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Electroencephalography (EEG) and Unconsciousness

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1. Introduction

The commonest and simplest operational definition of consciousness is, the state of the patient's awareness of self and environment and his responsiveness to external stimulation and inner need. Therefore, unconsciousness has the opposite meaning, that is, a state of unawareness of self and environment or a suspension of those mental activities by which people are made aware of themselves and their environment, coupled with a diminished responsiveness to environmental stimuli. Loss of consciousness can have many different causes, for example, stroke, traumatic brain injury, anesthesia, brainstem lesions and sleep, the various causes of unconsciousness primarily interfering with different brain functions. Clinically, impaired consciousness such as coma, vegetative state (VS) and minimally conscious state (MCS) is a very common manifestation in subjects with acquired brain injury. Unconsciousness does not always consist of a general suppression of the entire activity of the central nervous system. Depending on the actual cause(s), many functions, such as protective reflexes and various cognitive processes, can remain intact. The Management of such a patient in VS or MCS requires carefully reaching the correct diagnosis, pronouncing an evidence-based prognosis, and thoughtfully considering the medical, ethical, and legal elements of optimum treatment (Bernat, 2006).

1.1. The anatomy and neurophysiology of unconsciousness

The pioneering studies of Moruzzi and Magoun in the 1940s showed that, electrical stimulation of the medial midbrain tegmentum and adjacent areas just above this level caused a lightly anesthetized animal to become suddenly alert and its EEG to change correspondingly, i.e., to become "desynchronized," in a manner identical to normal arousal by sensory stimuli. The sites at which stimulation led to arousal consisted of a series of

points extending from the nonspecific medial thalamic nuclei down through the caudal midbrain. These points were situated along where anatomists had referred to as the reticular system or formation. Fibers from the reticular formation ascend to the thalamus and project to various nonspecific thalamic nuclei. From these nuclei, there is a diffuse distribution of connections to all parts of the cerebral cortex. This whole system is concerned with consciousness and is known as the ascending reticular activating system (ARAS). Moreover, sensory stimulation has a double effect—it conveys information to the brain from somatic structures and the environment and also activates those parts of the nervous system on which the maintenance of consciousness depends. The cerebral cortex not only receives impulses from the ascending reticular activating system but also modulates this incoming information via corticofugal projections to the reticular formation (Ropper and Brown, 2005). Intact consciousness requires normal functioning of the cortex of both cerebral hemispheres.

Consciousness can be divided into two main components: arousal (wakefulness and vigilance) and awareness (awareness of the environment and the self). Arousal is supported by several brainstem neuronal populations that directly project to both thalamic and subcortical neurons. Awareness is dependent upon the integrity of the cerebral cortex and its subcortical connections. Each of its many parts is located, to some extent, in anatomically defined regions of the brain (Zeman, 2001). Impairments of consciousness may thus be caused either by the simultaneous impairment of function of both cerebral hemispheres, or by damage to the reticular formation in the brainstem, and/or to its ascending projections (uncoupling of the cortex from the activating input of the reticular formation).

1.2. Clinical definition of unconsciousness

1.2.1. Coma

Coma is a state of unresponsiveness in which the patient lies with the eyes closed, cannot be aroused, and has no awareness of self and surroundings. Coma may result from bilateral diffuse cortical or white matter damage or brainstem lesions bilaterally, affecting the subcortical reticular arousing systems, or from sudden large unilateral lesions that functionally disrupt the contralateral hemisphere. Coma is distinguished from syncope or concussion in terms of its duration, which is at least 1h. In general, comatose patients who survive begin to awaken and recover gradually within 2–4 weeks (Plum and Posner, 1983). Many factors such as etiology, age, the patient's general medical condition, clinical signs, and complementary examinations influence the management and prognosis of coma. Traumatic etiology is known to have a better outcome than non-traumatic anoxic cases.

1.2.2. Vegetative state

Patients in a vegetative state (VS) are awake but are unaware of themselves or their environment. The VS is usually caused by diffuse lesions on the gray and white matter.

