

Complexity analysis of spontaneous brain activity: effects of depression and antidepressant treatment

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Abstract

Magnetoencephalography (MEG) allows the real-time recording of neural activity and oscillatory activity in distributed neural networks. We applied a non-linear complexity analysis to resting-state neural activity as measured using whole-head MEG. Recordings were obtained from 20 unmedicated patients with major depressive disorder and 19 matched healthy controls. Subsequently, after 6 months of pharmacological treatment with the antidepressant mirtazapine 30 mg/day, patients received a second MEG scan. A measure of the complexity of neural signals, the Lempel-Ziv Complexity (LZC), was derived from the MEG time series. We found that depressed patients showed higher pre-treatment complexity values compared with controls, and that complexity values decreased after 6 months of effective pharmacological treatment, although this effect was statistically significant only in younger patients. The main treatment effect was to recover the tendency observed in controls of a positive correlation between age and complexity values. Importantly, the reduction of complexity with treatment correlated with the degree of clinical symptom remission. We suggest that LZC, a formal measure of neural activity complexity, is sensitive to the dynamic physiological changes observed in depression and may potentially offer an objective marker of depression and its remission after treatment.

Keywords

Depression, dynamical disease, Lempel-Ziv Complexity, mirtazapine, MEG, symptoms' remission

Introduction

Major depressive disorder (MDD) affects one out of five women and one out of ten men during their lifespan (Stein et al., 2006). According to the World Health Organization, depression was the third leading contributor to the Global Burden of Disease in terms of Disability Adjusted Life Years in 2004 (WHO, 2004). Currently, there is no consensus about the pathophysiology of depression, and there are no biological measures widely used in clinical practice for the diagnosis of depression or in order to monitor treatment response.

Neuroimaging techniques such as functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) have revealed changes in cerebral blood flow and metabolism in several brain areas, but findings are complex and often contradictory (Steele et al., 2006). Brain regions in which functional disturbances have been observed include the orbitofrontal cortex, ventromedial and ventrolateral prefrontal cortex, pregenual and subgenual portions of the anterior cingulate cortex, posterior cingulate cortex, parahippocampal cortex, superior temporal cortex, ventromedial striatum, amygdala, and medial thalamus. Metabolic rates in these regions are either positively or negatively correlated with the degree of symptomatology in patients assessed with instruments such as the Hamilton Rating Scale for Depression

(HAMD) (Kennedy et al., 2001; Preskorn and Drevets, 2009).

Electroencephalography (EEG) and magnetoencephalography (MEG) have also been used to investigate neurophysiological changes in depression. Compared with fMRI and PET they offer the advantage of a much higher temporal resolution, allowing the real-time recording of neural activity

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and oscillatory activity in distributed neural networks. Compared with EEG, MEG offers a better spatial resolution and is sensitive to a broader frequency spectrum than EEG, because the skull acts as a low-pass filter for electric currents, but not for magnetic fields (Breier et al., 1999; Ilmoniemi, 1993; Lounasmaa et al., 1996; Nunez et al., 2001).

For example, several studies have reported increased alpha power over left frontal sites, a finding referred to as the frontal alpha asymmetry (Davidson, 2004; Debener et al., 2000; Hughes and John, 1999; Knott et al., 2001; Monakhov and Perris, 1980). This has been considered a marker of reduced left frontal activation, associated with negative affective tendencies, given that alpha oscillations are thought to reflect a reduced activation.

However, results from EEG/MEG studies have not provided consistent results either. Other EEG studies, for example Knott et al. (2001), described increased beta activity and mean frequency values in depressed patients compared with controls, and did not find any significant changes in the alpha band (Knott et al., 2001). Similar results, affecting the beta but not the alpha band, were found by Pizzagalli et al., (2002). Wienbruch et al. studied the brain's slow focal activity in depressed patients using MEG and found reduced slow-wave (delta and theta band) activity in prefrontal and frontal areas when compared with controls (Wienbruch et al., 2003), yet Fernández et al. described significantly *higher* right occipital delta activity in depressive patients versus controls (Fernandez et al., 2005).

All of these studies used a conventional approach to the analysis of EEG/MEG data, namely frequency-power analysis: simply speaking, measuring the amplitude of neural oscillations within a given predefined frequency band. However, while useful in many cases, this approach only measures one aspect of the EEG/MEG time series, which contains much rich information which is not captured by such an analysis.

