Progress in Neuro-Psychopharmacology & Biological Psychiatry 45 (2013) 258–266

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Review article

Complexity of spontaneous brain activity in mental disorders

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A R T I C L E I N F O

Article history:
Received 30 January 2012
Received in revised form 5 April 2012
Accepted 1 May 2012
Available online 8 May 2012

Keywords:
Mental disorders
Aberrant neural connectivity
Complexity
Nonlinear analysis
Multiple temporal scales

A B S T R A C T

Recent reports of functional and anatomical studies have provided evidence that *aberrant neural connectivity* lies at the heart of many mental disorders. Information related to neural networks has elucidated the nonlinear dynamical complexity in brain signals over a range of temporal scales. The recent advent of nonlinear analytic methods, which have served for the quantitative description of the brain signal complexity, has provided new insights into aberrant neural connectivity in many mental disorders. Although many studies have underpinned aberrant neural connectivity, findings related to complexity behavior are still inconsistent. This inconsistency might result from (i) heterogeneity in mental disorders, (ii) analytical issues, (iii) interference of typical development and aging. First, most mental disorders are heterogeneous in their clinical feature or intrinsic pathological mechanisms. Second, neurophysiologic output signals from complex brain connectivity might be characterized with multiple time scales or frequencies. Finally, age-related brain complexity changes must be considered when investigating pathological brain because typical brain complexity is not constant across generations. Future systematic studies addressing these issues will greatly expand our knowledge of neural connections and dynamics related to mental disorders.

Contents

1. Introduction

The human brain is a complex system, characterized by its dynamical neural communications in functionally specialized assemblies and long-range mutual interactions across these assemblies (Barabasi, 2009; Schnitzler and Gross, 2005; Sporns, 2011; Varela et al., 2001). This remarkable dynamical neural network is organized with a hierarchical organization that remains little understood (Horwitz, 2003), but which is universally characterized as a scale-free network (Barabasi, 2009; Ravasz and Barabasi, 2003; Steinke and Galan, 2011) that is regarded as fractal (self-similar structure over a range of scales). Output neurophysiologic signals derived from electroencephalography (EEG) and magnetoencephalography (MEG) therefore exhibit complex temporal fluctuations which are not simply attributable to noise but which instead reflect nonlinear dynamical processes (Abarbanel and Rabinovich, 2001; Friston, 1996; Sporns et al., 2000; Tononi et al., 1994, 1998). Consequently, the application of nonlinear analyses to neurophysiologic signals has presented a new avenue for ascertaining the intrinsic complex activity of the human brain and has provided a novel understanding of physiological processes in both healthy and pathological conditions (Fernandez et al., 2010; Stam, 2005). Historically, an algorithm developed

Abbreviations: AD, Alzheimer's disease; ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorders; C_N, neural complexity; D_2, correlation dimension; DTI, diffusion tensor imaging; EEG, electroenchaphalography; fMRI, functional MRI; MEG, magnetoencephalography; MSE, multiscale entropy.

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doi:10.1016/j.pnpbp.2012.05.001

Table 1
Brief explanations of each complexity analysis method reviewed in this paper.

Analysis methods	Brief explanation
Correlation dimension (D_2)	The first and the most frequently used measure. D_2 is a reflection of the 'degrees of freedom' necessary to describe the dynamics of the system (Grassberger and Procaccia, 1983a).
Omega-complexity	Global coordination across spatially distributed brain regions can be assessed as omega-complexity in multi channel EEG by assessing the structure of the covariance matrix across all EEG channels (Wackermann, 1996). Omega-complexity is by definition a global estimate of the number of uncorrelated brain processes active during the analysis period.
Neural complexity (C_N)	C_N is the measure that developed to quantify brain complexity relating functional segregation and integration in the nervous system. C_N is low when systems consist either completely uncorrelated or completely correlated. C_N is high when systems such as a neural system that displays local specialization with global integration. (Tononi et al., 1994)
Multiscale entropy (MSE)	MSE is a proposed entropy-based index of physiological complexity, evaluating signals at multiple temporal scales using temporal coarse-graining procedures, in recognition of the likelihood that the dynamical complexity of biological signals might operate across a range of temporal scales (Costa et al., 2005).
Coarse-grained entropy information	Coarse-grained entropy information is a measure of the chaoticity or complexity, and provides the same classification of states of chaotic systems.
Lempel-Ziv complexity (LZC)	LZC is based on counting the number of distinct substrings and their recurrence rate along the analyzed signal, assigns higher values to more complex data, and is well suited to the analysis of non-stationary biomedical signals of short length. (Lempel and Ziv, 1976)
Lyapunov exponent	Lyapunov exponents can be considered dynamic measures of attractor complexity. Lyapunov exponents estimate the mean exponential divergence (positive exponents) or convergence (negative exponents) of nearby trajectories of the attractor in the phase space. This reflects the sensitive dependence on initial conditions. A system possessing at least one positive Lyapunov exponent is chaotic.
Approximate entropy (ApEn)	ApEn is a family of statistics that quantifies the complexity or a signal irregularity, despite its stochastic or deterministic origin. ApEn assigns a nonnegative number to a sequence, with larger values corresponding to more complexity or irregularity in the data (Pincus, 1991).

by Grassberger and Procaccia has enabled the practical application of nonlinear analysis to various observations (Grassberger and Procaccia, 1983a,b). Rapp et al. (1985) and Babloyantz et al. (1985) initially applied nonlinear analyses to practical EEG data in 1985. Beginning with these studies, the potential utility of nonlinear analyses in the field of psychiatry was recognized in the nineties (Globus and Arpaia, 1994). Later, several nonlinear dynamical analytic methods were introduced (Table 1), offering a range of new insights into normal and altered brain function along with recent advances in computer technology (Fernandez et al., 2010; Stam, 2005).

