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Quantitative study of the sleep onset period via detrended fluctuation analysis: Normal vs. narcoleptic subjects

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ABSTRACT

Objective: To examine the process of the sleep onset quantitatively and explore differences between narcoleptics and controls during the sleep onset period (SOP).
Method: Dynamic detrended fluctuation analysis (DFA) was applied to electroencephalograms recorded during multiple sleep latency tests of 11 drug-free narcoleptic patients (19.3 ± 4.4 yrs; 8 males) and 9 healthy controls (23.8 ± 6.3 yrs; 6 males). The SOP of each group was estimated by fitting the time courses of the DFA scaling exponents to a parametric curve.
Results: The sequence of DFA exponents showed that electrophysiological brain activity was changing rapidly across the SOP. This transition was also verified by a conventional method (i.e., dynamic spectral analysis). The SOP durations of narcoleptics and controls were estimated as 239 ± 25 s and 145 ± 20 s, respectively.
Conclusions: The significantly larger SOP of narcoleptics, compared to controls, is consistent with the wake state of narcolepsy being more susceptible to sleep due to a lower barrier to transitioning to sleep.
Significance: Our results suggest that electrophysiological signatures of narcolepsy could be quantified by dynamic DFA, so the method may have promise as a potential tool to help the diagnosis of narcolepsy despite the present study's limited sample size.

1. Introduction

Sleep onset consists of a flip-flop transition between the two fundamentally different behavioral stages, wake and sleep, over several minutes. This episode, often referred to as the sleep onset period (SOP), marks a period of gradual change involving a progressive reduction in the arousal level until the achievement of definite sleep. In parallel with physiological, cognitive, subjective, and behavioral changes that take place during the SOP, there are remarkable changes in the electroencephalogram (EEG), which indicates that falling asleep is a continuous process over a time interval of a few minutes.

At what point can a subject be said to be really asleep, or what is the moment of sleep onset? There have been many studies on these questions (for reviews, see Ogilvie (2001), and Merica and Fortune (2004)). For example, using a 30 s resolution, Rechtschaffen and Kales (1968) defined sleep onset based on criteria of reduction of alpha band density. However, the most frequently used definition is the first appearance of sleep spindles or K-complexes (stage 2), chiefly because this can be more precisely pinpointed (Rechtschaffen and Kales, 1968). The first occurrence of one 30 s epoch of unequivocal sleep (stage 2, 3, or rapid eye movement sleep (REM)), or three consecutive stage 1 sleep epochs also indicates the sleep onset (Mitler et al., 2005). Hori et al. (1994) traced the sequence of changes in the EEG that leads from wake to the sleep onset, by subdividing the standard stages (wake, stage 1, and stage 2) into nine sub-stages (two from wake, six from stage 1, and one from stage 2 sleep) using a finer 5-s resolution. On the other hand, dynamic spectral analysis (e.g., see Merica and Gaillard (1992)) has been applied to examine quantitatively the temporal interrelationship between the spectral constituents of the EEG. It has been reported that the delta band (0.5–4 Hz) power increases, while the beta band (15–30 Hz) power decreases during the SOP (Freedman, 1986; Merica and Gaillard, 1992; Lamarche and Ogilvie, 1997; Alloway et al., 1999).

Exploring the SOP is important, not only because it links the two most fundamental states, wake and sleep, but also because many

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sleep disorders are often linked to difficulties in either falling asleep (insomnia) or remaining awake or asleep (narcolepsy). Narcolepsy, a chronic sleep disorder that affects about 0.05% of humans (Ohayon et al., 2002; Wing et al., 2002; Nishino and Kanbayashi, 2005) and is characterized by excessive daytime sleepiness, cataplexy, and other abnormal manifestations of REM sleep (American Academy of Sleep Medicine, 2005), is of particular interest in the current study. Nocturnal polysomnography and multiple sleep latency tests (MSLT) are a set of laboratory tests for diagnosis of narcolepsy (for details on diagnostic categories, see the international classification of sleep disorder (ICSD-2) (American Academy of Sleep Medicine, 2005)). However, underlying physiology related to brain activity characterizing narcolepsy still remains unclear. Some attempts to develop new measures (Alloway et al., 1999; Ferri et al., 2005; Kim and Shin, 2008) to associate the disorder with the quality of sleep, as well as mathematical models (Phillips and Robinson, 2007) to explain aspects of narcolepsy have been reported recently. Determining electrophysiological properties of narcolepsy directly from the EEG obtained from the MSLT is one of the main aims of this paper.

Among various methods developed to analyze EEGs is detrended fluctuation analysis (DFA), which was originally developed to characterize DNA sequences (Peng et al., 1993). DFA has been applied to various fields including physics, economics, and biology, where the relation between the variance of some measure is discovered as a function of time scale after local trends are removed. When a signal exhibits a scaling behavior via conventional methods such as spectral analysis, the DFA shows similar scaling behavior as well (Peng et al., 1993; Robinson, 2003). The DFA often yields more robust results, in particular, under non-stationary conditions (Kantz and Schreiber, 2004). It is thus a useful tool to analyze EEGs that often show non-stationary behaviors (e.g., reference voltage drifts). Examples of applying the DFA to EEGs can be found in previous literature (Linkenkaer-Hansen et al., 2001; Lee et al., 2002; Kim and Shin, 2008).

