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Analysis of brain complexity and mental disorders

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Knowledge on the brain processes underlying mental disorders has significantly increased in recent decades, but in spite of the very important research efforts being made, there is no biological marker available for such disorders. For example, neurophysiological techniques (EEG or MEG), have been widely utilized in the investigation of the most important psychiatric syndromes such as schizophrenia, major depression, bipolar disorder or obsessive/compulsive disorder. The outcomes of some of those neurophysiological studies have made it possible to develop statistical models having very high sensitivity and specificity, although those models have not been incorporated into the day to day clinical practice. A possible explanation for this situation is that an inadequate analysis procedure which might be missing some important quantums of information contained in brain signals is being used. In this sense, new methods of non-linear analysis have been proposed for the investigation of neurophysiological data. Particularly, the analysis of brain signal complexity has been widely utilized in the investigation of psychiatric disorders. Parameters of EEG or MEG complexity usually estimate the predictability of brain oscillations and/or the number of independent oscillators underlying the observed signals. More importantly, complexity parameters seem to be sensitive to the temporal components of brain activity, and therefore might reflect the dynamical nature of psychiatric disorders. This paper reviews some of the most relevant studies within this field, especially those focusing on the diagnosis, follow-up and prediction of response to treatment.

Keywords:
biological markers, complexity, EEG, MEG

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Análisis de complejidad de la actividad cerebral y trastornos mentales

El conocimiento sobre los procesos cerebrales que subyacen tras los trastornos mentales ha incrementado significativamente en las últimas décadas, pero a pesar del importante esfuerzo investigador no disponemos de ningún marcador biológico para estos trastornos. Por ejemplo, las técnicas neurofisiológicas (EEG o MEG) se han utilizado ampliamente en la investigación de los síndromes psiquiátricos más importantes como la esquizofrenia, la depresión mayor, el trastorno bipolar o el trastorno obsesivo/compulsivo. Los resultados de algunos de estos estudios permitieron la construcción de modelos estadísticos con alta sensibilidad y especificidad, aunque estos modelos no han alcanzado la práctica clínica diaria. Una posible explicación para está situación sería la utilización de procedimientos de análisis inadecuados que podrían perder elementos importantes de la información contenida en la señal cerebral. En este sentido se han propuesto nuevos métodos de de análisis no-lineal para los datos neurofisiológicos. De particular interés resulta el análisis de complejidad de la señal cerebral que se ha utilizado ampliamente en la investigación de trastornos psiquiátricos. Los parámetros de complejidad EEG o MEG generalmente estiman la predictibilidad de las oscilaciones cerebrales y/o el número de osciladores independientes que subyacen tras las señales observadas. Más importante aun, los parámetros de complejidad parecen ser sensibles a los componentes temporales de la actividad cerebral y por tanto podrían reflejar bien la naturaleza dinámica de los trastornos psiquiátricos. Este artículo revisa alguno de los estudios más importantes dentro de este campo, en especial aquellos que se centran en el diagnóstico, el seguimiento y la respuesta al tratamiento.

Palabras clave:
marcadores biológicos, complejidad, EEG, MEG

INTRODUCTION: MAGNETOENCEPHALOGRAPHY IN MENTAL DISORDERS, THE PROBLEM OF BIOLOGICAL MARKERS

During recent years, there has been a very important increase in knowledge about brain processes underlying mental disorders. We also expect that this knowledge will play a fundamental role in the diagnosis and treatment of mental diseases and in the follow-up of their evolution. The neurophysiological techniques form a part of this large group of methods that aim to solve the important problem we are currently encountering: there are no biological markers for most of the mental disorders. Even more so, when we speak of "markers," we are not only referring to the basic question of the diagnostic marker but also to those aimed at the follow-up of the disease and prediction of the therapeutic response.

MEG, as a neuromagnetic counterpart of the EEG, is a relatively recent technique and therefore its use in the psychiatric population is currently focused on the basic or basic-clinical research and is still not based on diagnosis and follow-up of psychiatric patients. However, the MEG has an extensive application in the investigation of psychiatric disorders, which is indicated by a brief review of the literature. Already by 1999[1], there was sufficient data to compile a monographic article on the application of the MEG in psychiatry. Since then, there has been a growing number of investigations and there is no "major" psychiatric disorder that has not been approached by MEG studies. Although it would be extraordinarily long-winded to refer to all of them, we must indicate some examples: major depression[2-10], schizophrenia[11-19], bipolar disorder[20-26], attention deficit hyperactivity disorder (ADHD)[27-34], obsessive-compulsive disorder (OCD)[35-40], etc.

