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Lempel–Ziv complexity in schizophrenia: A MEG study

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HIGHLIGHTS

- Schizophrenic patients show higher complexity values as compared to controls.
- Schizophrenic patients showed a tendency to reduced complexity values as a function of age while controls showed the opposite tendency
- The tendency observed in schizophrenic patients parallels the tendency observed in Alzheimer disease patients.

ABSTRACT

Objective: The neurodevelopmental–neurodegenerative debate is a basic issue in the field of the neuropathological basis of schizophrenia (SCH). Neurophysiological techniques have been scarcely involved in such debate, but nonlinear analysis methods may contribute to it.
Methods: Fifteen patients (age range 23–42 years) matching DSM IV-TR criteria for SCH, and 15 sex- and age-matched control subjects (age range 23–42 years) underwent a resting-state magnetoencephalographic evaluation and Lempel–Ziv complexity (LZC) scores were calculated.
Results: Regression analyses indicated that LZC values were strongly dependent on age. Complexity scores increased as a function of age in controls, while SCH patients exhibited a progressive reduction of LZC values. A logistic model including LZC scores, age and the interaction of both variables allowed the classification of patients and controls with high sensitivity and specificity.
Conclusions: Results demonstrated that SCH patients failed to follow the "normal" process of complexity increase as a function of age. In addition, SCH patients exhibited a significant reduction of complexity scores as a function of age, thus paralleling the pattern observed in neurodegenerative diseases.
Significance: Our results support the notion of a progressive defect in SCH, which does not contradict the existence of a basic neurodevelopmental alteration.

1. Introduction

Schizophrenia (SCH) is a serious psychiatric disorder with a range of "positive" symptoms including paranoia, delusions and hallucinations, as well as "negative" symptoms such as cognitive impairment, flattened affect and disorganised thinking. Symptoms most commonly present in late adolesence in males and somewhat later in females, and the first psychotic episode is commonly preceded by a "prodromal" phase of progressively more severe symptoms which can last months or years.

Clinically, it is a common observation that a functional decline starts around the time of the late prodromal phase or around the first psychotic episode (Tully and McGlashan, 2006), suggesting that a neurodegenerative process may be at the core of SCH. However, this neurodegenerative perspective has been challenged by the so-called neurodevelopmental theory (Murray and Lewis, 1987; Rapoport et al., 2005) which considers SCH as the product of a deviation in neurodevelopmental processes that occurs before the onset of clinical symptoms (Rapoport et al., 2005). The neuro-

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developmental vs. neurodegenerative debate is therefore a basic issue in the biology of SCH.

Magnetoencephalography (MEG) has been widely used in SCH research. MEG studies have replicated the well-known pattern of fronto-temporal low-frequency activity observed in EEG, and have also demonstrated abnormal sensory gating and basic cognitive processing (Canive et al., 1996; Kissler et al., 2000; Fehr et al., 2003; Wienbruch et al., 2003; Edgar et al., 2005; Lopez-Ibor et al., 2008; Naatanen and Kahkonen, 2009). A further step in this research is non-linear dynamics analysis (NDA). Complexity analysis is a particular form of NDA as applied to human brain activity, e.g. as measured using electroencephalography (EEG) or magnetoencephalography (MEG). EEG–MEG complexity analyses usually measure the regularity/predictability of brain oscillations and/or attempt to estimate the number of independent oscillators underlying the observed signal (Lutzenberger et al., 1995; Jeong et al., 1998). Numerous complexity measures have been proposed (see Tononi et al., 1998) including: dimensional complexity, algorithmic complexity, neural complexity, fractal dimension, first Lyapunov component, correlation dimension, Lempel–Ziv Complexity (LZC), etc. (Elbert et al., 1992; Koukkou et al., 1993; Jeong et al., 1998; Kim et al., 2000; Kotini and Anninos, 2002; Li et al., 2008). For example, the dimensional complexity refers to the classical method of the so-called correlation dimension. The algorithmic or Kolmogorov complexity is defined as the length of the string shortest description in some fixed description language. Finally, the neural complexity is a statistical measure that captures regularities based on the deviation from independence among subsets of a system. In our study we have used the LZC, a measure for finite sequences that assigns larger values to more complex data (Lempel and Ziv, 1976). LZC is an appropriate measure of complexity in Kolmogorov's sense.

