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Application of nonlinear dynamics analysis in assessing unconsciousness: A preliminary study

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ABSTRACT

Objectives: To quantify the degree of unconsciousness with EEG nonlinear analysis and investigate the change of EEG nonlinear properties under different conditions.
Methods: Twenty-one subjects in persistent vegetative state (PVS), 16 in minimally conscious state (MCS) and 30 normal conscious subjects (control group) with brain trauma or stroke were involved in the study. EEG was recorded under three conditions: eyes closed, auditory stimuli and painful stimuli. EEG nonlinear indices such as Lempel–Ziv complexity (LZC), approximate entropy (ApEn) and cross-approximate entropy (cross-ApEn) were calculated for all the subjects.
Results: The PVS subjects had the lowest nonlinear indices followed by the MCS subjects and the control group had the highest. The PVS and MCS group had poorer response to auditory and painful stimuli than the control group. Under painful stimuli, nonlinear indices of subjects who recovered (REC) increased more significantly than non-REC subjects.
Conclusions: With EEG nonlinear analysis, the degree of suppression for PVS and MCS could be quantified. The changes of brain function for unconscious subjects could be captured by EEG nonlinear analysis.
Significance: EEG nonlinear analysis could characterise the changes of brain function for unconscious state and might have some value in predicting prognosis of unconscious subjects.

1. Introduction

Clinically, impaired consciousness such as coma, persistent vegetative state (PVS) and minimally conscious state (MCS) is a very common manifestation in subjects with acquired brain injury. However, the assessment and prognosis of unconsciousness currently depends mainly on clinical scales and experience. The limitations of those scales are obvious. Subtle changes in levels of unconsciousness cannot be clearly and accurately captured, but depend greatly on the experience of the examiner (Stevens and Bhardwaj, 2006). Psychological scales and clinical assessments largely are subjective because they assess the subject's mental functions on the basis of behaviour and clinical signs and symptoms. Research of the neurophysiological basis of coma lacks objective examination, real-time monitoring and dynamic change. Establishment of quantitative measures to evaluate the degree of brain function statically and dynamically could provide the fundamental basis for further studies to evaluate the effectiveness of resuscitation therapies, monitor recovery and prognosticate recovery from coma.

Event-related potentials (ERPs) have been used for a long time to evaluate both sensory and cognitive functions of subjects with severe disorders of consciousness. Many studies of ERPs have confirmed that the absence of cortical somatosensory-evoked potentials (SSEPs) such as N20 is good evidence to predict recovery from coma (Young et al., 2004; Robinson and Micklesen, 2004; Amantini et al., 2005; Carter and Butt, 2005). Mismatch negativity (MMN) and the P300 component also were found to be promising candidates for predicting outcome. A meta-analysis of Daltrozzo et al. (2007) indicated that MMN and P300 appeared to be reliable predictors of awakening in low-responsive patients with stroke or haemorrhage, trauma and metabolic encephalopathy aetiologies. In PVS or MCS, ERP components frequently indicate complex information processing in the association cortex (Lew et al., 2003; Fischer et al., 2004; Kotchoubey et al., 2005; Wijnen et al., 2007).

Electroencephalography (EEG) can also provide a direct and dynamic measurement of electrical brain activity induced by neuro-

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nal functional activity in the cortex. Most subjects in the vegetative state (VS) have profound generalised slowing of background activity with delta (δ) rhythms that do not react to stimuli; subjects with the most severe forms of VS show electrocerebral silence (Bernat, 2006). Most subjects in MCS show diffuse slowing in the theta (θ) or δ range (Giacino and Whyte, 2005), or in the θ or slow alpha (α) (7.5–8 Hz) range (Kotchoubey et al., 2005). Because the spectrum of EEG malignant categories (suppression, burst-suppression, α and θ coma and generalised periodic complexes combined) is greatly variable (Young, 2000), it is difficult to quantify different EEG features of malignant categories. Certain EEG features are associated with a poor outcome and, in some cases, useful in predicting eventual survival. However, the predictive value of individual classifications has not been adequately addressed (Young, 2000; Husain, 2006).

During the past two decades, nonlinear dynamics analysis (NDA) has become a common way to study neural mechanisms underlying cognition. The EEG is complex and of limited predictability because its ultra-high-dimensional nature makes it, in essence, a stochastic system (Jansen, 1991; Pritchard and Duke, 1995). NDA can characterise the dynamics of the neural networks underlying the EEG (Jelles et al., 1999). Thus, it is suggested that NDA provides a useful tool for studying dynamic changes and abstracting correlations within cortical networks, such as the degree of synchronisation within local neural networks and the coupling between distant cortical neural networks.