These studies are focused on investigating both baseline brain activity of the patients and its response to certain cognitive tasks. In general, MEG investigations have confirmed what we already knew thanks to the literature on EEG: baseline brain activity is somehow altered in patients with mental disorders and their cognitive activity has significant variations compared to the control subjects. It should be mentioned that most of the cognitive studies have focused on pure basic research and the diagnostic power for these disorders has not been calculated. The studies performed on spontaneous brain activity of the patients and especially those in which an analysis has been made of the traditional power spectrum of the signal registered (delta, theta, alpha bands, etc.) have aimed to propose these tests as clinical tools - with what results?

The first answer to this question is that the reality is obstinate and it is clear that neither the EEG (of long tradition) nor the MEG are currently used as diagnostic tests in mental disorders. This is true even though some studies (see for example Monastra et al.,[41]) throw light on sensitivity/specificity values that are truly important. What is the problem than? We cannot rule out that within the "paradigm change" that has occurred in the psychopathological research, the neurophysiological techniques have come off badly compared to the neuroimaging techniques that offer results having much more intuitive understanding given they are visual character. However, this is only a partial explanation.

If we review the literature, it is clear that most of the disorders that affect the mental condition of the individuals produce a very similar variation in baseline brain activity, that is, that the so-called "slowing" of the traces. This slowing pattern, that is defined in an operative way as an increase in low frequency band waves (delta and especially theta) versus high frequency ones (alpha and beta), appears at least in schizophrenia, OCD, ADHD, dementias, cognitive deterioration and partially in depression and bipolar disorders[41-50]. Some disorders have special characteristics, as the "dysrhythmia" of schizophrenia[51] or the "small sharp spike pattern" (paroxysmal activity similar to the epileptic) of the bipolar disorder[52]. Depression shows a somewhat special pattern, since several works have described an asymmetric increase of the alpha band power in the frontal cortex, accompanied by a decrease in delta power[53, 54]. It is interesting to also see that this pattern changes with effective antidepressant treatment[55].

Having seen all these data, it seems that we could make a more solid response to explain the limited success of the neurophysiological techniques: the current studies may be very sensitive but they are extremely non-specific. If different conditions share a same "sign," the utility of this sign is very relative. To add more wood to the fire, most of the EEG-MEG studies have been carried out in patients who were receiving treatment with psychopharmaceuticals which, by themselves, produce a significant variation in the brain activity pattern which is well known[56].

Faced with this situation, the investigators in the area considered some time ago of whether the techniques used to analyze the EEG or MEG activity were the adequate ones and, especially, if they were taking into account the physical characteristics of the electrical and magnetic signals to extract all the information they contained from them. A completely new line of investigation, the non-linear analysis methods, arose from this approach.

An alternative proposal: the non-linear analysis of brain activity methods

Non-linear analysis of brain activity has led to a radical advance, because of the problems of traditional analysis

methods to extract all the information offered by the neurophysiological techniques[57]. The fundamental assumption of these methods is that the EEG or MEG signals are generated by deterministic processes that reflect non-linear associations between neuron populations. Even more, it is assumed that the non-linearity of the brain is involved from the neural level[58], since the dynamic behavior of the individual neurons is governed by threshold and saturation phenomena. These two phenomena, that are based on the behavior of the neuron, are typically non-linear, that is, they reflect that the response of the neuron is not proportional to the stimuli received at each moment.

The first studies to apply this theoretical framework were conducted in 1985 in the monkey motor cortex[59] and was called "chaos analysis." Since then, these measures have been developing until reaching the current situation in which we have several nonlinear estimators, among which the estimators of brain signal complexity stand out. Many of these non-linear estimators take another basic characteristic of the brain signals into account that are overlooked by the traditional analysis methods: non-stationarity[57]. In a formal way, we could define stationarity as the property through which the basic statistical characteristics of the signal (mean, standard deviation, etc.) are maintained stable over time. This property is fundamental because it incorporates one of the essences of brain activity: change over time. The spectrum analysis methods assume that the brain signal collected over an ideal period of 5 minutes remains stable over time (it is stationary) so that we do not lose relevant information if we extract the power from a frequency band considering this period as a "whole." We now know that this is not true and that only during very variable periods of time does the brain signal remain stable so as to meet the stationarity requirements. The brain signal is essentially changeable and thus non-stationary.

