Progress in Neuro-Psychopharmacology & Biological Psychiatry xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Complexity and schizophrenia

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ARTICLE INFO

Article history:
Received 2 February 2012
Received in revised form 27 March 2012
Accepted 31 March 2012
Available online xxxx

Keywords:
Complexity
Schizophrenia
Positive symptoms
Negative symptoms
Neuroleptics
Age

ABSTRACT

Complexity estimators have been broadly utilized in schizophrenia investigation. Early studies reported increased complexity in schizophrenia patients, associated with a higher variability or "irregularity" of their brain signals. However, further investigations showed reduced complexities, thus introducing a clear divergence. Nowadays, both increased and reduced complexity values are reported. The explanation of such divergence is a critical issue to understand the role of complexity measures in schizophrenia research. Considering previous arguments a complementary hypothesis is advanced: if the increased irregularity of schizophrenia patients' neurophysiological activity is assumed, a "natural" tendency to increased complexity in EEG and MEG scans should be expected, probably reflecting an abnormal neuronal firing pattern in some critical regions such as the frontal lobes. This "natural" tendency to increased complexity might be modulated by the interaction of three main factors: medication effects, symptomatology, and age effects. Therefore, young, medication-naïve, and highly symptomatic (positive symptoms) patients are expected to exhibit increased complexities. More importantly, the investigation of these interacting factors by means of complexity estimators might help to elucidate some of the neuropathological processes involved in schizophrenia.

1. Introduction

Schizophrenia is a chronic and severe neuropsychiatric disorder that produces a disruption of patients´ lives at different functional levels: neurochemical, neurophysiological, neuroanatomical, emotional, cognitive, and even social and familial. Clinically, schizophrenia presents with a range of "positive" symptoms including paranoia, delusions and hallucinations, as well as "negative" symptoms such as cognitive impairment, flattened affect and disorganized thinking. The intriguing characteristics of this disorder have attracted the interest of clinicians and basic investigators for decades. An important source of the attention focused on schizophrenia research derived from chaos and nonlinear systems theory. The connection between chaos and schizophrenia has some very deep cultural roots, and it is not surprising that relatively early studies were devoted to address such connection (Schmid, 1991). In the colloquial sense chaos connotes disorder, unpredictability and confusion (Schmid, 1991), and an intuitive interpretation might understand schizophrenia patients' behavior as unpredictable and therefore chaotic.

However, perhaps the most important feature of nonlinear analysis related to schizophrenia investigation is its capability to study the evolution of physical and biological systems over time (Paulus and Braff, 2003). Nonlinear analysis, including most of complexity estimators, is a suitable approach to characterize random-appearing series of events across time. For example, Paulus et al. (1994) investigated behavioral responses in schizophrenia patients and controls with a binary choice task paradigm to determine the sequential organization of their responses. According to authors' reports, schizophrenia patients exhibited both fixed and random behavioral responses over time that nonlinear methods may be able to quantify.

This notion of time-dependent disorders is closely related to the concept of dynamical diseases proposed by Mackey (Mackey and Glass, 1977; Mackey and Milton, 1987). The dynamical diseases are characterized by abnormal oscillations that suddenly appear in previously intact physiological systems (cardiac, hormonal, motor, etc.). Such systems are characterized by a certain rhythmicity. An der Heiden (2006) proposed that schizophrenia is another example of dynamical disease, since abnormal variations of dopamine levels might lead to erratic or chaotic patterns of neuronal activity. Such apparently chaotic neuronal activity can only be detected by methods with a high

Abbreviations: AMI, auto mutual information; ApEn, approximate entropy; CMI, cross mutual information; CN, neural complexity; CPT, continuous performance test; CΩ, omega complexity; D2, correlation dimension; EEG, electroencephalography; FD, fractal dimension; HFD, Higuchi's fractal dimension; LZC, Lempel-Ziv complexity; L1, first Lyapunov exponent; MEG, magnetoencephalography; MI, mutual information; MSE, multiscale entropy; SampEn, sample entropy..

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doi:10.1016/j.pnpbp.2012.03.015

temporal resolution such as the electroencephalography (EEG) or the magnetoencephalography (MEG). Nonlinear analysis methods applied to EEG and MEG signals have been broadly utilized to investigate abnormal brain dynamics in schizophrenia, and particularly complexity estimators (the subject of this special issue) acquired a high relevance.

Nonetheless, previously to any further comment, a key question should be answered: is it adequate to study the brain dynamics in schizophrenia using these measures? Breakspear (2006) answered this question in his excellent paper. First, the basic dynamical properties of neural systems are nonlinear. Second, the symptoms of schizophrenia are dynamic in nature, suggesting a disruption in nonlinear processes as state transitions in cortical systems. Moreover, the fluctuation of symptoms' severity during acute psychosis has a complex behavior. Finally, schizophrenia psychosis produces a failure of the stability, self-regulation and hierarchical ordering of brain systems. Due to all these reasons, the use of complexity measures to study the dynamical activity in schizophrenia is justified. Once this question was answered, we proceed to describe and discuss the application of complexity estimators to schizophrenia investigation.

