD-R and MDD-NR for posterior APF, but there was a significant difference in anterior APF, where MDD-NR had an APF of 8.3 Hz and MDD-R had an APF of 9.16 Hz ($p = .005$; $F = 8.303$, DF = 1, 84).

3.1. LZC differences between MDD-R and NR

An interesting observation was that there was an interaction between MDD-R and MDD-NR for the LZC comparing the values for the 1st vs. the 2nd minute, also see Fig. 1a. For MDD-R, LZC increased from minute 1 to minute 2, whereas for MDD-NR the opposite occurred. This was also confirmed by a repeated measures ANOVA with factor time (minute 1 and minute 2) and site (OP and Fz) and between subject factor responder status with a significant responder status X time interaction ($p = .013$; DF = 1, 88; $F = 6.435$) and a significant site effect ($p < .000$; DF = 1, 88; $F = 31.513$) and no main effect of responder status ($p = .996$, DF = 1; $F = .000$). Therefore, we also calculated the difference scores between minute 1 and minute 2 (LZC-diff), and indeed this LZC-diff was significantly different at Pz ($p = .032$; df = 1, 88; $F = 4.764$). We also looked at alpha spectral power (7–13 Hz, log transformed) for minute 1 vs. minute 2, which did not demonstrate this time X responder status interaction ($p = .551$) and also did not demonstrate a significant difference between MDD-R and MDD-NR ($p > .587$), suggesting this is a specific non-linear EEG phenomenon. This phenomenon was also specifically related to the alpha band since the same non-linear analysis applied to a broader frequency band from 0.5–20 Hz did not demonstrate any significant findings.

3.2. LZC differences between MDD and healthy participants

We further analysed the LZC in a subgroup of unmedicated MDD patients ($N = 17$) matched (on gender and age) to a group of healthy controls ($N = 17$) in order to further understand the above finding, also see Fig. 1b. A repeated measures ANOVA with factor time (minute 1 and minute 2) and site (OP and Fz) and between subject factor diagnosis, did not yield any main effects nor interactions, except a significant site effect ($p < .001$; DF = 1, 32; $F = 45.019$). One-way ANOVA's also failed to find a difference in LZC and LZC-diff between MDD and healthy controls (all p>.271), suggesting there are no differences in these metrics between MDD and HC. This MDD sub-group contained 2 MDD-NR, excluding these from the sample did not change these findings.

Note from Fig. 1a and b that both MDD-R, MDD and HC demonstrated a slight increase in LZC from minute 1 to minute 2, and only

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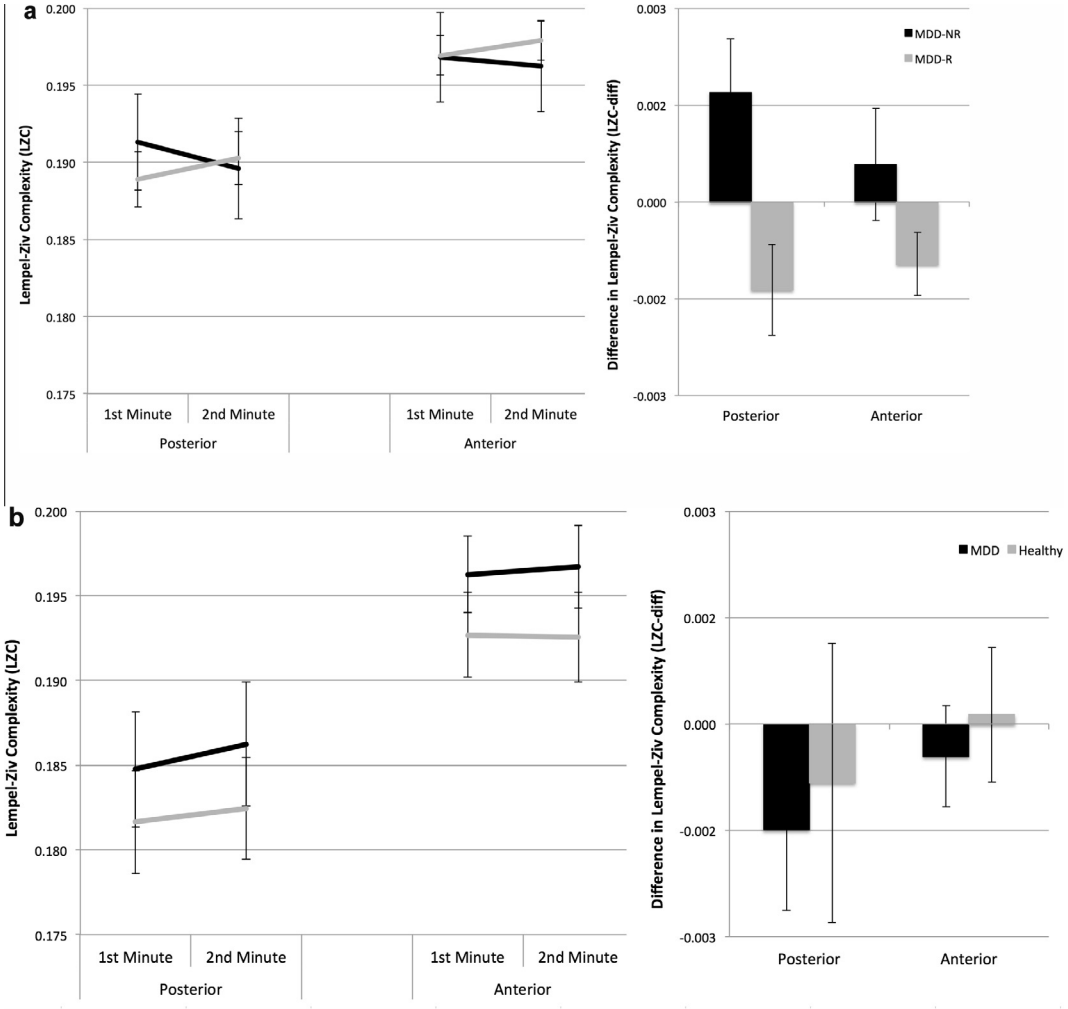