By chance, leaving aside the field of Alzheimer's disease and cognitive deterioration, the Psychiatry setting has been where non-linear analysis has been used most and specifically, in the analysis of brain complexity. This is indicated by the large amount of works published up to date[60-69]. These studies focus on the application of the complexity-variability estimators as a diagnostic supportive element or in their use for the prediction of the therapeutic response in depression as well as in schizophrenia. However, first we are going to see in more detail what the non-linear methods of analysis of brain complexity consist in.

Introduction to the complexity concept: Lempel-Ziv Complexity

A basic characteristic describing the biological systems is their complexity. This complexity is due to the interaction of an uncountable number of structural units that operate within a large range of time and space scales that permit the body to adapt to the environment. To describe and quantify the mechanisms of these behaviors, the investigators have used new techniques derived from the complexity theory. However, what do we understand by complexity in the framework of biological signals? It is very complicated to offer a simple definition. Nonetheless, the complexity algorithms that are being used at present measure, in a general way, two aspects of the biological systems: 1. The grade of entropy or "predictability" of the system (approximate entropy, spectral entropy, etc.) and 2. The minimum number of variables, components or generators that make it possible to describe the behavior of this system (dimension of correlation, Lyapunov components, Lempel-Ziv complexity, etc., see Pereda et al.,[70]). If we follow the theory of Goldberger[71], healthy biological systems are the most complex and any disease or aging itself would produce a decrease in their complexity. After, we will see that things are more complicated and certain disorders are characterized by an increase in the complexity values[72].

As we have been able to verify, there are many estimators of the complexity of the biological systems that can be applied to the brain signals. However, for some time now, our research group has been working with an estimator called Lempel-Ziv complexity (LZ)[73] that is ideal for several reasons. Higher values of LZ complexity (on a scale from zero to one) correspond to greater complexity in the data analyzed. This measurement does not depend on whether the signal to be analyzed has been generated by a random or deterministic process[73]. Furthermore, it contains the notion of complexity in the statistical sense of the term (Shannon entropy) and in the deterministic one (Kolmogorov complexity)[74]. That is, the complexity of a sequence depends on the number of bits of the shortest program capable of generating it[73]. Therefore, this complexity measurement is related with the number of subsequences present in the original series and with their repetition rate[75].

Due to these characteristics, the LZ complexity has been applied in many different settings. For example, this metric has been used to analyze EEG and MEG signals of patients with Alzheimer's disease and mild cognitive deterioration[73, 76, 77] and to measure the depth of the anesthesia[78]. In addition, it has been demonstrated that the LZ complexity makes it possible to predict epileptic attacks[75]. Within the field of psychiatry, Li et al. have used the LZ complexity in patients with psychotic depression and schizophrenia[66] and our group has used this parameter with patients with ADHD[31], major depression[79] and schizophrenia[80].

Now that we know what the LZ complexity is used for and what its technical characteristics are, we should

understand what it means in the setting of brain signals. One of the forms of intuitively defining the LZ complexity is that this measure captures the temporal structure of the brain signal, that is, the LZ complexity is sensitive to changes that are produced in brain activity over time. We have already seen that change is one of the basic characteristics of the healthy brain. Healthy brains are in general more changing than the brains of patients with some conditions such as epilepsy or Alzheimer's disease. Equally, some drugs, such as some anesthetics, influence brain activity, making this more homogenous, that is, again decreasing this "normal" tendency to change[78]. However, this concept of "capacity to detect the change" is merely intuitive, and while we do not know the real meaning of this complexity measure, its clinical application is doubtful.