We decided to adopt a complementary approach, complexity analysis, in order to investigate neural activity in major depression. The theoretical background to this approach has been discussed previously (Glass and Mackey, 1979; Mackey and Milton, 1987; Sarbadhikari and Chakrabarty, 2001) with reference to the concept of 'dynamical disease': essentially, the idea that depression is a certain pattern or stable state of brain activity which the brain can become fixed into as a result of genetic, biological or environmental factors (Belair et al., 1995).

A non-linear analysis of MEG/EEG time series offers an approach to understanding such states. The Lempel–Ziv complexity (LZC) (Lempel and Ziv, 1976) is a complexity measure which has been used to analyse EEG and MEG signals in patients with Alzheimer's disease (Abasolo et al., 2006; Gomez et al., 2006), attention-deficit hyperactivity disorder (ADHD) (Fernandez et al., 2009), as well as to measure the depth of anaesthesia (Zhang et al., 2001), amongst other conditions.

The LZC is essentially a measure of the unpredictability, complexity or 'randomness' of the neural signal. Aboy et al. (2006) investigated the factors which affect this complexity estimate and concluded that the main determinant of the LZC is the bandwidth of the signal. In other words, the more the variability in frequency components, the higher the LZC values. Other similar measures of complexity have been applied to resting-state neural activity using fMRI, for example the Hurst exponent in autism (Lai et al., 2010).

In this study, we decided to further investigate the relationship between depression and neural complexity. We hypothesized that there would be a pattern of increased LZC values in major depression (see Li et al., 2008), especially in anterior brain regions. We also expected an interaction of diagnosis with age, given the fact that previous studies have shown an increased frontal EEG/MEG complexity as a function of age in healthy controls (Anokhin et al., 1996). Finally, we studied the effects of 6 months of antidepressant treatment in order to elucidate whether changes seen in currently depressed patients represent a 'trait' vulnerability marker or a 'state' marker of active depression.

Methods

Subjects

In total, 20 right-handed patients (12 female, eight male) referred from the Hospital Central de la Defensa Psychiatry unit, Madrid, Spain, who fulfilled the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) criteria for MDD participated in the study. None of the patients had a history of substance abuse, other neurological or medical conditions, or Axis I or Axis II psychiatric disorders. Clinical interviews and diagnosis were performed by their treating psychiatrist.

The mean age of patients with depression was 47.55 ± 12.98 years. Patients were moderately to severely depressed as reflected by the 17-item HAMD scores (Hamilton, 1960), (mean: 24.75 ± 5.78). In order to avoid the confounding effects of medication in the baseline measures and to allow the effects of subsequent treatment to be assessed, all patients completed a minimum 3-week medication washout before the first MEG recordings.

Immediately after the first (baseline i.e. pre-treatment) MEG scan, patients started antidepressant pharmacotherapy with mirtazapine 30 mg once a day. Following 6 months of treatment, patients received a second MEG (post-treatment) scan.

Some 19 right-handed healthy control subjects (13 female, six male) also participated in the study. None of them had a history of MDD, substance abuse, or a neurologic or medical disorder. Their HAMD scores were under the normal range (mean: 4.26 ± 1.52). Controls were recruited by advertisement in the Madrid area and selected after a preliminary phone interview. The mean age of controls was 45.89 ± 16.48 years. No statistically significant differences were found between patients and controls, in terms of mean ($p=0.728$) or variance ($p=0.309$). Handedness was evaluated using the Edinburgh Inventory (Oldfield, 1971).

Before entering the study, all participants provided written informed consent. The study was approved by the Investigation and Ethics Committee of the Hospital Central de la Defensa 'Gómez Ulla'.

Data collection

MEGs were acquired with a 148-channel whole-head magnetometer (MAGNES 2500 WH[®], 4D Neuroimaging, San Diego, CA, USA) located in a magnetically shielded room.

Subjects were awake and in a resting state with their eyes closed and under observation control during the recording. They were asked to avoid blinking and making movements. For each subject, 5 min of MEG signal were acquired at a sampling frequency of 678.17 Hz using a hardware band-pass filter of 0.1–200 Hz. Afterwards, these recordings were down-sampled by a factor of 4 (169.549 Hz). Artefact-free epochs of 20 s (3392 time points) were selected. Finally, these epochs were filtered between 1.5 and 40 Hz then copied to a computer as ASCII (American Standard Code for Information Interchange) files for further complexity analyses.

