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Is mental illness complex? From behavior to brain

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ABSTRACT

A defining but elusive feature of the human brain is its astonishing complexity. This complexity arises from the interaction of numerous neuronal circuits that operate over a wide range of temporal and spatial scales, enabling the brain to adapt to the constantly changing environment and to perform various amazing mental functions. In mentally ill patients, such adaptability is often impaired, leading to either ordered or random patterns of behavior. Quantification and classification of these abnormal human behaviors exhibited during mental illness is one of the major challenges of contemporary psychiatric medicine. In the past few decades, attempts have been made to apply concepts adopted from complexity science to better understand complex human behavior. Although considerable effort has been devoted to studying the abnormal dynamic processes involved in mental illness, unfortunately, the primary features of complexity science are typically presented in a form suitable for mathematicians, physicists, and engineers; thus, they are difficult for practicing psychiatrists or neuroscientists to comprehend. Therefore, this paper introduces recent applications of methods derived from complexity science for examining mental illness. We propose that mental illness is loss of brain complexity and the complexity of mental illness can be studied under a general framework by quantifying the order and randomness of dynamic macroscopic human behavior and microscopic neuronal activity. Additionally, substantial effort is required to identify the link between macroscopic behaviors and microscopic changes in the neuronal dynamics within the brain.

1. Introduction

For most layperson and even non-psychiatric medical professionals, mental illness is considered as a complex disorder, not only because the diagnosis of psychiatric disorders is rarely one simple term that describes the patient's psychopathology, but also the multidimensional nature of mental illness requires integrated care that includes biological, psychological, and social management. Intriguingly, notable pioneers of psychiatry, such as Sigmund Freud, contended that the complexity of mental illness can be understood by studying the dynamics of psychic function (Freud and Strachey, 1989). When constructing his psychodynamic theory, Freud applied information from the field of physics to the human mind, using physical models to describe how psychic energy is connected within the components of the mind.

Although Freud's dynamic view of the human mind is appealing, understanding of the psychodynamic processes of the mentally ill has been hindered by a lack of rigorous analysis methods (Rapp et al., 1991). By the late twentieth century, research on the human brain had become a fascinating interdisciplinary science that no longer only belonged to the fields of psychiatry, neurology, and neuroscience (Haken, 2002). Concepts from mathematics, physics, and computer science are increasingly applied to the study of the brain and the dysfunctions associated with the mentally ill. In the past few decades, attempts to employ these non-medical disciplines to better the understanding of complex human behaviors have been conducted. Additionally, a new discipline called the science of complexity is emerging (Ehlers, 1995). The cognitive disorganization of schizophrenia or the unstable mood fluctuations of bipolar disorder support the notion that analysis of nonlinear dynamics (or a broader term, complexity science) may increase insight into complex human behaviors (Freeman, 1992).

The roots of complexity science were established by Poincare at the end of nineteenth century (Poincare, 1881), and have been significantly developed in the past decades. The central concepts of complexity science, such as fractals and chaos, have been applied to the study of cardiac electrical activities (Glass and Mackey, 1988; Goldberger et al., 1984, 1985). Most of these pioneering studies found that the physiological output of healthy people is typically more complex than their output in a pathological state or when aging (Goldberger et al., 2002b; Lipsitz and Goldberger, 1992; Vaillancourt and Newell, 2002). The methods derived from complexity science have also shown potential for quantifying the behavioral problems or disease courses of various psychiatric

Abbreviations: BOLD, blood oxygen level dependent; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MSE, multiscale entropy.

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disorders (Paulus and Braff, 2003). For example, schizophrenic patients showed more predictable behavior (i.e., less complex) compared to healthy controls in a consecutive binary choice task (Paulus et al., 1996). Similarly, a self-rated consecutive daily record of mood completed by patients with bipolar disorder had a more organized pattern (i.e., less complex) than that completed by healthy controls (Gottschalk et al., 1995).

In recent years, the concept of complexity has also been applied to the analysis of neurophysiological data, such as an electroencephalogram (EEG). Among the various types of mental illness, the normal organization of EEG activities deteriorates and is replaced by a number of abnormal dynamics (Fernandez et al., 2010a). For example, schizophrenic patients were found to have abnormal EEG complexity, which can be reversed using antipsychotics (Takahashi et al., 2010). A similar reversing effect of antidepressants on abnormal EEG complexity was also found for depressive disorders (Mendez et al., 2012). In this context, the concept of complexity provides a useful and promising tool for clinical psychiatry that may benefit the evaluation of the disease process or treatment outcome.