In this sense, Aboy et al.[81] conducted a fundamental study. The authors tested what type of characteristics of the signal would produce significant changes, in the sense of increase or decrease, in the LZ complexity. A first important piece of information, considering the limitations of the MEG and other neuroimaging techniques, is that noise (external interferences) does not significantly influence the LZ values. If we consider the predominance of certain frequency patterns, we observe that the predominance of low frequency activity (typical in some conditions as we have already seen) produces a marginal decrease of the complexity values. The factor that really produces an increase in the LZ complexity values is the "number of components of frequency" that a signal has. That is, as the changes in the patterns of frequency increase in the given recording of brain activity, it will show higher values in the LZ complexity. If the activity remains stable (or synchronized) in the given frequency (alpha, theta, beta, delta, gamma, etc.) the values of complexity significantly decrease. A larger variability in frequencies induces higher values of complexity. The clearest example of this tendency is found in generalized epileptic attacks, that are precisely characterized because the brain is synchronized pathologically during them (see " absence of attacks"). Immediately before the episode, and during it, the values of complexity decrease dramatically and then increase when the episode disappears[75]. A less dramatic but also significant case is that recently demonstrated in Alzheimer's patients[73, 77], in whom the complexity of their brain activity decreases in a generalized way when compared with healthy elderly subjects. Contrarily, we find conditions such as schizophrenia in which greater variability of the brain activity (remember the "dysrhythmia") is associated with an increase in the values of LZ complexity[66, 80].

It is clear that the application of this method in clinical populations is very recent and therefore there is much to be determined. However, it can be expected that any condition in which a functional alteration occurs in the brain, whether globally or focalized, would be a candidate for investigation with the LZ complexity parameter.

Lempel-Ziv complexity and mental disorders: diagnosis, evolution and prediction of the therapeutic response

Up to now, we have described some general characteristics of the non-linear analysis and of the LZ complexity, also on the benefits and technical characteristics of the parameter. However, we are still facing the most important challenge: to justify the grounds that support the motivation of using a complexity parameter for diagnosis, the follow-up of the evolution and prediction of the therapeutic response of the mental disorders. This motivation has three fundamentals that interact and that we are going to define in order of importance in the following:

1. The LZ complexity is, as we have already seen, less sensitive to external factors (noise) that may affect the physiological recordings. Based on our experience, the consequence of this lower sensitivity is that the brain signal recorded is not as affected by additional sources of variability, with the exception of those imposed by the conditions of the subject in whom the recording is being done. Within the setting of the MEG recordings, this property acquires special importance, since it is well known that the methods of traditional analysis are greatly influenced by the conditions of magnetic noise and artifacts that appear in the recording. This converts the measure of LZ complexity into an ideal one to perform follow-up studies that evaluate, for example, the effect of a certain psychopharmaceuticals and in which the patient undergoes a recording on several occasions to verify the changes produced by the drug in the brain activity. In this case, we could expect that these potential variations in the brain signal would be due exclusively to a change in the physiological condition of the patient and not to a change in the environmental conditions under which the recording is being performed. This has a fundamental importance to assure the relevance of the studies.
2. The LZ complexity is an index of the variability of the patterns of frequency of our brain activity. What does this variability depend on? The classical literature on EEG[82] mentions the importance of the preservation of the thalamocortical connections and corticocortical connections in the generation of brain rhythms. In fact, it is well known how neurodegenerative conditions in which there is significant disconnection (a clear example being that of Alzheimer's) produce a decrease in the variability of these rhythms and the tendency towards

the predominance of low-frequency bands.

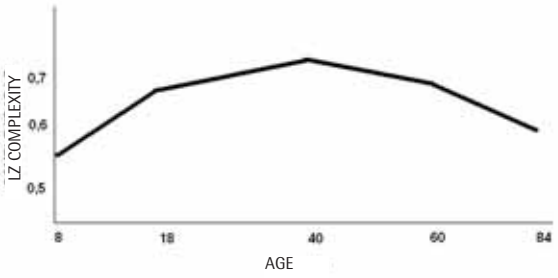
With these backgrounds, we could hypothesize that the variations in complexity also depend on the greater or lesser grade of connectivity of the brain generated by the signals we are recording. This hypothesis has been evaluated by at least two authors with contradictory results. Karl Friston (83, 84) tested this hypothesis in the context of research on neuropathology of schizophrenia. For Friston, the basic neurobiological problem underlying schizophrenia is disconnection between brain areas more than the lesion of a specific brain area. Under these conditions, he performed a study, programming a neural network that would simulate the characteristics which could be called a "brain with schizophrenia" and calculating the consequences of the functioning of this network in terms of complexity. Their results indicated that the disconnection is associated with an increase of the values of complexity. To some degree, this would be contradictory to the neurophysiological knowledge we have. Sporns et al.[85] performed a review of the literature on brain connectivity and complexity, focusing on the relationship between neuroanatomy and dynamics of the brain activity. The hypothesis of Sporns was that the most connected brains produce more complex functionings. To test their hypothesis, they also performed several simulations, verifying in this case that the most connected neural networks had higher functional complexity values.