Fig. 1. The Lempel–Ziv Complexity (LZC) for posterior and anterior locations. (1a) MDD-Responders versus MDD-Non-responders; (1b) unmedicated MDD patients compared to a matched group of HC. Note the interaction for MDD-R and MDD-NR from minute 1 to minute 2, further illustrated by the LZC-diff score plotted on the right. All groups (MDD, HC and MDD-R) exhibit an increase in LZC, whereas only the MDD-NR demonstrate a decrease in LCZ across time, evidenced by the significant difference in LZC-diff (on the right). Error bars are standard error of the mean (SEM).

the MDD-NR demonstrated a decrease in LZC from minute 1 to minute 2, confirmed by the significant interaction and significant difference in posterior LZC-diff.

3.3. Treatment prediction

For responders vs. non responders there was no difference for BDI at intake ($p = .257$; DF = 1, 88; F = 1.301), age ($p = .926$; DF = 1, 88; $F = .009$) nor gender (Chi-square; $p = .572$).

There was no correlation between depression severity at intake and the LZC measure (all $p > .131$), in agreement with the lack of a difference between MDD and healthy participants. However, LZC-diff at Fz correlated with %BDI ($p = .011$; DF = 90; $r = -.267$) and incremental change of BDI-per-session ($p = .003$; DF = 90; $r = -.306$).

Adding the 2 measures that were significantly different between MDD-R and MDD-NR (LZC-diff at Pz) and that were significantly associated with treatment outcome (LZC-diff at Fz) to a discriminant analysis yielded a significant Wilks' Lambda ($p = .046$; Wilks' Lambda = .932; Chi-square = 6.163; df = 2) and an area under the ROC curve of 0.697 (see below Fig. 2a).

Performing the same analysis on the APF from the Arns et al. (2012) study yielded a significant Wilks' Lambda ($p = .005$; Wilks' Lambda = .910; Chi-square = 7.870; df = 1) and an area under the ROC curve of 0.697 (see below Fig. 2b). Combining both APF and the LZC-diff measures at Fz and OP yielded a significant Wilks' Lambda ($p = .001$; Wilks' Lambda = .830; Chi-square = 15.410; df = 3) and an area under the ROC curve of .793 (see below Fig. 2c), suggesting both measures have added value and do not represent the same information.

Repeating the above steps with the difference in spectral alpha power for the first and second minute for both anterior and posterior did not yield a significant discriminant analysis (p = .846; Wilks' Lambda = .996; Chi-square = .335; df = 2) and adding APF into this discriminant analysis worsened the model ($p = .030$; Wilks' Lambda = .897; Chi-square = 8.974; df = 3) as compared to APF alone. Therefore, the above effects cannot be explained by the effects from linear measures such as spectral alpha power.

The LZC-diff measures did not correlate to the already reported 4 discriminants used in Arns et al. (2012), hence they were added to the discriminant analysis as reported in that study. This yielded a significant Wilks' Lambda ($p = .001$; Wilks' Lambda = .745; Chi-square = 22.366; df = 6) and an area under the curve of .835 (which is an improvement from the originally reported 0.814), also see Fig. 2d below.