Although considerable efforts have been devoted to examining the abnormal dynamic processes involved in mental illness, unfortunately, the main features of complexity science are typically presented in a form suitable for mathematicians, physicists, and engineers; thus, they are difficult for practicing psychiatrists or neuroscientists to comprehend. Therefore, this study introduces recent applications of methods derived from complexity science for examining mental illness.

2. What is complexity?

Generally, complexity refers to a system with multiple components that are intricately entwined together, such as the subway network of the New York City. In the analogy of human physiology, such complexity can be viewed as numerous body components interacting at levels ranging from molecules, cells, to organs. Conventionally, scientists employ a reductionist approach to disassemble the system into constituent pieces, examine each component, and, finally, reassemble them, recreating the original entity. However, this approach is often unrealistic. In most circumstances, we can only observe the macroscopic output of physiological functions, such as an EEG, heart rate, and respiration, and mental functions, such as cognition, mood, and behavior. Even using the most sophisticated imaging techniques that employ functional magnetic resonance imaging (fMRI), a change in the intensity of a single brain voxel still represents compound responses from millions of neurons.

Therefore, a reasonable method for measuring complexity is to observe a system's behavior in temporal time scales. A system may behave in either an ordered or random manner. However, the physical meaning of the randomness does not equal that of the complexity (Goldberger et al., 2002a). The measurement of complexity should also incorporate the amount of information conveyed in the system. Differences in the physical meaning of randomness and complexity can be illustrated intuitively using texts as an example (Fig. 1). A monkey typing produces random and incomprehensible text (Fig. 1A), whereas the unfortunate writer in the psychological horror movie *The Shining* (1980) repeatedly typed the sentence "all work and no play makes Jack a dull boy" on reams of paper (Fig. 1C). The monkey typing represents a random process, and the unfortunate writer display compulsive and ordered behavior. Unlike Shakespeare's famous quote (Fig. 1B), both random and ordered conditions barely convey information that is rich enough to be "complex."

3. Quantification of complexity

The difference in the physical meaning between complexity and randomness can be further shown using the heart rate as an example. Randomness is typically assessed using entropy-based methods by quantifying the regularity (orderliness) of a time series (Pincus, 1991; Richman and Moorman, 2000; Rosso et al., 2002). Fig. 2A shows that conventional entropy increases in correlation with irregularity, reaching a maximum in completely random systems. In this context, the heart rate of a healthy person has higher entropy than that associated with pathological conditions, such as myocardial infarctions (Makikallio et al., 1997) or heart failure (Ho et al., 1997). However, this conventional entropy-based approach can yield contradictory results, where a high degree of entropy is observed in certain pathological conditions, such as the heart rate rhythm during atrial fibrillation (Costa et al., 2003a). Therefore, a meaningful measure of complexity should be justified between the order and randomness, as shown in Fig. 2B (Peng et al., 2009).

A meaningful measure of complexity has been proposed by quantifying entropy over multiple time scales, also known as multiscale entropy (MSE) (Costa et al., 2002, 2005). MSE was developed based on sample entropy (Richman and Moorman, 2000) and has been successfully applied to differentiate the complexity of heart rate rhythms in various physiological conditions (Cheng et al., 2009; Norris et al., 2008a, 2008b; Yang et al., 2011). MSE has also been applied to other types of biomedical signals, such as electromyograms (Istenic et al., 2010), the human gait (Costa et al., 2003b) and postural sway (Costa et al., 2007), and EEGs (Catarino et al., 2011; Escudero et al., 2006; Mizuno et al., 2010; Park et al., 2007; Protzner et al., 2011; Takahashi et al., 2010).