LZC calculation

LZC is a non-parametric measure for finite sequences related to the number of distinct substrings and the rate of their occurrence along the sequence, with larger values corresponding to greater complexity in the data (Lempel and Ziv, 1976).

In this study, we used the simplest method for pre-processing data into a form which allows the calculation of the LZC: a binary sequence conversion (zeros and ones). By comparison with a threshold T_d , the original data are converted into a 0–1 sequence. We used the median as the threshold T_d due to its well-known robustness to outliers. Essentially, therefore, the MEG time series is converted into a string of 1s and 0s, with a 1 representing that the signal at that point in time is higher than the median while a 0 indicates that it is lower than the median signal at that channel.

The LZC is then calculated by scanning the string from left to right and increasing a complexity counter $c(n)$ by one unit every time a new subsequence of consecutive characters is encountered (Zhang et al., 2001).

In order to obtain a complexity measure which is independent of the sequence length n , $c(n)$ should be normalized. In general, $b(n) = n/\log_2(n)$ is the upper bound of $c(n)$ for a binary sequence (Lempel and Ziv, 1976). Thus, $c(n)$ can be normalized via $b(n)$: $C(n) = c(n)/b(n)$. The normalized LZC, $C(n)$, reflects the rate at which new patterns occur along with the sequence.

Data reduction

LZC values were obtained for each of the 148 channels for each participant. Hence, 148 LZC scores per subject were submitted to statistical analyses. In order to avoid the statistical problem of multiple comparisons, these 148 scores were grouped into five regions (see Figure 1) as performed previously: Anterior, Central, Left Lateral, Right Lateral, and Posterior (Fernandez et al., 2009, 2010) and the average LZC score across all channels within a region was used in all subsequent analyses.

Statistical analyses

We examined the differences between groups' means and standard deviations for statistical significance with a one-way analysis of variance (ANOVA) with a covariate. The relationship between LZC scores and age was determined using linear regression models. A Spearman Rho's correlation coefficient was utilized to examine the relationship between age and

changes in HAMD scores. Finally, we fitted a logistic regression model to evaluate the contribution of LZC variables and age to the explanation of depression versus control group differences. A Receiver Operating Characteristic (ROC) curve was used to evaluate the precision of the final model.

Results

Age and sex effects

We first studied the effect of age and sex on LZC scores. Following our analysis design, we found that in the depressed group, neither Sex (all p -values were >0.438) nor Age (all p -values were >0.125) were correlated with LZC.

In the control group, Sex had no effect (all p -values were >0.271), but there was a strong association between Age and LZC values in all five regions (all p -values <0.008). Because the variable Sex had no effect on LZC values, both samples were grouped independently of it for further analysis, while Age was entered as a covariate.

Differences in LZC variables between depression and control group were evaluated using a one-way ANOVA with one covariate (Age). Age showed a significant effect on all LZC variables (p -values <0.003). Only the variables Anterior ($p=0.045$) and Right ($p=0.035$) were statistically different between the two groups.

Following this, the relationship between Age and LZC was analysed with two linear regression models, one for each group. In both groups all regression coefficients were positive (see Table 1), indicating a tendency to increased LZC scores as a function of age. While in controls LZC values increased significantly as a function of age in all sensor groups (all p -values <0.007), this tendency was not significant within the depression group (all p -values >0.140). The last row in Table 1 shows the p -values of the comparison of regression lines' slopes between controls and MDD patients. The significantly different slope values in the Anterior ($p=0.0491$), Central ($p=0.0501$), Left ($p=0.038$) and Right ($p=0.038$) regions supports the notion of a significant positive tendency in controls that patients did not show.

Comparison of patients and controls

The statistical tendency observed in Figure 2 indicates that LZC values were greater in the depression group when compared with controls, and that this tendency was present in all brain regions. Furthermore, LZC scores were age dependent.