3.4. Surrogate analysis on LZC measures

This study was performed under assumption of nonlinear determinism in the EEG data. In order to probe this assumption, the

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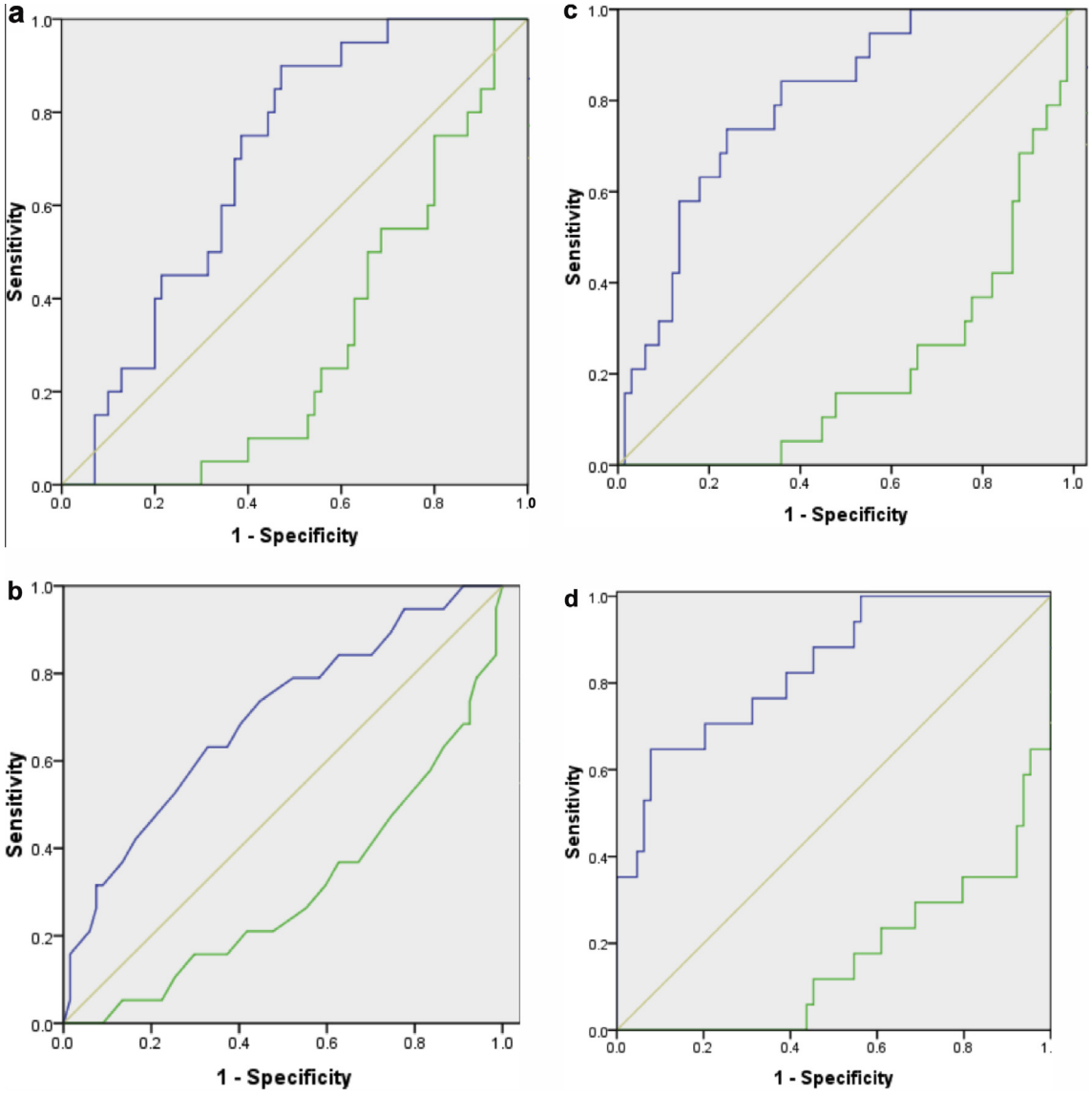

Fig. 2. The ROC curve for the results from different discriminant analysis with (2a) non-linear EEG metrics alone (LZC-diff for Fz and posterior; Top left); (2b) The same analysis using the APF measure from the previous Arns et al. (2012) publication (top right); (2c) The ROC from the combined discriminant analysis (LZC-diff for Fz, posterior and APF, bottom right) and (2d) The total discriminant analysis from Arns et al. (5; bottom left) with the non-linear measures added resulting in an increased area under the curve from 0.814 (5) to 0.835. Note that the area under the curve for (2a) and (2b) is identical (.697).

method of surrogate data was applied by randomly shuffling time indices within each of the EEG datasets. This procedure allows destroying the deterministic characteristics of the EEG time series keeping their probability distributions and single value statistics (Small, 2005). If the values of the measure of LZC are the same for the non-surrogate and the surrogate data, this would be an indication that there is no nonlinear determinism in the EEG time series that can be detected by the measure of LZC.