Other measures of complexity have also been proposed and applied to the study of mental illness based on various biomedical signals, as shown in Table 1. These methods include approximate entropy (Caldirola et al., 2004; Glenn et al., 2006; Yeragani et al., 2003), the correlation dimension (Gottschalk et al., 1995), Hurst exponent (Lai et al., 2011), Lempel–Ziv complexity (Fernandez et al., 2009, 2010b, 2011; Mendez et al., 2012), and the Lyapunov exponent (Chae et al., 2004; Roschke et al., 1995; Srinivasan et al., 2002). Significantly, essential differences in the physical meanings exist among these methods. For example, the correlation dimension, Hurst exponent, and Lyapunov exponent are chaos-based estimations of complexity; Lempel–Ziv statistics are based on algorithmic complexity (i.e., Komologrov complexity) by reducing the fluctuation of a time series to a symbolic sequence. Additionally,

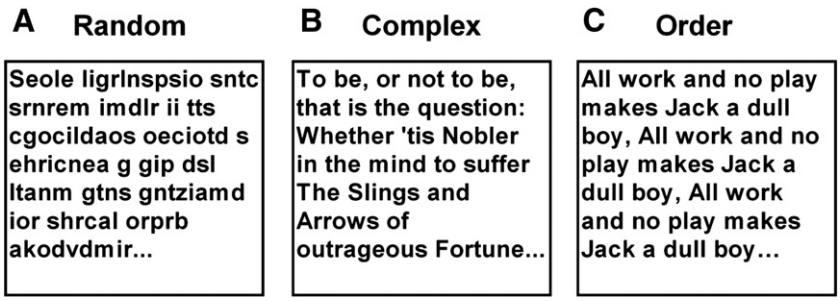

Fig. 1. The working definition of complexity using texts as examples: (A) Random text produced by a monkey typing; (B) a famous quote from Shakespeare's play *Hamlet*; and (C) a sentence repetitively typed by an unfortunate character in the psychological horror movie *The Shining* (1980).

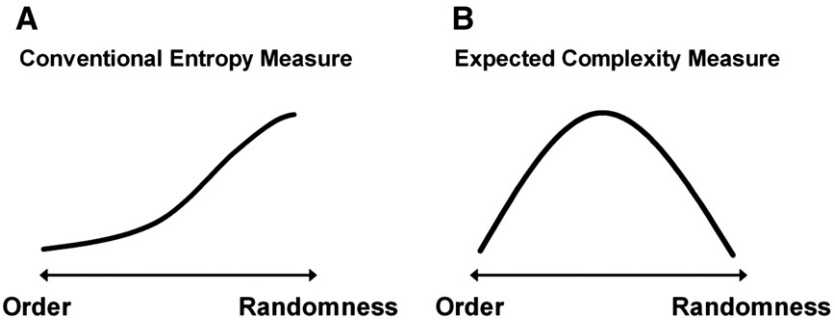

Fig. 2. The difference in physical meaning between (A) a conventional entropy and (B) expected complexity measures.

as mentioned previously, the conventional entropy-based method is merely a measure of randomness.

4. The evaluation of complexity analysis for the study of mental illness

How are these seemingly elaborate results interpreted? Are complexity measures simply up and down in the mentally ill? Do these results merely prove the obvious? Interpreting the complexity measures calculated from neurophysiological signals has not been thoroughly addressed. Most previous studies have focused on schizophrenia. However, both increased and decreased complexity in electrical activity in the brain of schizophrenic patients has been reported based on different complexity methods (Table 1) (Fernandez et al., 2011; Hoffmann et al., 1996; Koukkou et al., 1993; Li et al., 2008; Na et al., 2002; Takahashi et al., 2010). Such discrepancy in interpreting complexity can be also found in studies of daily self-ratings of mood (Glenn et al., 2006; Gottschalk et al., 1995; Yeragani et al., 2003) and dementia (Escudero et al., 2006; Fernandez et al., 2010b; Mizuno et al., 2010). The inconsistent results of these studies may be because of the different physical meanings of complexity methods or the time scale examined. Furthermore, EEG investigations may be limited by the relatively poor resolution of spatial dimensions for isolating changes in complexity in certain brain regions that are related to the pathophysiology of mental illness.

Recent advances in fMRI imaging and magnetoencephalography (MEG) have enhanced understanding of the neural correlates of complexity measures. Application of the Lempel–Ziv statistics for MEG data have shown that abnormal complexity can be pinpointed in the frontal lobe during depression (Mendez et al., 2012), dementia (Fernandez et al., 2010b), and attention-deficit/hyperactivity disorders (Fernandez et al., 2009). A recent study of the Hurst exponent calculated from the resting-state fMRI time series found a shift to randomness in brain

Table 1
The application of methods derived from complexity science in the study of mental illness.