It is clear that these works on simulation should be considered with great care and that we need studies that correlate the "real" brain connectivity with the complexity values of the neurophysiological signal. In this sense, our research group is carrying out an investigation that could be important to elucidate this basic problem. Following the hypothesis of Sporns et al. who proposed a positive relationship between complexity and connectivity, we performed a correlational study in which, on the one hand, we obtained the values of LZ complexity and on the other, we calculated the values of fractional anisotropy using magnetic resonance diffusion tensor imaging of 17 healthy adult patients[86]. The fractional anisotropy values are an indicator of axonal integrity and thus evaluate real brain connectivity. As we expected, there is a significant, and always positive, correlation between fractional anisotropy values and complexity values, that appears in zones that are fundamental for brain functioning, as the corpus callosum or the medial temporal lobe white matter. This indicates that better anatomical connectivity is associated with higher values of complexity.

What is the importance of this for the investigation of mental disorders? From our point of view, it is fundamental. However, in order to justify this statement, we are going on to the next point.

3. As we have just seen, it seems that several lines of evidence converge in a positive relationship between brain connectivity and complexity of the signal and this would be the reason why the conditions that occur with some type of disconnection process, such as dementias, would produce lower complexity values. However, things are not so simple. There is schizophrenia in which, generally, the highest values of complexity are found and in which one of the most important neuro-pathological hypothesis is that of disconnection. Isn't this contradictory? It is, unless we take into account the last piece of the puzzle: the evolutive character of the brain connectivity linked with neurodevelopment. Up to now, we have considered studies in which, as on another part is common, only the existence of significant differences between control groups and pathological groups has been considered. The patients sometimes have higher complexity values and sometimes lower ones, but the investigations do not go much beyond this. However, Anokhin et al.[87] and Meyer-Lindenberg[88] describe the fundamental fact: there is a rule that associates complexity values with the maturation process, in such a way that these values rise abruptly from childhood to adolescence, maintaining this tendency, although with sustained but not abrupt increase, until 60 years of age, when the samples of both authors ended. That is, there would be a standardized process of evolution of complexity associated with age.

   Recently, our group confirmed the finding for the age segment between childhood and adolescence[77], but demonstrated that the process of increase of complexity reaches the stabilization point after which the complexity values begin to slowly decrease until late old age[77]. All of the authors who have contributed to this line of investigation support that there should be a clear link between this pattern of growth-stabilization-reduction of the EEG-MEG complexity values and some basic process of neurodevelopment. At present, and considering the data that we have and that have been partially described, the process having the firmest base is that of maturation of the white matter and therefore (we return to the previous point) of establishment of effective nerve connections. In agreement with Bartzokis[89], the gray matter reaches its maximum volume in adolescence and begins to decrease on a negative slope until the old-age. The white matter evolves in a totally different way. First, there is a process of a very important increase of volume until adolescence, and this has a sustained maintenance until a maximum of 44 years when it slowly begins to decrease until old age. In fact, as we have been able to verify in figure 1, it is a process that almost perfectly emulates what we have described for the LZ complexity (figure 1).



The figure shows the relationship between complexity of the brain activity and age. As can be observed, the complexity values increase sharply until adolescence, maintain a sustained growth until approximately 40 years and after this age begin to decrease slowly. This reduction is more important after the ages of 65-70 years

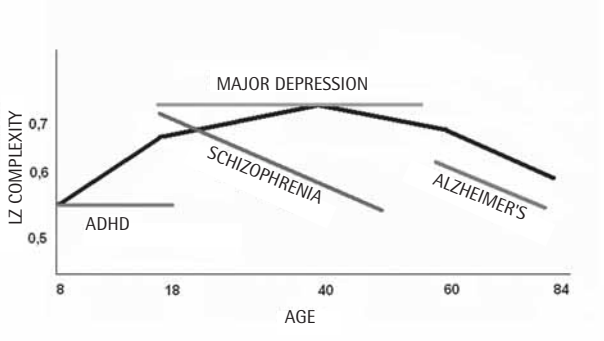
Figure 1

The consequences of these findings are very important. The first one is that we should not contemplate the differences between patients and control in a static way, but rather evolutively. The patients may have higher or lower complexity values, but what is truly important is to observe what their value is within the evolution process. Thus, patients with ADHD have lower frontal LZ values than the control children. However, even more important, while the controls sharply increase their complexity values until the age of 14, children with ADHD do not follow this tendency. Thus, the differences between patients and controls grow with age until reaching a sensitivity of 92% and specificity of 100% in children over 9 years (31).