Considering this tendency, we carried out a logistic regression model to understand the contribution of the five regional LZC variables (see above), and Age, to the differences between depression versus control group. Following the operation as suggested by Hosmer and Lemeshow (1989), the final model which optimizes its discriminating capability contained Age (coefficient = 1.763), Anterior LZC (coefficient = 15.641) and Age*Ln(Age) (coefficient = -0.370) variables. The statistical relevance of the logarithmic term (Age*Ln(Age)) indicates that Age exhibits a non-linear behaviour, thus explaining why both groups tend to show an intersection point at certain Age values when the increase in LZC scores in healthy controls reach an upper limit.

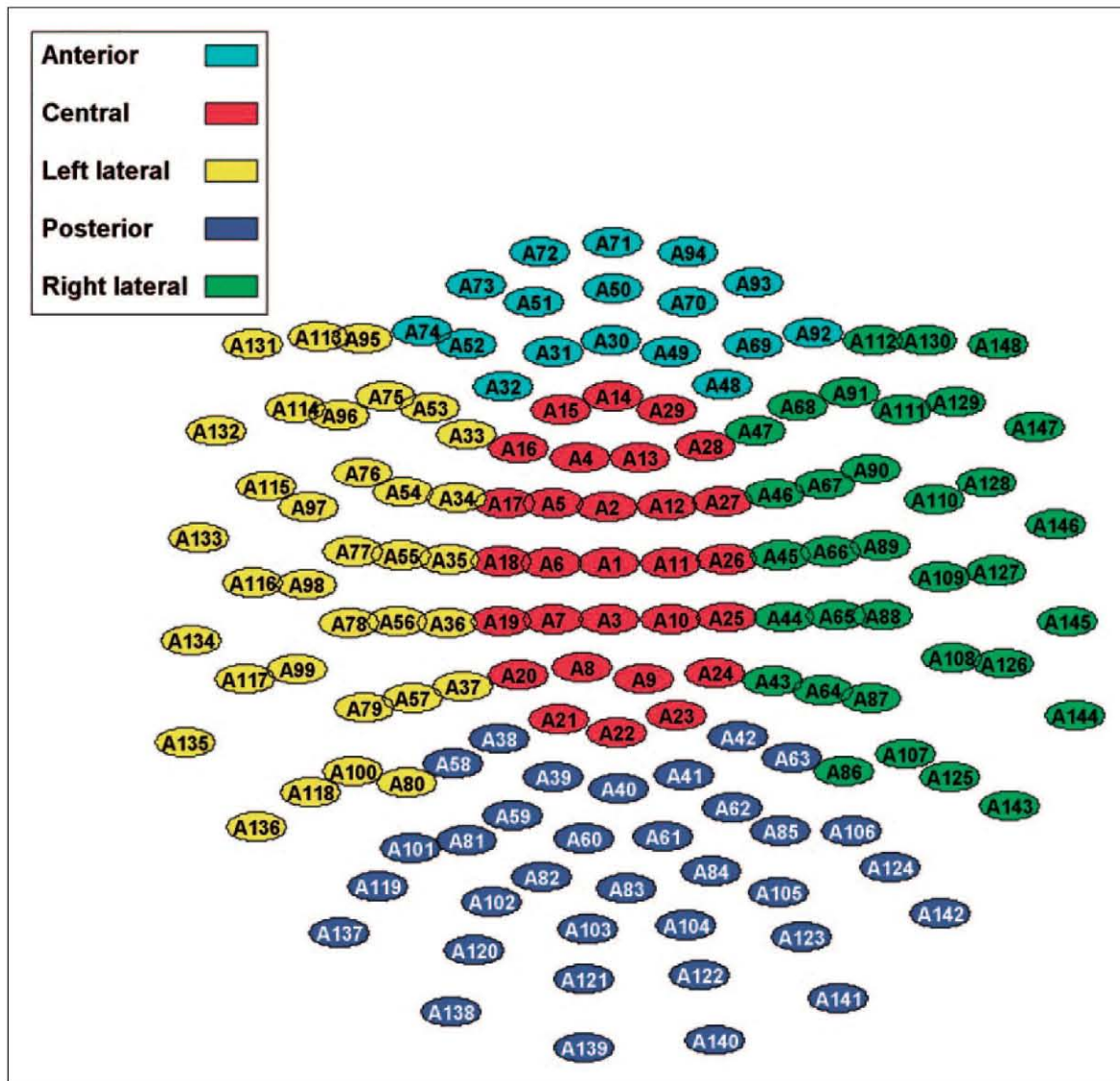


Figure 1. Sensor space representation of the five regions submitted to statistical analyses: Anterior, Central, Left lateral, Right lateral and Posterior.