Characterized by 'wakefulness without awareness', patients regain their sleep–wake cycle, and may be aroused by painful or salient stimuli, but show no unambiguous signs of conscious perception or deliberate action, including communicative acts.

Persistent vegetative state (PVS) has been defined as a vegetative state remaining 1 month after acute traumatic or non-traumatic brain damage. It does not imply irreversibility. According to the Multi-Society Task Force on persistent vegetative state (PVS), the criteria for the diagnosis of VS are the following (1994): (1) no evidence of awareness of self or environment and an inability to interact with others; (2) no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; (3) no evidence of language comprehension or expression; (4) intermittent wakefulness manifested by the presence of sleep–wake cycles; (5) sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care; (6) bowel and bladder incontinence; and (7) variably preserved cranial nerve and spinal reflexes. However, permanent vegetative state is irreversible. According to the Multi-Society Task Force on Permanent Vegetative State (1994), vegetative state may be regarded as permanent 3 months after non-traumatic brain damage or 12 months after traumatic injury. These guidelines are best applied to patients who have diffuse traumatic brain injuries and postanoxic events. Recovery from a vegetative state often occurs: younger age and a traumatic, rather than hypoxic–ischemic etiology.

1.2.3. Minimally conscious state

According to Giacino's definition (Giacino et al. , 2002), the minimally conscious state (MCS) is a condition of severely altered consciousness in which limited but clearly discernible evidence of self or environmental awareness must be demonstrated on a reproducible or sustained basis by at least one of the following behaviors: (1) following simple commands; (2) gestural or verbal yes/no responses (regardless of accuracy); (3) intelligible verbalization; (4) purposeful behavior, including movements or affective behaviors that occur in contingent relation to relevant environmental stimuli and are not due to reflexive activity, such as, appropriate smiling or crying in response to the linguistic or visual content of emotional but not to neutral topics or stimuli; vocalizations or gestures that occur in direct response to the linguistic content of questions; reaching for objects that demonstrates a clear relationship between object location and direction of reach; touching or holding objects in a manner that accommodates the size and shape of the object; pursuit eye movement or sustained fixation that occurs in direct response to moving or salient stimuli.

Like the VS, the MCS may be chronic and sometimes permanent. Emergence from the MCS is defined by the ability to exhibit functional interactive communication or functional use of objects. Similar to the VS, traumatic etiology has a better prognosis than non-traumatic anoxic brain injuries. Preliminary data show that the overall outcome in the MCS is more favorable than in the VS (Giacino and Whyte, 2005, Laureys et al. , 2004a).

1.2.4. Brain death

Most countries have published recommendations for the diagnosis of brain death but the diagnostic criteria differ from country to country. Some rely on the death of the brainstem only; others require death of the whole brain including the brainstem. However, the clinical assessments for brain death are the same and require the loss of all brainstem reflexes and the demonstration of continuing apnea in a persistently comatose patient (Laureys, Owen, 2004a). The central considerations in the diagnosis of brain death are: (1) absence of all cerebral functions; (2) absence of all brainstem functions, including spontaneous respiration; and (3) irreversibility of the state (Ropper and Brown, 2005). At present, no recovery from brain death has been reported.

1.2.5. Locked-in syndrome

The locked-in syndrome (LIS), characterized by anarthria and quadriplegia with general preservation of cognition, must be distinguished from disorders of consciousness. The locked-in syndrome describes patients who are awake and conscious, but have no means of producing speech, limb, or facial movements, resembling patients in VS, and is most often caused by a lesion of the ventral pons (basis pontis) as a result of basilar artery occlusion. Locked-in syndrome is defined by sustained eye opening (bilateral ptosis should be ruled out as a complicating factor), awareness of the environment, aphonia or hypophonia, quadriplegia or quadriparesis, and vertical or lateral eye movement or blinking of the upper eyelid to signal yes/no responses (Giacino et al. , 1995). Eye or eyelid movements are the main method of communication. Since there is only motor output problem, LIS is not a disorder of consciousness (DOC).

Table 1 outlines the clinical features of disorders of consciousness and the locked-in syndrome.