NDA is derived from the mathematical theory of nonlinear dynamical systems. NDA has demonstrated that the decreased complexity of EEG patterns and reduced functional connections in the cerebral cortex likely are due to decreased nonlinear cell dynamics as well as linear and nonlinear couplings between cortical areas (Jeong, 2004). Lempel and Ziv proposed a useful complexity measure that characterises degrees of order in and development of spatiotemporal patterns. Lempel–Ziv complexity (LZC) quantifies the complexity of time series and is well suited to the analysis of non-stationary biomedical signals of short length. Several studies showed that $C(n)$ (a nonlinear index of complexity) is a useful and promising EEG-derived parameter for characterising the depth of anaesthesia (Zhang et al., 2001).

Entropy, when considered as a physical concept, is related to the amount of 'disorder' in the system. Approximate entropy (ApEn) can quantify the irregularity of data time series, that is, the predictability of subsequent amplitude values based upon the knowledge of the previous amplitude values. Entropy of the EEG measures the regularity of the signal: high levels of entropy during anaesthesia demonstrate that the subject is awake, whereas low levels of entropy correlate with deeper unconsciousness (Bruhn et al., 2003; Vakkuri et al., 2004; Anderson et al., 2004; Hans et al., 2005). Cross-approximate entropy (cross-ApEn) measures the degree of dissimilarity between two concurrent series. A thematically similar quantification of two-variable asynchrony can aid in uncovering subtle disruptions in complicated network dynamics (Pincus, 2006).

The objectives of this study were to establish an objective method to quantify the degree of unconsciousness with NDA and to investigate the changes of nonlinear EEG properties under different conditions (i.e., eyes closed, auditory stimuli and painful stimuli). Our hypotheses were that: (1) subjects in an unconscious state had significantly lower nonlinear indices and poorer responses to auditory and painful stimuli than that of conscious brain-injured subjects; and (2) NDA could quantitate different unconscious states through measures of complexity of the neuron networks in the brain cortex. To accomplish this, we measured LZC, ApEn and cross-ApEn for all subjects in persistent vegetative (PVS), minimally conscious (MCS) and normally conscious states.

2. Materials and methods

2.1. Subjects

The study was performed in the Department of Rehabilitation, Xuanwu Hospital of Capital Medical University, Beijing, China. A total of 37 unconscious subjects after severe brain trauma or stroke were screened from 60 subjects. Twenty-seven males and 10 females, aged 19–80 years, were investigated. The experimental group included 21 subjects in PVS and 16 in MCS, aged 19–80 years and 37–64 years, respectively. A total of 30 normal conscious state subjects with brain injuries, 18 males and 12 females, aged 21–69 years were also investigated as the control group. All subjects were right handed. The hospital ethics committee approved the study. Informed written consent was obtained from the guardians or parents of the subjects.

Subjects were included in the study if: (1) the diagnosis of PVS or MCS was confirmed using the clinical definitions of the Multi-Society Task Force Report on PVS (1994) and Giacino et al. on MCS (2002) for the experimental groups and normal conscious state for the control group, (2) onset of brain injury took place less than 6 months from entrance to the study, (3) subjects had no previous brain injury and (4) subjects were right handed. Subjects were excluded if: (1) vital signs were unstable, (2) obvious communicating or obstructive hydrocephalus was present, (3) the subject was diagnosed with locked-in syndrome, (4) the subject had severe spasticity causing electromyography (EMG) artefact, (5) the subject had severe injury in the frontal poles (EEG positions FP1, FP2) or (6) the subject had obvious cognitive deficits if they were chosen for the control group.

2.2. Clinical assessment

All subjects in PVS and MCS were diagnosed using the clinical definitions of the Multi-Society Task Force Report on PVS (1994) and Giacino et al. on MCS (2002). Brain magnetic resonance imaging (MRIs) scans were obtained from all subjects to ensure the locations of brain injuries and exclude obvious communicating or obstructive hydrocephalus. The Glasgow Coma Scale (GCS), Rappaport Coma/Near-Coma Scale and JFK Coma Recovery Scale were used to evaluate the level of unconsciousness. For the Rappaport Coma/Near-Coma Scale, the results of the 'olfactory' parameter were eliminated because it was difficult to obtain these data from some subjects.

Brainstem auditory-evoked potential (BAEP), SSEP and traditional EEG tests were obtained after admission. BAEP, SSEP and traditional EEG were evaluated according to the Cant et al. (1986), Robinson and Micklesen (2004) and Young et al. (1997) criteria, respectively (Table 1). The Glasgow Outcome Scale (GOS) was used

Table 1
Classification system of BAEP, SSEP and EEG.

	Grade	Content
BAEP	Grade I	Normal bilaterally
	Grade II	Abnormal latencies, wave V present
	Grade III	Wave V absent on one or both sides
SSEP	Normal	Bilateral normal responses
	Abnormal	The waveform could be either bilaterally present but abnormal, unilaterally normal, or unilaterally present but abnormal. Abnormal amplitude or latency was defined as >2 SD from the norm
	Bilaterally absent	Bilateral absent responses
EEG	Grade I	Delta/theta > 50% of recording (not theta coma)
	Grade II	Triphasic waves
	Grade III	Burst-suppression pattern
	Grade IV	Alpha/theta/spindle pattern coma (no reactivity)
	Grade V	Suppression (generalised)