The area under the ROC curve was 0.763 ($p=0.005$). The fitted model shows that Anterior is the sensor group with the greatest predictive power for depression.

Effects of antidepressant treatment

HAMD scores for all patients were lower after treatment (mean 5.10 ± 2.36 ; $p=0.000$) indicating that patients improved considerably. There was no significant correlation between age and the pre-post decrease in HAMD score ($p=0.120$, Spearman Rho's correlation coefficient ($\rho = -0.359$)).

As described previously, LZC scores in the Anterior sensor group could discriminate between patients and controls at baseline. In order to discover whether this measure was also sensitive to clinical improvement, we computed a new variable called 'Anterior-Dif', which represented the change in Anterior LZC scores before and after treatment.

The mean value of Anterior-Dif variable was positive (0.00950 ± 0.4100), indicating that LZC scores in the Anterior area generally decreased with treatment in MDD patients, bringing them into line with controls' baseline LZC scores (see Figure 3) but the pre-treatment versus post-treatment mean comparison was not statistically significant ($p=0.156$). However, since Age was previously associated with LZC values, and younger patients showed a slightly better clinical outcome than older patients, we studied the role of the variable Age in the post-treatment reduction of LZC values within the MDD group.

Taking into account the mean age of the sample (47.55 years), we divided the MDD sample in two groups: younger (<47 years) and older (≥ 47 years). As shown in Figure 4; we found a significant reduction ($p=0.048$) of Anterior LZC values in younger patients; however, this was not observed in the older ones ($p=0.546$). Interestingly, these results indicate a parallel tendency between HAMD and LZC values.

Table 1. Slope coefficients of regression lines for the five areas. p -values and correlation coefficients (r) in patients with major depressive disorder (MDD) and controls for Lempel-Ziv Complexity (LZC) scores. The last row shows p -values of regression lines' slopes in controls and MDD patients

	Anterior	Central	Left lateral	Right lateral	Posterior
MDD Group	0.0006 ($r=0.2081$) $p=0.3785$	0.0005 ($r=0.1864$) $p=0.4312$	0.0009 ($r=0.2929$) $p=0.2101$	0.0010 ($r=0.3423$) $p=0.1396$	0.0010 ($r=0.3035$) $p=0.1932$
Control Group	0.0024 ($r=0.5974$) $p=0.0069$	0.0019 ($r=0.6589$) $p=0.0022$	0.0027 ($r=0.7220$) $p=0.0005$	0.0028 ($r=0.7123$) $p=0.0006$	0.0020 ($r=0.7164$) $p=0.0006$
Slope test	$p=0.0491$	$p=0.0501$	$p=0.0389$	$p=0.0380$	$p=0.1234$