1.3. Epidemiology of unconsciousness

Three categories of disorder can cause VS: acute traumatic and non-traumatic brain injuries; degenerative and metabolic brain disorders, and severe congenital malformations of the nervous system. However, the most common cause of VS and MCS is traumatic brain injury. Non-traumatic causes in adults include acute hypoxic-ischemic neuronal injury suffered during cardiopulmonary arrest, stroke, and meningoencephalitis (Tresch et al. , 1991). For children, causes of VS include trauma, meningitis, asphyxia, congenital malformations, and perinatal injuries (Ashwal et al. , 1992).

The Multi-society Task Force claimed that in the USA there are 10,000–25,000 adults and 4,000-10,000 children (about 56-140 per million) in a PVS (1994). This estimate was almost certainly high given that their prevalence model assumed that many patients with neurodegenerative diseases eventually progressed to a vegetative state and that many children were in a vegetative state from developmental malformations. According to an epidemiological survey of persistent vegetative state and minimally conscious state in

Austria, the point prevalence was 33.6 patients per million for VS and 15 per million for MCS in long-term care facilities (Donis and Kraftner, 2011). Without reliable epidemiologic measures, patients in MCS remain silent victims, unheard and uncounted.

Clinical feature	Coma	Vegetative state	Minimally conscious state	Locked-in syndrome
Consciousness	None	None	Partial	Full
Sleep/wake	Absent	Present	Present	Present
Motor function	Reflex and postural responses only	Postures or withdraws to noxious stimuli Occasional nonpurposeful movement	Localizes noxious stimuli Reaches for objects Holds or touches objects in a manner that accommodates size and shape Automatic movements (e.g., scratching)	Quadriplegic
Auditory function	None	Startle Brief orienting to sound	Localizes sound location Inconsistent command following	Preserved
Visual function	None	Startle Brief visual fixation	Sustained visual fixation Sustained visual pursuit	Preserved
Communication	None	None	Contingent vocalization Inconsistent but intelligible verbalization or gesture	Aphonic/Anarthric Vertical eye movement and blinking usually intact
Emotion	None	None Reflexive crying or smiling	Contingent smiling or crying	Preserved

Quotes from Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58:349-53.

Table 1. Clinical features of disorders of consciousness and the locked-in syndrome

Patients with MCS may follow a survival time course distinguishable from other brain-injured patients. It has been suggested that patients in VS due to TBI have a lower mortality rate and longer survival compared with those with anoxia (Childs et al. , 1993). Survival in MCS depends on age; quality of care; comorbid illness and injury; and decisions to withhold or withdraw life-sustaining therapy. Survival estimates with severe brain injury are variable (Fins et al. , 2007). Young patients with MCS retain limited mobility and have longer life spans; 81% have an 8-year survival (Childs, Mercer, 1993).

2. Clinical assessment methods of unconsciousness

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). Clinical commonly used scales of unconsciousness, such as the Glasgow Coma Scale (GCS), Rappaport Coma/Near-Coma Scale and JFK Coma Recovery Scale would be introduced as follows.

2.1. Glasgow Coma Scale (GCS)

The GCS is used to assess the level of consciousness after head injury and is now applicable to all acute medical and trauma patients. The scale comprises three tests: eye, verbal and motor responses. The three values separately as well as their sum are considered. The lowest possible GCS (the sum) is 3 (deep coma or death), while the highest is 15 (fully awake person).

The GCS, which was developed, validated, and used widely to assess the level of consciousness and prognosis of patients with acute traumatic brain injuries (Rowley and Fielding, 1991) and non-traumatic causes of coma (Mullie et al. , 1988), is insufficient for the assessment of vegetative state and minimally conscious state because of its crude measurement of awareness and its omission of relevant neurological functions (Howard and Hirsch, 1999).