Paired sample *t*-test indicated that LZC values for the whole group were significantly different for non-surrogate LZC and surrogate LZC values (all $p < .001$). Average LZC values for the surrogate data were 1.006 for Fz and 1.006 for OP and the non-surrogate LZC values were 0.1972 for Fz and 0.1898 for OP.

3.5. Other non-linear measures: largest Lyapunov exponent and false nearest neighbors

The above analyses were also performed on the False Nearest Neighbor (FNN) and Largest Lyapunov Exponent (LLE). For LLE and FNN there were no differences between MDD-R and MDD-NR (all $p > .121$). There were also no significant correlations between FNN and%BDI, BDI at intake and BDI at outtake. For LLE there was only a significant correlation between BDI at outtake and LLE at Fz for the 1st min ($p = .046$; DF = 90; $r = .211$). Entering this value in a discriminant analysis did not produce a significant model ($p = .152$; Wilks' Lambda = .977; Chi-square = 2.056; df = 1). This measure also correlated significantly to pre-frontal Delta Cordance from the Arns et al. (Arns et al., 2012) study and hence could not be added to the discriminant analysis incorporating all discriminants.

4. Discussion

This study demonstrated that there is no difference in non-linear metrics between depressed patients and healthy participants (no between group difference, nor a correlation with baseline MDD severity), in line with other findings using linear approaches, which have revealed EEG has no diagnostic value for MDD (reviewed in Arns, 2012) or for ADHD in (Arns et al., 2013). However, this study

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did demonstrate there is utility for non-linear metrics, specifically the Lempel–Ziv Complexity measure, in predicting treatment outcome, which has also been found for other linear EEG measures (Arns et al., 2012). This study focused on earlier findings obtained in the alpha band, specifically the APF (Arns et al., 2012) and by using the same EEG channels and frequency band it was demonstrated that the LZC measure contained complementary information to linear measures (both APF and alpha power), as can be seen in Fig. 2. LZC alone resulted in the same area under the ROC curve as APF did, albeit both measures did not correlate significantly.

The above detailed analyses, in line with the results from the surrogate test, suggest that the LZC measure quantified some higher order non-linear complexity in the alpha band, which is not captured by linear methods. To our knowledge this is the first study investigating the prognostic use of non-linear methods to antidepressant treatments, in this case rTMS.

The averaged non-linear measures did not yield prognostic value, however, the change of the LZC from 1-min to another yielded the most reliable information. Both the healthy participants, the unmedicated MDD patients and the MDD-R exhibited the same pattern of increased complexity from minute 1 to minute 2, further demonstrating that the MDD-NR deviated on this measure with a decreased complexity from minute 1 to minute 2. Given that the MDD-NR did not respond to the rTMS treatment this is an important finding warranting further study, since understanding this phenomenon could have implications for more effectively identifying and treating this group of non-responders. It is known that depression is often characterized by a rigid EEG vigilance regulation during eyes closed (Hegerl and Hensch, 2012; Hegerl et al., 2012), characterized by a continuous posterior alpha. ADHD on the other hand is characterized by a more labile vigilance regulation, expressed by more anterior theta and alpha (for review see: Arns and Kenemans, 2012). It is also known that MDD patients with this more labile vigilance regulation are more often non-responders to antidepressant treatments (see: Arns, 2012 for review). Therefore, it is tempting to speculate if this reduced complexity in the 2nd minute in MDD-NR is somehow related to a more labile vigilance regulation. However, when alpha power in minute 1 and minute 2 were entered into the analysis, they did not add to the discriminant analysis, and only the LZC measure did. Therefore, future studies should investigate the LZC dynamics over longer EC recording periods, and investigate the association to EEG vigilance regulation.

The lack of a finding from the FNN analysis might be related to the discrete nature of the NN metric, which varied in our study between 5 and 8, and hence might not contain enough resolution, though the FNN analysis exhibited the same trends as the LZC analysis (unpublished observation). Therefore, future non-linear analysis should investigate further how non-linear metrics can employ more continuous measures as opposed to discrete metrics in order to improve the sensitivity in statistical analysis.

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