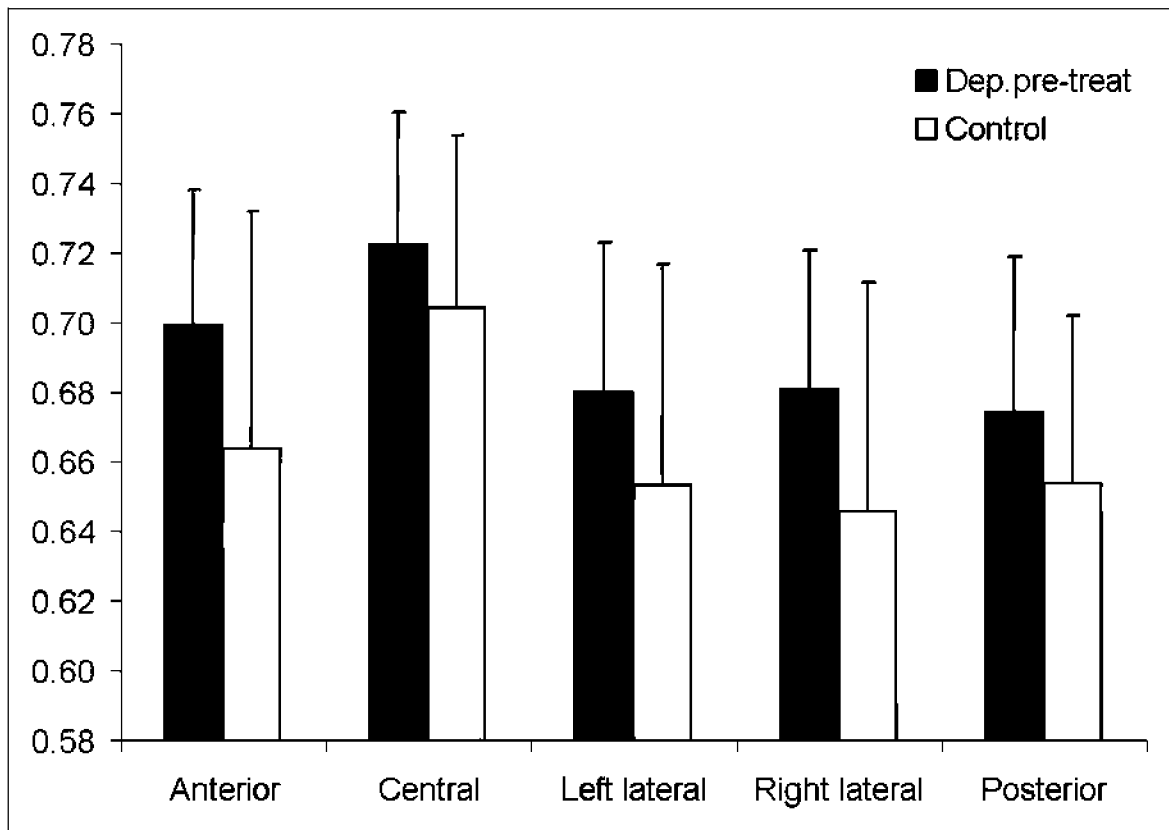


Figure 2. Mean and Standard Deviation of Lempel-Ziv Complexity (LZC) variables, for control and major depressive disorder (MDD) groups.

A greater reduction in LZC values in younger patients seems to be associated with a better clinical outcome according to the HAMD severity scale.

Figure 5 displays the regression lines of the variables Anterior versus Age for MDD patients before treatment, MDD patients after treatment, and controls. The regression coefficient of Anterior LZC scores after treatment was positive and statistically significant ($p=0.008$), which suggests that the most important effect of an effective pharmacological treatment in patients with MDD was to recover the 'normal' tendency initially observed in controls, with greater complexity values as a function of age. Furthermore, in post-treatment evaluation no statistically significant differences

were found between the slopes ($p=0.2360$) and intercepts ($p=0.1383$) of regression lines in controls and patients.

Discussion

We found that neural complexity, as measured using MEG and quantified using the LZC, was abnormal in patients with depression. LZC scores increased linearly with age in control subjects but this tendency was not observed in patients with depression.

Secondly, we found that LZC values were higher in depressive patients in the anterior brain regions when compared with controls and this difference, combined with the