However, considering that about 50% of the brain's energy is used to derive signals along axons and across synapses, effective neural interactions are functionally necessary (Laughlin and Sejnowski, 2003). Recent morphological and neurophysiological studies support the existence of *aberrant neural connectivity* related to many mental disorders. For example, the pathology of Alzheimer's disease (AD), characterized as generalized neuronal cell loss, neurofibrillary tangles, and senile plaques in different widespread brain regions, entails local neuronal death and deficiency of neurotransmitters (Dringenberg, 2000) and altered long cortico–cortical association fibers (Kavcic et al., 2008). These pathological changes can be understood in terms of a neocortical *disconnection syndrome* (Delbeuck et al., 2003). As for schizophrenia, the idea of dysfunctional integration has been postulated since Bleuler (Bleuler, 1911) coined the term *schizophrenia*. Since the *disconnection hypothesis* was first proposed as a pathophysiologic mechanism in schizophrenia (Friston, 1996, 1998), evidence of abnormal functional connectivity in schizophrenia has been accumulating. The hypothesis has become widely accepted. In recent years, commonality of aberrant neural connectivity has also been inferred for autism spectrum disorders (ASD), a set of pervasive neurodevelopmental conditions with onset in early childhood and widely various life-long signs and symptoms characterized by deficits in social interaction, communication, and restricted stereotyped or repetitive behaviors (American Psychiatric Association, 2000). The theory of 'local overconnectivity and long-distance underconnectivity' has attracted considerable attention. Evidence from structural and functional studies support this theory as a core underlying pathological mechanism of ASD (Belmonte et al., 2004; Courchesne and Pierce, 2005; Geschwind and Levitt, 2007; Wass, 2011). Although few studies have been conducted on the issue and although systematic review is lacking, other mental disorders such as mood disorders (Carballedo et al., 2011; Frodl et al., 2010), dissociative disorders (Bob and Svetlak, 2011), attention-deficit hyperactivity disorder (ADHD) (Clarke et al., 2008; Murias et al., 2007) and dyslexia (Paulesu et al., 1996) apparently share a similar pathological background. Consequently, the notion of 'aberrant neural connectivity' might play a crucial role in the pathology of mental disorders.

Aberrant neural connectivity in mental disorders might be reflected by abnormal complexity behavior in neurophysiologic signals. For example, Friston assessed the effect of the degree of connectivity within neuronal populations and measures of complexity using synthetic neuronal models, reporting that aberrant or reduced connectivity increased EEG complexity (Friston, 1996). Sporns et al. (2000) reviewed studies of brain connectivity and complexity, particularly addressing the relation of neuroanatomy and brain activity dynamics. They inferred that disconnection is associated with an increase of complexity (Sporns et al., 2000). Given the importance of aberrant neural connectivity in various mental disorders and assuming that complexity parameters are sensitive to the disconnection of the brain activity, it is natural to apply nonlinear methods to quantify the intrinsic dynamic complexity of neurophysiologic signals.

Large-scale integration is performed by synchronization among neurons and neuronal assemblies evolving in different frequency ranges. For that reason, specific frequency bands might have their own different functional roles; several rhythms can temporally coexist (Basar et al., 2001; Klimesch, 1999; Klimesch et al., 2007; Varela et al., 2001; von Stein and Sarnthein, 2000). In general, higher-frequency oscillations originate from a smaller neuronal populations, whereas low-frequency oscillations encompass larger populations or long-range coordination (Hutcheon and Yarom, 2000; Schnitzler and Gross, 2005; von Stein and Sarnthein, 2000) and, depending on the efficiency of short-range and long-range connectivities, correspond to various cognitive processes (Buzsaki and Draguhn, 2004). Based on these findings, it is reasonable it infer that complexity with multiple temporal scales or frequencies can provide additional insights into the network controlling mechanisms in the human brain that can index the underlying abnormal physiological dynamics that are known to be altered in mental disorders.

Recent advances in nonlinear dynamics applied to neurophysiologic signals have elucidated the physiological complexity of mental disorders in terms of neural connections. Various complexity measures have been developed and have been applied to quantify neurophysiologic signal complexity. Extensive reviews of nonlinear analyses have been conducted with intelligible descriptions of the respective measures (Breakspear, 2004, 2006; Dauwels et al., 2010; Fernandez et al., 2010; Jeong, 2004; Pincus, 2006; Stam, 2005).

Hereinafter, empirical studies of complexity analyses in respective mental disorders are overviewed, with particular note of their clinical implications in terms of aberrant neural connectivity. Their potential importance in the investigation of complexity with multiple temporal