Previous studies of neural activity complexity have provided somewhat contradictory results, with increased or decreased complexity values seen in SCH patients, depending upon the characteristics of the patient sample and the particular complexity parameter utilised. However, many studies revealed a pattern of increased complexity values, especially in frontal areas, in SCH patients (Elbert et al., 1992; Saito et al., 1998; Na et al., 2002; Irisawa et al., 2006; Li et al., 2008). This may be related to the increased "irregularity" of SCH patients' behaviour (Koukkou et al., 1993).

Interestingly, according to Anokhin et al. (1996) and Meyer-Lindenberg (1996), there is an association between brain maturation and complexity scores, with a brisk increase of EEG complexity from childhood to early adolescence, and a further sustained increase from adolescence to late adulthood. Thus "normal" brain development seems to be characterised by an increase of complexity scores, at least until early senescence (Fernández et al., 2010).

However, Fernández et al. (2009) found that this normal pattern of increasing complexity with age is absent in attention deficit-hyperactivity disorder (ADHD), a disease with clear neurodevelopmental components (Shaw et al., 2007). In order to further investigate the possible involvement of abnormal complexity in neurodevelopmental disorders, we therefore decided to measure LZC scores in a group of SCH patients and healthy controls. Our objective was twofold; first we tested a potentially abnormal pattern of complexity evolution as a function of age in SCH patients. Subsequently, the pattern of increased complexity in SCH was tested.

2. Methods

MEG epochs were analysed by means of LZC. LZC is a measure of finite sequences and is essentially a measure of the number of distinct substrings and the rate of their occurrence along the sequence (Lempel and Ziv, 1976). (Aboy et al. (2006) investigated the factors that affects LZC and concluded that LZC represents an estimate of the number of different frequency components that actually compose the brain signals. See the Appendix A for details of the analysis.

2.1. Subjects

Fifteen right-handed patients receiving care at the San Carlos University Hospital Institute of Psychiatry and Mental Health, who fulfilled the DSM-IV diagnostic criteria for SCH, were included in the study. Diagnosis was made with the Spanish version of the SCID-I (First et al., 1997). In order to obtain a homogeneous sample, we only included patients exhibiting a high degree of positive psychotic symptoms. The Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) was used to evaluate positive symptoms of schizophrenia. According to a previous study (Lopez-Ibor et al., 2008), a minimum score of 70 (of a maximum of 165), and a minimal score of 29 (of maximum of 65) in the delusional activity subscale, were required to enter in the study.

The control group consisted of fifteen right-handed sex- and age-matched control subjects with no history of psychiatric disorder (Table 1). Subjects with a history of neurological diseases, head trauma, or drug abuse were excluded from the study. Consequently, the data set consists of 30 sex- and age- jointly matched case-control pairs.

Patients matching the above described criteria were consecutively submitted to MEG scans. At the time of the study, all of the schizophrenic patients were using atypical antipsychotic medication. In addition, two were on the typical antipsychotic haloperidol. Table 1 shows the dose equivalent of the medications and the duration of the illness. Prior to MEG recording, all subjects provided informed consent after being informed as to the technical and ethical considerations of the research. The study was approved by the ethics committee of the San Carlos University Hospital in Madrid. This sample has been partially described elsewhere (Lopez-Ibor et al., 2008).

2.2. Data collection

MEG recordings were acquired with a 148-channel whole-head magnetometer (MAGNES 2500 WH®, 4D Neuroimaging, San Diego, CA) placed in a magnetically shielded room at "Centro de Magnetoencefalografía Dr. Pérez-Modrego" (Madrid, Spain). Subjects were in an awake but resting state with their eyes closed and under supervision during the recording. They were asked to avoid blinking and making movements. For each subject, five minutes 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, 50863 samples). This process consisted of filtering the data to avoid aliasing (Nyquist criterion) and downsampling the recordings. The anti-aliasing filter was a second-order Butterworth IIR routine applied to the signals in both forward and reverse directions to avoid net phase shift with cut-off frequency at 76.30 Hz (45% of the final sample rate: 169.549 Hz).

Artifact-free epochs of 20 s were selected off-line by a technician who was blind to diagnosis (mean = 13.7 artifact-free epochs per channel and subject). Of note, no significant differences in terms of artifact-free epochs were found between patients and controls. Finally, all epochs were filtered between 1.5 and 40 Hz, and copied to a computer as ASCII files for further complexity analysis.

2.3. Lempel–Ziv complexity calculation

LZC analysis is based on a coarse-graining of measurements. Therefore, the MEG signal must be previously transformed into a