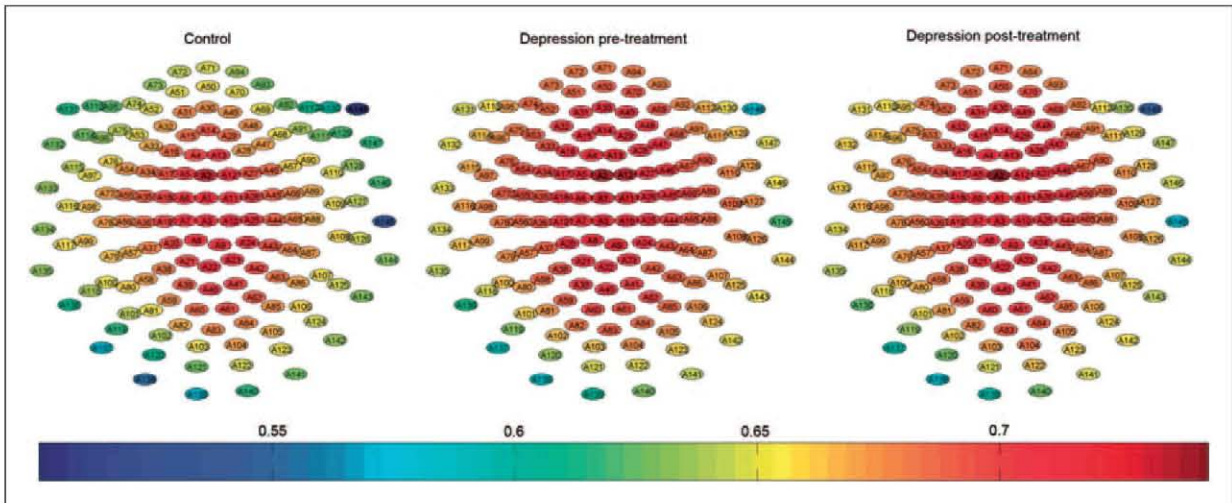


Figure 3. Average Lempel-Ziv Complexity (LZC) values in major depressive disorder (MDD) patients and control subjects for all channels, from A1 to A148, displayed in a colour scale. A significant reduction of Anterior scores can be observed in the sensor space representation within the MDD group.

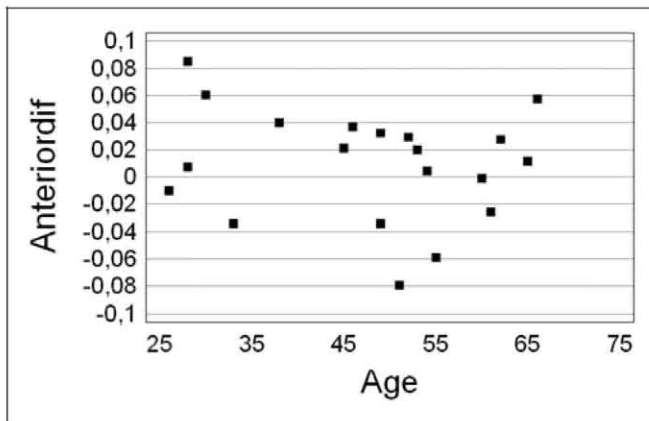


Figure 4. This figure displays the age distribution of the Anterior-dif variable. Positive values indicate an increase of Lempel-Ziv Complexity (LZC) after treatment, negative values indicate a decrease of LZC after treatment, and 'zero' indicates no change. Only two patients within the younger or A group (age <47 years) exhibited negative values of this variable, and these scores are very close to the 'zero' point.

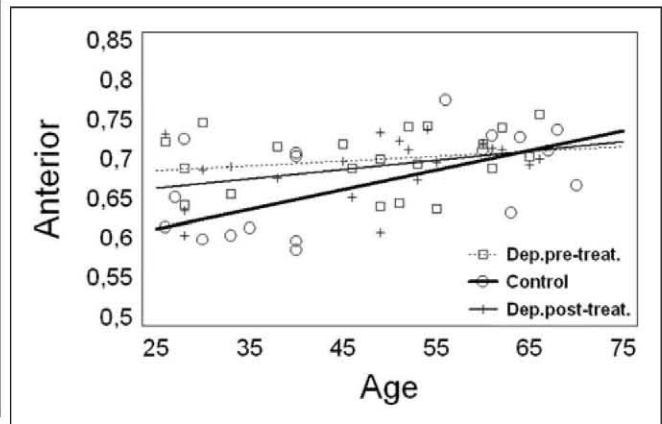


Figure 5. Anterior sensor group Lempel-Ziv Complexity (LZC) \times Age relationship in major depressive disorder (MDD) patients pre-treatment (Dep.pre-treat), MDD patients post-treatment (Dep.post-treat) and controls.

effect of age, allowed the classification of patients and controls in a logistic regression model. Finally, we found that after 6 months of treatment with 30 mg of mirtazapine, LZC values decreased in patients with depression, especially in the younger patients, bringing them close to the controls' LZC values. However, the main effect of mirtazapine was to recover the tendency observed in controls, where LZC values increased linearly with age.

The linear association of complexity with age in healthy people has been observed in previous studies (Anokhin et al., 1996; Fernandez et al., 2009) Anokhin et al. found increased EEG dimensional complexity (another measure of complexity) with age and a regional heterogeneity in the increase of EEG dimensional complexity within the first two decades of life, suggesting faster maturational changes in the anterior

areas of the brain (Anokhin et al., 1996). Their findings suggest that an increase in the complexity of brain dynamics lasts throughout the whole life span.