Eye Response	Does not open eyes	1 point
	Opens eyes in response to painful stimuli	2 points
	Opens eyes in response to voice	3 points
	Opens eyes spontaneously	4 points
Verbal Response	Makes no sounds	1 point
	Incomprehensible sounds	2 points
	Utters inappropriate words	3 points
	Confused, disoriented	4 points
	Oriented, converses normally	5 points
Motor Response	Makes no movements	1 point
	Extension to painful stimuli (decerebrate response)	2 points
	Abnormal flexion to painful stimuli (decorticate response)	3 points
	Flexion / Withdrawal to painful stimuli	4 points
	Localizes painful stimuli	5 points
	Obeys commands	6 points

Table 2. Glasgow Coma Scale (GCS)

2.2. Rappaport coma/Near-coma scale

The Coma/Near Coma (CNC) scale was developed to measure small clinical changes in patients with severe brain injuries who function at very low levels characteristic of near-vegetative and vegetative states. The CNC was designed to provide reliable, valid, easy, and quick assessment of progress or lack of progress in low-level brain injured patients. The CNC has five levels, based on 11 items that can be scored to indicate severity of sensory, perceptual, and primitive response deficits. For the details, See *Rappaport, M. (2000). The Coma/Near Coma Scale. The Center for Outcome Measurement in Brain Injury. http://www.tbims. org/combi/cnc (accessed October 1, 2011).*

2.3. JFK Coma Recovery Scale-Revised

The JFK Coma Recovery Scale-Revised (CRS-R) comprises 6 subscales addressing auditory, visual, motor, oromotor/verbal, communication, and arousal processes. Scoring is based on the presence or absence of specific behavioral responses to sensory stimuli administered in a standardized manner. The lowest item on each subscale represents reflexive activity or no response, whereas the highest items represent cognitively mediated behaviors.

The CRS-R appears to meet minimal standards for measurement and evaluation tools designed for use in interdisciplinary medical rehabilitation. The scale can be administered reliably by trained examiners and produces reasonably stable scores over repeated assessments. Diagnostic application of the CRS-R suggests that the scale is capable of discriminating patients in an MCS from those in VS (Giacino et al. , 2004).

According to the report of a systematic review of behavioral assessment scales for disorders of consciousness (DOC), the CRS-R has excellent content validity and is the only scale to address all Aspen Workgroup criteria and may be used to assess DOC with minor reservations, while CNC may be used to assess DOC with major reservations (Seel et al. , 2010).

3. Functional neuroimaging and unconsciousness

Although bedside clinical assessment examination remains the criterion standard for establishing diagnosis in clinical practice, behavioral findings are often limited or ambiguous. Recently, the evidence from the non-invasive functional imaging techniques, especially functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) provided clues to brain function in unconscious populations, suggests that some patients with DOC exhibit partially preserved conscious processing despite having no clinical or verbal output (Owen et al. , 2006) and may serve an adjunctive and useful information to the diagnosis and prognosis of these patients.

Recent advances in functional neuroimaging use so-called 'activation' studies to assess residual brain function in altered states of consciousness without the need for any overt response on the part of the patient. fMRI can capture precisely and visualize localized physiologic change in the brain induced by neuronal activity. Several fMRI and PET findings demonstrated that some MCS or VS patients retain islands of preserved cognitive, sensory and auditory function.

Auditory Function Scale	Consistent Movement to Command*	4
	Reproducible Movement to Command*	3
	Localization to Sound	2
	Auditory Startle	1
	None	0
Visual Function Scale	Object Recognition*	5
	Object Localization: Reaching*	4
	Visual Pursuit*	3
	Fixation*	2
	Visual Startle	1
	None	0
Motor Function Scale	Functional Object Use†	6
	Automatic Motor Response*	5
	Object Manipulation*	4
	Localization to Noxious Stimulation*	3
	Flexion Withdrawal	2
	Abnormal Posturing	1
	None/Flaccid	0
Oromotor/Verbal Function Scale	Intelligible Verbalization*	3
	Vocalization/Oral Movement	2
	Oral Reflexive Movement	1
	None	0
Communication Scale	Oriented†	3
	Functional: Accurate†	2
	Non-Functional: Intentional*	1
	None	0
Arousal Scale	Attention*	3
	Eye Opening without Stimulation	2
	Eye Opening with Stimulation	1
	Unarousable	0

*Denotes MCS.
†Denotes emergence from MCS.