2. Complexity estimators

Over the past 40 years, complexity estimators have revealed new insights into how to characterize nonlinear systems. Complexity methods can reveal features that are not available when other techniques are used. Therefore, nonlinear complexity algorithms for time series analysis can lead to a thorough understanding of the signals (Kantz and Schreiber, 1997). For this reason, these measures have been applied to very different fields. For instance, Lyapunov exponents have been used to demonstrate the occurrence of hyperchaos in chemical reactions (Eiswirth et al., 1992). Hirata (1989) estimated the fractal dimension of earthquakes, as seismicity has fractal structures in space, time and magnitude distributions. Correlation dimension (D2) has been estimated on bearing vibration acceleration time series for vibration fault diagnosis (Logan and Mathew, 1996). Complexity analysis has also been performed on the output power time series data from a synchronized transmitter-receiver pair of semiconductor lasers (Kane et al., 2006). Zhang et al. (2000) applied Lempel–Ziv complexity (LZC) measure and a new definition of the information complexity rate to electrocardiography recordings to recognize ventricular tachycardia and ventricular fibrillation.

Among all these insights, the brain has focused a great attention in the last years. The theory of nonlinear dynamics analysis has provided new complexity methods to comprehend the dynamics of the brain underlying processes. Complexity measures have been employed to study a broad variety of pathological and physiological states (for a review, see Stam, 2005). The complexity methods most widely applied to brain recordings (as EEG and MEG) are D2 and the first Lyapunov exponent (L1). L1 is a dynamic complexity measure that describes the divergence of trajectories starting at nearby initial states, while D2 computes the geometric complexity of the reconstructed attractor (Jelles et al., 1999). These measures have shown changes of the cerebral dynamics in different brain pathologies such as Alzheimer's disease (Besthorn et al., 1997), vascular dementia (Jeong et al., 2001a), Parkinson's disease (Anninos et al., 2000), epilepsy (Hornero et al., 1999), alpha coma (Kim et al., 1996), depression (Nandrino et al., 1994), or Creutzfeldt–Jakob disease (Babloyantz and Destexhe, 1988). Nevertheless, these classical measures have some drawbacks. Reliable estimation of D2 and L1 requires a large quantity of data and stationary and noise free time series (Eckmann and Ruelle, 1992). Since it is difficult to achieve these assumptions in physiological data, other complexity measures have been used for the analysis of brain time series. The dimensional complexity of a signal can also be estimated directly in the time domain using the fractal dimension algorithms proposed by Higuchi (1988), Maragos and Sun (1983), Petrosian (1995) or Katz (1988). Finally, other complexity measures, such as LZC, neural complexity (CN), omega complexity (CΩ) or multiscale entropy (MSE), have also been used to characterize the brain activity in several pathological states.

Schizophrenia has been widely studied with nonlinear measures due to its high prevalence and importance. Among these nonlinear measures, several complexity estimators have acquired a great significance in order to characterize the brain dynamics in this disorder. The complexity estimators applied to EEG and MEG recordings in schizophrenia are the following:

- Correlation dimension (D2) is a measure of complexity of the process being investigated, which characterizes the distribution of points in the phase space (Hornero et al., 1999). The dimension of an attractor can be thought of as a measure of the degrees of freedom or the complexity of the dynamics (Stam, 2005). Therefore, the larger the D2 of the attractor, the more complicated the behavior of the system. The estimation of D2 provides the lower bound to the actual number of variables required to model the system. Usually, D2 is computed by applying the method proposed by Grassberger and Procaccia (1983). In this procedure, D2 is based on determining the relative number of pairs of points in the phase-space set that are separated by a distance less than r (Hornero et al., 1999). There are two primary limitations in using D2 for analyzing EEG/MEG recordings. The first is that the D2 algorithms assume stationarity of the signals. The second limitation is that 10,000–50,000 data points are required to simulate space filling, in order to achieve good accuracy (Kroll and Fulton, 1991). As both requirements are difficult to achieve for EEG/MEG analysis, this method is not a good option for complexity analysis in schizophrenia.
- Lyapunov exponents can be considered dynamic measures of attractor complexity. Lyapunov exponents indicate the exponential divergence (positive exponents) or convergence (negative exponents) of nearby trajectories of the attractor in the phase space (Stam, 2005). The first Lyapunov exponent (L1), the highest value of the Lyapunov exponents of the attractor, reflects the sensitive dependence on the initial conditions. Thus, L1 is considered a measure of dynamical complexity (Kim et al., 2000). As for D2, Lyapunov exponents were also developed for stationary dynamics systems. Due to nonstationarity, the exponents exhibit random fluctuations with time and thus complexity estimation can vary with time (Serquina et al., 2008).
- Omega complexity (CΩ) is a single-value measure of the complexity of multichannel brain electromagnetic field data. The multichannel data are viewed as a series of momentary maps whose sequence over time forms a trajectory in the K-dimensional state space, where K denotes the number of channels (Saito et al., 1998). The geometric structure of this trajectory contains information about the complexity of the dynamics. The simpler the geometry of the trajectory, the smaller the subspace onto which it can be projected (Stam et al., 2000). CΩ ranges from a minimum value of 1, which corresponds with maximal coupling between the channels, to a maximum value of K that corresponds with no coupling at all among channels (Stam et al., 2000).
- Mutual information (MI) quantifies the amount of information gained about one signal from the measurement of another. Furthermore, MI between two time series is zero when those series are completely independent, while MI has a maximum value if both series are equal. MI is a measure of the linear and non-linear statistical dependencies between two time series (Jeong et al., 2001b). We can define two measures derived from MI: cross mutual information (CMI) and the auto mutual information (AMI). First, CMI quantifies the information transmitted from one signal to another (Jeong et al., 2001b). Applied to brain signals, the CMI measures the amount of information transmitted between certain areas of the brain. Second, AMI is defined as the MI between one signal and a time-delayed

Please cite this article as: Fernández A, et al, Complexity and schizophrenia, Prog Neuro-Psychopharmacol Biol Psychiatry (2012), doi:10.1016/j.pnpbp.2012.03.015