The example of ADHD is important because it indicates the LZ complexity could be a diagnostic marker in all those mental and/or behavior disorders in which there is a neuromaturation component. Considering this premise, we should test the sensitivity of the LZ complexity in a disorder in which the debate between the neuromaturation and neurodegenerative hypotheses have attained great importance: that is, schizophrenia. Our results (80) were conclusive. The younger patients with schizophrenia had higher values of complexity than the controls of their same age. However, while the controls fulfilled the "rule" of increasing the LZ values based on age, patients with schizophrenia had the opposite tendency. At this point, it is important to indicate that the complexity values in ADHD children did not increase with age, but rather that the tendency was for these values to remain relatively stable. Patients with schizophrenia had a clearly significant negative slope, identical to that shown by Alzheimer's patients. These data would speak of a component of alteration of the "normal" process of maturation but also of a neurodegenerative component. Again, the fact that the scores of complexity have an evolutive process increases the model's sensitivity and specificity.

Finally, we are faced with a disorder in which there is no clear neuromaturation or neurodegenerative component but in which it is essential to establish a marker to try to predict the success of the therapy: major depression. In this case, the results would be especially interesting (see 79). Patients with major depression have higher initial values of complexity than the controls, but again their scores do not involve positively based on age but rather remained stable, showing a flat growth line. After 6 months of treatment with mirtazapine, that was effective in every case, the complexity values of the patients decreased in the entire brain, and even more important, the patients recovered the "normal" tendency for the complexity values to increase with age. Was there any data that would allow us to predict the good therapeutic response? The answer was complicated since all the patients improved significantly. Thus, we had to divide them into those with "improvement" (score on 17-item Hamilton scale between 7 and 10 points) and "total remission" (score on 17-item Hamilton scale less than 7 points). The results show: 1. that the younger patients, and above all, those with higher initial complexity values were within the group of "total remission" and 2. that those patients in which the complexity values had decreased more in the post-treatment measure were again those found within the group of "total remission."

In accordance with the data that we have presented in three conditions having enormous importance: that is, ADHD, schizophrenia and major depression, the calculation of LZ complexity allows us to establish a potential marker for the diagnosis, evolution and prediction of the therapeutic response. This statement is supported by the existence of a "normal" process of evolution of the complexity values based on age that is probably determined by the maturation of the brain white matter and by the establishment of effective brain connections. The condition itself may increase or decrease the complexity values but in every case "it breaks" this natural process of evolution. When, as in the ADHD, the disorder means a delay in the neuromaturation process, the scores of the LZ complexity also have a delay in their process of age-based increase. When the condition has a neurodegenerative component (Alzheimer and perhaps schizophrenia), this rupture is characterized by a sudden and progressive decrease of the values of complexity based on age and is not modified with the treatment. When the treatment is effective, as in our study on major depression, the values of complexity recover this natural tendency to growth.



The figure again shows the relationship between complexity of the brain activity and age, now including the variations associated with certain conditions. As can be observed, there are patterns that we consider merely "quantitative" differences, as in the case of Alzheimer's disease. Here, healthy subjects and patients have identical tendencies towards lower values based on age but in Alzheimer's, this reduction is sharper. In the remaining samples (ADHD, major depression, schizophrenia) the tendency of the values of complexity represent a rupture compared to the "normal" course of the evolution.

Figure 1

However, these last lines summarize the essence of change of the perspective that we are proposing with our study: against the traditional static point of view, we state that it is possible to capture the evolutive and dynamic component of mental disorders (90) and, what is more important, that this evolutive component maximizes the diagnostic and prognostic powers of the evaluation tools. Figure 2 presents a summary of these findings and of the relationship between the "normal" process of evolution of the LZ complexity and their variations in the conditions studied (figure 2).

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