Table 3. JFK Coma Recovery Scale-Revised (CRS-R)

The VS patients show cortical activation limited to 'lower level' primary cortical areas. Noxious somatosensory stimulation, such as high-intensity electric stimulation of the median nerve at the wrist, induced activation of midbrain, contralateral thalamus, and primary somatosensory cortex. The somatosensory cortex was functionally disconnected from 'higher order' associative cortical areas, encompassing anterior cingulate, insular, prefrontal and posterior parietal cortices. In healthy controls, such stimuli activated primary and secondary somatosensory cortices, bilateral insular, posterior parietal and anterior cingulate cortices (Laureys et al. , 2002). In line with the results of the somatosensory

activation study described above, the activated primary auditory cortex by auditory stimulation was also functionally disconnected from higher order areas encompassing posterior parietal, anterior cingulate and hippocampal areas, whereas in control subjects, stimuli activated bilateral primary and contralateral auditory association cortices (Boly et al. , 2004, Laureys et al. , 2000). Likewise, visual stimulation elicited activation in primary visual cortex (Giacino et al. , 2006). These studies support the view that simple somatosensory, auditory and visual stimuli typically activate primary cortices in patients with VS and fail to show robust activation in higher order associative cortices.

It is important to differentiate a patient in PVS from a patient in MCS, as the latter patient has a much higher chance of a favorable outcome. Some MCS patients may retain widely distributed cortical systems with potential for cognitive and sensory function, despite their inability to follow simple instructions or communicate reliably (Schiff et al. , 2005). PET and fMRI case reports incorporating complex auditory stimuli have shown large-scale network activation in the minimally conscious state that is not observed in unconscious vegetative patients (Bekinschtein et al. , 2005, Laureys et al. , 2004b).

However, it remains controversial whether the VS patients with atypical 'higher order' associative cortical activation have a good outcome. In some fMRI or/and PET studies, patients with higher-level associative cortical activation in VS progressed to MCS or recovered consciousness (Bekinschtein, Tiberti, 2005, Coleman et al. , 2007, Di et al. , 2007), which seem to show that atypical 'higher order' associative cortical activation in VS heralds recovery of some level of consciousness some months later. Other VS patients with 'higher level' associative cortical activation failed to subsequently recover (Staffen et al. , 2006), which was in line with the viewpoint that VS patients with atypical behavioral fragments can show residual isolated brain processing in the absence of clinical recovery (Schiff et al. , 2002) .

Functional connectivity of the brain, measured with fMRI techniques, seems to play a more important role for consciousness. Recently, the brain activity fluctuations in the default resting state have received increasing interest. The default mode network is defined as a set of areas encompassing the posterior-cingulate/precuneus, anterior cingulated/mesiofrontal cortex and temporo-parietal junctions, showing more activity at rest than during attention-demanding tasks. Some studies on resting state activity in DOC show that functional connectivity is disrupted in the task-negative or the default mode network. Cauda et al. studied three patients in a vegetative state, found the decreased connectivity in several brain regions, including the dorsolateral prefrontal cortex and anterior cingulated cortex, especially in the right hemisphere, the results showed a dysfunctional default mode network (Cauda et al. , 2009). Boly et al. demonstrated absent cortico-thalamic functional connectivity but partially preserved cortico-cortical connectivity within the default network in a vegetative state patient following cardio-respiratory arrest (Boly et al. , 2009). In this patient, anticorrelations could also be observed between the posterior cingulate/precuneus and a previously identified task-positive cortical network, but both correlations and anti-correlations were significantly reduced as compared to healthy controls. In the same study, a brain death patient studied two days after a massive cranial hemorrhage and evolution to a comatose state showed no residual functional connectivity (Boly, Tshibanda, 2009). In a

more comprehensive study, fourteen non-communicative brain-damaged patients and fourteen healthy controls participated in a resting state fMRI protocol. Functional connectivity in all default network areas was found to be non-linearly correlated with the degree of consciousness, ranging from healthy volunteers and locked-in syndrome, to minimally conscious, vegetative and comatose patients. Furthermore, connectivity in the precuneus was found to be significantly stronger in MCS patients compared with VS patients, while locked-in syndrome patients' default network connectivity was shown to be not significantly different from that of healthy control subjects (Vanhaudenhuyse et al. , 2010).