In this paper, we investigate the electrophysiological characteristics of the sleep onset process applying the DFA to EEG recorded during the MSLT. Using a moving window technique, we obtain the time courses of the DFA scaling exponents during the sleep onset of 9 healthy controls and 11 narcoleptic patients. The transitional behavior between wake and sleep during the SOP is explored and compared with results from the conventional method (i.e., dynamic spectral analysis). The SOP of narcoleptics and controls are estimated by fitting the sequences to a parametric curve (sigmoidal function). Finally, the clinical significance of the SOP of the two groups is discussed.

2. Materials and method

2.1. EEG during the MSLT

We investigated EEG of 21 subjects: 9 healthy controls free of any sleep disorder (6 males, 23.8 ± 6.3 yrs) and 11 drug-free narcolepsy patients (8 males, 19.3 ± 4.4 yrs), referred to the Eulji university hospital, Seoul, Korea. All subjects were examined according to protocols including clinical interviews, physical and neurological examinations, nocturnal polysomnography and the MSLT. The final diagnosis of narcolepsy was made following ICSD-2 (American Academy of Sleep Medicine, 2005). As the standard procedure of the MSLT (Littner et al., 2005), subjects tried to sleep five times with 2-h-intervals during daytime. Subjects attempted to nap in a sound-attenuated dark room for 20–35 min. After a trial, subjects were kept to be completely awaken for about 1.5 h and then attempted to nap again. EEG at C3/A2, F4/A1, O1/A2, and P4/A1 channels in the 10/20 system (Somnologica, Medcare Co., USA) were recorded every 0.005 s. This 200 Hz sampling rate gives a Nyquist frequency of 100 Hz for the dynamic spectral analysis, but dynamic DFA examines much longer time scales and there is little EEG power above 100 Hz, so this is not a significant limitation in the present context. Two channels of electrooculogram, electrocardiogram, and submentalis electromyogram were also recorded, but not analyzed in our study. The impedance of electrodes was set below 5 kΩ. A low-pass filter with the cut-off frequency at 2 kHz and a notch filter at 60 Hz (Embla, Flaga hf. Medical Devices, Iceland, 2000) were applied to remove interference by apparatus. Since DFA analyzes signals in the time domain, no software bandpass filter (e.g., via the Fourier transformation) was applied prior to the DFA procedure. For each nap trial, each 30 s epoch of EEG was scored to find the sleep onset defined as either the first occurrence of unequivocal sleep (stage 2, 3, or REM), or three consecutive stage 1 sleep epochs. After that, EEGs were trimmed as 10-min segments across the sleep onset. Sometimes, healthy controls did not fall asleep in 20 min and EEGs of such a case were excluded, but all subjects fell asleep at least once. EEGs showing extraordinary fluctuations were excluded as well. For example, one control subject showed seizure-like behaviors (hypnic jerks (Mahowald and Schenck, 1997)) and, accordingly, was omitted from all analyses (i.e., there were 10 controls).

2.2. Detrended fluctuation analysis

The DFA method consisted of the following steps (Peng et al., 1993; Kantz and Schreiber, 2004):

Step I. For a given sequence $x(t)$, computed an integrated sequence $y(t)$,

$$y(t) = \int_0^t [x(t') - \langle x \rangle] dt', \tag{1}$$

where $\langle x \rangle = T^{-1} \int_0^T x(t) dt$.

Step II. Fluctuations of $y(t)$, after detrending by fitting kth order polynomials (see below), were computed as

$$v^{(k)}(\tau; t) = \sqrt{\frac{1}{\tau_0} \int_t^{t+\tau} [y(t') - p^{(k)}(t')]^2 dt'}, \tag{2}$$

where τ_0 was a normalization factor. $\tau_0 = \tau - (k+1)\delta t \approx \tau$ ($\delta t \ll 1$, the inverse of the sampling rate) was used to compensate a bias toward too small value of $v^{(k)}(\tau; t)$ for very small τ (Kantz and Schreiber, 2004). Here, underlying trends of y were estimated as kth order polynomials $p^{(k)}$ via least-squares fitting over a given time interval $t \leqslant t' < t + \tau$, and then subtracted to calculated $v^{(k)}(\tau; t)$. We set $k = 2$ because linear detrending ($k = 1$) was often insufficient to find a proper scaling when the baseline of EEG was drifting (Kim and Shin, 2008).

Step III. The scaling exponent could be found by averaging $v^{(k)}(\tau)$ over all time intervals of length τ, which was

$$\langle v^{(k)}(\tau) \rangle \sim \tau^{\kappa}. \tag{3}$$

To demonstrate the usefulness of the DFA, we applied the method to various artificial signals: Brownian, $1/f$, and random noise. In the literature, noise is often named after its spectral density of the form $P(f) \sim f^{-\beta}$, where f was frequency and $0 \leqslant \beta \leqslant 2$. For example, $\beta = 0$ means that the signal has equal power in any band of the spectrum, giving a random sequence in the time domain. Brownian noise, with its spectral density is proportional to f^{-2} ($\beta = 2$), can be produced by integrating this random noise. It implies that Brownian noise has more energy at lower frequencies, whereas $1/f$ noise has intermediate properties between random noise and Brownian noise. As shown in Fig. 1, the estimated DFA scaling exponents of these short intervals were approximately 1.5, 1.0, and 0.5 for Brownian, $1/f$, and random noise, respectively,