Study	Observed entity	Method	Findings in patients compared to healthy controls
Schizophrenia			
(Koukkou et al., 1993)	EEG	Dimensional complexity	Increased dimensional complexity
(Roschke et al., 1995)	EEG	Lyapunov exponent	Increased fractal complexity
(Paulus et al., 1996)	Consecutive binary choice task	Dynamical entropy	Both fixed and random behavioral sequence responses.
(Hoffmann et al., 1996)	EEG	Dimensional complexity	Reduced dimensional complexity
(Na et al., 2002)	EEG	Mutual information analysis	Reduced complexity
(Mujica-Parodi et al., 2005)	ECG	Symbolic dynamic complexity	Reduced symbolic dynamic complexity
(Bar et al., 2007)	ECG	Approximate entropy	Reduced approximate entropy
(Li et al., 2008)	EEG	Lempel–Ziv complexity	Increased Lempel–Ziv complexity
(Takahashi et al., 2010)	EEG	Multiscale entropy	Increased multiscale entropy for long-term scales
(Fernandez et al., 2011)	MEG	Lempel–Ziv complexity	Increased Lempel–Ziv complexity
Mood disorder			
(Nandrino et al., 1994)	EEG	Nonlinear forecasting	Reduced complexity
(Gottschalk et al., 1995)	Daily self-rated mood	Correlation dimension	Low-dimensional chaotic process
(Glenn et al., 2006)	Daily self-rated mood	Approximate entropy	Increased approximate entropy 60 days before a mood episode
(Leistedt et al., 2011)	ECG	Multiscale entropy	Reduced heart rate complexity
(Mendez et al., 2012)	MEG	Lempel–Ziv complexity	Increased Lempel–Ziv complexity
Anxiety disorder			
(Srinivasan et al., 2002)	ECG	Lyapunov exponent	Reduced fractal complexity
(Caldirola et al., 2004)	Respiration	Approximate entropy	Increased approximate entropy for respiratory parameters
(Chae et al., 2004)	EEG	Lyapunov exponent	Reduced fractal complexity
Dementia			
(Escudero et al., 2006; Mizuno et al., 2010)	EEG	Multiscale entropy	Decreased and increased multiscale entropy in short- and long-term scales, respectively
(Fernandez et al., 2010b)	MEG	Lempel–Ziv complexity	Reduced Lempel–Ziv complexity
Autism			
(Lai et al., 2011)	Resting fMRI	Hurst exponent	Shift to randomness
Attention-deficit/hyperactivity disorder			
(Fernandez et al., 2009)	MEG	Lempel–Ziv complexity	Reduced Lempel–Ziv complexity
Sleep disorder			
(Yang et al., 2011)	ECG	Multiscale entropy	Reduced multiscale entropy during sleep period

regions related to social, motor organization, and connection hubs (Lai et al., 2011). We have recently applied the MSE complexity method to the analysis of blood oxygen level dependent (BOLD) signals obtained from resting state fMRI in older and younger normal adults, and found that complexity of BOLD signals was reduced in older adults, compared with younger people (Yang et al., 2012). Importantly, we also found that the complexity of BOLD signals in default mode brain network was correlated positively to the various domain of cognitive functions, thus providing a quantitative measure of brain function using the complexity analysis (Yang et al., 2012). Future studies should examine the structural and functional correlates of complexity measures of intrinsic brain activity among various psychiatric disorders. Such studies may provide new insights into diagnosing and differentiating subtypes of mental illness.

In addition, to advance the use of complexity measures in psychiatry, more studies are required to correlate psychopathology with complexity analysis. This issue has been primarily explored in heart rate studies. For example, although not based on complexity analysis, reduced vagal activity measured by high-frequency components of heart rate variability were found to be associated with the increased severity of psychosis or elated moods (Henry et al., 2010). Reduced physiological complexity of the heart rate measured using the MSE method was found to be correlated exclusively to poor sleep ratings among patients with major depression and primary insomnia (Yang et al., 2011). For EEGs, studies of Alzheimer's dementia found that an altered MSE complexity in the surface EEG may be correlated to cognitive functions (Mizuno et al., 2010; Tsai et al., 2012).

Another issue of complexity analysis is whether the measure can evaluate the treatment effect or predict the outcome of mentally ill patients. Two pioneering reports explored the use of complexity analysis in the treatment effect of antipsychotics for schizophrenia (Takahashi et al., 2010) and antidepressants for depression (Mendez et al., 2012). To date, no study has evaluated the use of complexity analysis in the outcome evaluation of psychiatric disorders, such as predicting relapses in mood episodes.