Certainly, the two main approaches, hypothesis-driven seed-voxel and data-driven independent component analysis, employed in the analysis of resting state functional connectivity data present multiple methodological difficulties, especially in non-collaborative DOC patients. Improvements in motion artifact removal and spatial normalization are needed before fMRI resting state data can be used as proper biomarkers in severe brain injury.

In a word, we can only say functional imaging activation studies can provide valuable prognostic information, and future efforts should be needed.

4. Evoked potentials (EPs) and unconsciousness

4.1. Auditory evoked potentials (AEPs) and unconsciousness

Auditory evoked potentials (AEPs) can be used to trace the signal generated by a sound through the ascending auditory pathway. The evoked potential is generated in the cochlea, goes through the cochlear nerve, through the cochlear nucleus, superior olivary complex, lateral lemniscus, to the inferior colliculi in the midbrain, on to the medial geniculate body, and finally to the cortex. Brainstem auditory-evoked potentials (BAEPs) do not play a role in the prognosis for awakening, but only play a prognostic role in survival (Lew et al. , 2003, Young et al. , 2004).

A study of long-latency responses (LLRs) reported that a P300 component was observed in response to the patient's name in all patients with locked-in syndrome, in all MCS patients, and in 3 of 5 patients in VS. However, a P300 response does not necessarily reflect conscious perception and cannot be used to differentiate VS from MCS patients (Perrin et al. , 2006). Another study also demonstrated that MCS patients presented a larger P300 to the patient's own name, in the passive and in the active conditions. Moreover, the P300 to target stimuli was higher in the active than in the passive condition, suggesting voluntary compliance to task instructions like controls. In contrast, no P300s were observed for VS patients in response to their own name (Schnakers et al. , 2008). In conclusion, auditory LLRs are clinically useful for assessment of higher-order neural functions and processing in TBI patients. Auditory P300 protocols can be used to assess cognitive functions in this population (Folmer et al. , 2011).

Mismatch Negativity (MMN) is generated by the brain's automatic response to physical stimulus deviation from the preceding stimulus in repetitive auditory input, revealing that

physical features of auditory stimuli are fully processed regardless whether they are attended to or not (Naatanen et al. , 2004). The auditory MMN (which can occur in response to deviance in pitch, intensity, or duration) is a fronto-central negative potential with primary generators in auditory cortex and a typical latency of 150–250ms after the onset of the deviant stimulus. Neural generators of the MMN might also include frontal cortex and thalamus (Naatanen et al. , 2007). Fischer et al. studied a series of 346 comatose patients and found that the presence of MMN is a predictor of awakening and precludes comatose patients from moving to a permanent vegetative state (Fischer et al. , 2004). Mismatch negativity has repeatedly shown to predict outcome after coma demonstrated that in the acute phase the presence of MMN predicted the exclusion of shifting into PVS. In the study of Kotchoubey et al., 6 months after the brain insult clinical improvement was observed more frequently in VS and MCS patients with a significant MMN than in those without the MMN (Kotchoubey et al. , 2005). Wijnen et al. recorded MMNs from 10 patients in VS every 2 weeks for an average period of 3.5 months and observed that with recovery to consciousness MMN-amplitudes increased and a sudden increase was seen in MMN amplitude when patients started to show inconsistent behavioral responses to simple commands. Thus, they concluded that MMN can be helpful in identifying the ability to recover from VS. Compared the prognostic value of MMN to auditory P300 elicited by the patient's own name, the use of novelty P3 elicited by the patient's name increases the prognostic value of MMN alone and improves the assessment of comatose patients by demonstrating the activation of higher-level cognitive functions (Fischer et al. , 2008). Moreover, a meta-analysis of Daltrozzo et al. indicated that MMN and P300 appeared to be reliable predictors of awakening in low-responsive patients with stroke or hemorrhage, trauma and metabolic encephalopathy etiologies (Daltrozzo et al. , 2007).