Our finding of higher LZC values in depressive patients in anterior brain regions mirrors Li et al.'s (2008) results using EEG to measure LZC in patients with schizophrenia and in patients with psychotic depression. Depressive patients showed higher LZC values in most electrode sites compared with controls (Li et al., 2008). Also, Thomasson et al. (2000) observed that averaged global entropy (an estimate of EEG/MEG complexity) slightly decreased during treatment in patients with depression (Thomasson et al., 2000).

How can we explain this increased complexity of neural activity in patients with depression? EEG/MEG neural complexity is closely related to the integrity of inter-neuronal

connectivity, and increases with the number of different oscillatory systems active at the same time (Tononi and Edelman, 1998).

Using other methods, several authors have described increased functional connectivity in depression. Greicius et al. (2007) described increased functional connectivity using fMRI in depressive patients between subgenual anterior cingulate cortex, thalamus, orbitofrontal cortex, and precuneus (Greicius et al., 2007). Fingelkurts et al. described 'strengthened' functional connectivity, mainly between short distance areas, using EEG structural synchrony in depressive patients during a resting condition (Fingelkurts et al., 2007). Increased functional connectivity might partially explain the elevated LZC values observed in patients with MDD, but as described in the introductory section, the key factor to explain higher complexity scores is increased frequency variability.

Is increased frequency variability seen in MDD? In their excellent study, Fingelkurts et al. examined the composition of EEG brain oscillations in unmedicated MDD patients (Fingelkurts et al., 2006). They demonstrated that the EEG of depressed patients was characterized by more segments of polyrhythmic/disorganized activity as compared with controls, and interpreted such disorganized activity as a sign of brain pathology.

Finally, we observed that after 6 months of treatment with mirtazapine, LZC values decreased in patients with depression (especially within the younger patients), thus bringing LZC scores closer to those observed in controls. This could be considered one of the critical findings of our study.

Our results indicate that clinical improvement, as revealed by a significant reduction in HAMD scores after 6 months of treatment with mirtazapine, is correlated with a decrease in complexity values which was significant in the group of patients younger than 47 years old. Marie-Mitchell et al. (2004) identified age as a non-specific predictor of treatment outcome in depression with both drug (fluoxetine or venlafaxine) and placebo treatment (Marie-Mitchell et al., 2004).

Our study was limited by a relatively small sample size. This limitation might particularly affect pre-treatment versus post-treatment statistical comparisons, hence preventing the tendency of lower post-treatment LZC scores to reach statistical significance. When we included the Age variable in the statistical model (either using linear regression or when the MDD sample was divided in two groups according to age) the reduction of post-treatment LZC scores emerged as a significant effect.

Also, because all of the patients in this study were treated with the same regimen of pharmacotherapy, it is not possible to determine whether the changes seen on the EEG after 6 months of treatment were specifically related to the drug treatment (mirtazapine 30 mg), or whether they are related more broadly to the clinical improvement which may have been driven by other factors such as the placebo effect and the passage of time.

Nevertheless, we conclude that complexity analysis of neural activity is a sensitive measure of detecting abnormal brain activity in clinical depression and may offer a potential approach in the evaluation of clinical improvement with treatment. To the best of our knowledge this is the first study to evaluate LZC after antidepressant treatment using EEG or MEG.

Future studies should aim to replicate and build on these results. Also, we suggest that it would be necessary to evaluate the effects of different treatment approaches such as psychotherapy (i.e. cognitive behavioural therapy) and/or selective serotonin reuptake inhibitors, which are widely used as first line of treatment of depression in clinical practice.

Funding

This study was partially supported by funding from Organon S.A. Spain. The sponsors had no role in the design or conduct of the study, in the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

Conflict of interest

Dr Alfonso Rodríguez-Palancas is not currently receiving research support from any sources, but has previously received research support from the following sources: AstraZeneca, Janssen Pharmaceuticals, Novartis, Organon and Pfizer.

Dr Alfonso Rodríguez-Palancas is currently a speaker for the following speakers' bureaus: Janssen, and in the past for Eli Lilly.

In previous years Drs. Ortiz and Fernández received research funding from Lilly S.A. Spain, Serono, Organon, and Pfizer.

The remaining of co-authors have nothing to declare.

Acknowledgements

To all patients and control volunteers for their patience and collaboration with the study. We thank Professor David Nutt, Professor Anne Lingford-Hughes, Dr Sue Wilson, Dr Jonathan Roiser and Dr Jamie Horder for their help in preparing this manuscript.

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