5. Systemic approaches to biological psychiatry

Although complexity analysis is still far from being practically applied in daily clinical practice, complexity science may play a crucial role in understanding the system dynamics of mental illness (Bender et al., 2006). The psychopathology observed in everyday practice follows the pattern of order and randomness. Fig. 3 shows that healthy mental function is complex and can deteriorate into two distinct pathological paths, that is, order and randomness. From a macroscopic perspective, patients with cluster-B personality traits often exhibit impulsive behaviors that have a sense of randomness, whereas patients with obsessive–compulsive personalities may perform actions in an orderly and rigid fashion. Similar concepts can be extended to the observation of cognition, emotion, speech, thought, and other mental functions, such as stereotypy versus irrational behavior, apathy versus confabulation, echolalia versus word salad, and fixed delusions versus flight of ideas. However, randomness is not complex regarding the information conveyed in random behavioral patterns.

The important question is whether these macroscopic observations of psychopathology can be linked to microscopic phenomenon, such as neuronal activity. From a systemic perspective, complexity reflects a system's ability to adapt to the constantly changing environment (Goldberger et al., 2002b; Peng et al., 2009). Such adaptation is often impaired in mentally ill patients, producing either ordered or random behavioral patterns. However, considering that the brain is the organ of mind, the adaptability of mental functions must result from the underlying neuronal plasticity, which can be plausibly measured by complexity analysis at the microscopic level. We propose that mental illness is loss of brain complexity (Fig. 3) and the complexity of mental illness can be examined under this generic framework. Furthermore, substantial effort is required to identify the link between macroscopic behaviors and microscopic changes in the neuronal dynamics within the brain.

In summary, to understand the complexity of mental illness, an approach that integrates mathematics, physics, and neuroscience is required. Psychiatry has long been considered a second-class field of science and medicine due to lack of biomarkers (Singh and Rose, 2009). Despite substantial efforts, the causes of numerous psychiatric disorders remain unclear; even categorizing such disorders precisely have been difficult. Complexity analysis may have the potential to provide a new dimension to the understanding of mental illness.

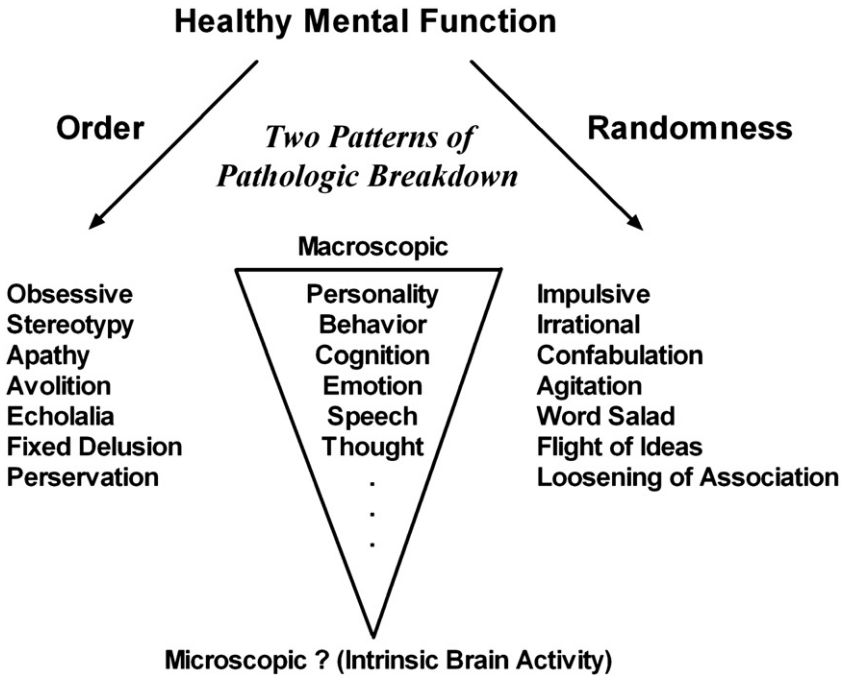

Fig. 3. Schematic illustration of the deterioration of healthy mental function into either an ordered or random pattern.

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