4.2. Somatosensory Evoked Potentials (SEPs) and unconsciousness

Somatosensory Evoked Potentials (SEPs) can trace the conduction of a sensory impulse (initiated by touch, painful stimuli, or mild electrical stimulation of the skin) from a patient's leg or wrist, through the limb and spinal column, and to record its arrival in contralateral somatosensory cortex. Short-latency somatosensory evoked potentials (SSEPs) refer to the primary response from the somatosensory cortex (S1).

Many studies have confirmed that the absence of cortical somatosensory-evoked potentials (SSEPs) such as N20 is good evidence to predict recovery from coma (Amantini et al. , 2005, Carter and Butt, 2005, Robinson et al. , 2003, Young, Wang, 2004). Lew et al. studied 22 patients who suffered severe TBI and observed that bilateral absence of median nerve SEP was strongly predictive of the worst functional outcome (Lew, Dikmen, 2003). However, these studies mainly focused on acute brain injury. Prolonged impaired consciousness (MCS and VS) have not been studied in such detail. Wu et al. studied 21 subjects in PVS and 16 in MCS and founded that SSEPs failed to distinguished subjects in PVS from those in MCS, which indicated that this measure might be limited in predicting outcome in this population (Wu et al. , 2011a).

5. EEG (traditional methods) and unconsciousness

Electroencephalography (EEG) can also provide a direct and dynamic measurement of electrical brain activity induced by neuronal functional activity in the cortex. EEG allows for an immediate examination of cortical or cortical–subcortical dysfunction in an inexpensive, safe, and readily available manner. It is an important tool in assessing unconscious patients.

5.1. Several scoring systems for grading the severity of EEG abnormalities

Changes in EEG patterns may indicate either deepening or lightening of coma, though orderly progression of coma through various EEG patterns does not always occur. Researchers have already agreed the following EEG patterns found after cardiac arrest are strongly associated with an poor neurologic outcome: generalized suppression; generalized burst–suppression; generalized periodic patterns, especially with epileptiform activity; and α- or α-/θ-pattern coma (Young, 2000).

Synek developed one of the first EEG classification systems for comatose patients (Synek, 1988). Table 4 lists the Synek EEG Classification System. In his view, favorable outcome with survival seems to occur with both grade 1 and the "reactive type" of grade 2 abnormalities, with preservation of normal sleep features, and with frontal mono-rhythmic delta activity; prognostically uncertain patterns are "nonreactive" grade 2 abnormalities; diffuse delta activity with grade 3 abnormality, and the "reactive type of alpha pattern coma."; the following patterns are suggested to be prognostically malignant if persistent: grade 3 abnormality with small amplitude, diffuse, irregular delta activity; grade 4 ("burst suppression pattern"), in particular when epileptiform discharges are present and with "low-output EEG"; and grade 5 ("isoelectric EEG"); fatal outcome is also common with the "nonreactive type of alpha pattern coma" and the recently reported "theta pattern coma."

Grade	Subgrade		Subsubgrade
I (Regular alpha, some theta - reactive)			
II (predominant theta)	a.	normal voltage, reactive	
	b.	low voltage, nonreactive	
III (delta/spindles)	a.	predominant delta, widespread, rhythmic, reactive	
	b.	spindle coma	
	c.	predominant delta, low voltage, irregular, nonreactive	
	d.	predominant delta, medium voltage, usually nonreactive	
IV (Burst suppression/alpha coma/theta coma/low voltage delta)	a.	burst suppression	(1) epileptiform activity (2) no epileptiform activity
	b.	alpha pattern coma	
	c.	theta pattern coma	(1) some reactivity (2) no reactivity
	d.	<20μV delta	
V (Suppression)	Electrocerebral silence (<2μV)		

Table 4. Synek (1988) EEG Classification System

Young et al. suggested a revised EEG Classification System (Young et al. , 1997). Table 5 lists the Young EEG Classification System. This system for classifying EEGs in comatose patients has a higher inter-observer reliability than the Synek's.

Category	Subcategory
I Delta/theta > 50% of recording (not theta coma)	(1) Reactivity (2) No reactivity
II Triphasic waves	
III Burst-suppression	(1) With epileptiform activity (2)Without epileptiform activity
IV Alpha/theta/spindle coma (unreactive)	
V Epileptiform activity (not in burst-suppression pattern)	(1) Generalized (2) Focal or multifocal
VI Suppression	(1) <20μV, but > 10μV (2) ≤10μV
Guideline: 1. Burst-suppression pattern should have generalized flattening at standard sensitivity for ≥ 1 second at least every 20 seconds. 2. Suppression: for this category, voltage criteria should be met for the entire record; there should be no reactivity. 3. When > 1 category applies, select the most critical: • Suppression is the most serious category. • Burst-suppression pattern is more important than the category of triphasic waves which is more significant than dysrhythmia or delta. • Alpha pattern coma is more important than focal spikes, triphasic waves, dysrhythmia or delta categories.	

Table 5. Young (1997) EEG Classification System

Husain presented a review of the EEG patterns commonly seen in coma (Husain, 2006). In this review, the author suggested that intermittent rhythmic delta activity (IRDA, consisting of 2 to 3 Hz sinusoidal waves occurring in a rhythmic but intermittent manner), triphasic waves (TW, blunt, delta (2 to 3 Hz) waves which consist of a high-voltage positive wave preceded and followed by lower amplitude negative waves) are seen in lighter stages of coma; continuous high-voltage delta activity has a poorer outcome than IRDA and TW; periodic lateralized epileptiform discharges (PLEDs), the prognosis depends on their etiology: those related to seizures often have a favorable outcome, whereas those due to infection and stroke have a more variable prognosis; generalized periodic epileptiform discharges (GPEDs), the prognosis depends on their etiology: if the GPEDs are due to medication overdose, outcome may be good, whereas the etiology is anoxia, outcome is usually poor; burst-suppression (generalized, synchronous bursts of high-voltage, mixed-frequency activity alternating with periods of suppression of EEG activity), prognosis is greatly dependent on etiology: patients manifesting this pattern after cardiac arrest are likely to have a much worse outcome; Low-voltage, slow, non-reactive EEG (the predominant activity is of theta and delta frequencies and the amplitude is less than 20μV) and electrocerebral inactivity (ECI), the prognosis is poor; spindle coma, the prognosis is

often favorable; alpha coma, the etiology due to cardiorespiratory arrest is poor, due to toxic encephalopathy is favorable, and due to locked-in syndrome is poor; beta coma, the most common cause for beta coma is overdose of sedative-hypnotic medications and the prognosis is usually favorable.

5.2. Quantitative EEG and unconsciousness

Signal processing and computer technology have enabled the quantification of conventional electroencephalogram (EEG) findings. Digital EEG is paperless recording, storage and display with many advantages over traditional paper recordings. Quantitative EEG (QEEG) is any mathematical or statistical analysis along with the various graphical displays made from digital EEG. The most commonly used method is frequency spectrum analysis based on fast Fourier transform.

Most subjects in VS have profound generalized slowing of background activity with delta 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 or delta range (Giacino and Whyte, 2005), or in the theta or slow alpha (7.5–8 Hz) range (Fingelkurts et al., 2012, Kotchoubey, Lang, 2005). Since the spectrum of EEG malignant categories (suppression, burst-suppression, alpha and theta coma, and generalized 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 (Husain, 2006, Young, 2000).

5.3. Other EEG analytical methods and unconsciousness

Other QEEG techniques include: monitoring and trending, source analysis, coherence analysis, EEG brain maps, et al. Coherence analysis, defined as a statistical measure of cross-correlation between two EEG signals in the frequency domain, and associated with functional coupling, is another commonly used method. Kane et al. investigated the relationship between quantitative EEG and BAEP measures and outcome, in 60 comatose patients after severe, closed head injury and the result indicated that there was regional information in EEG power spectra over the left hemisphere, which could be used in prognostic predictions for patients in coma after severe TBI (Kane et al. , 1998). Leon-Carrion et al. studied 7 MCS patients and 9 patients with severe neurocognitive disorders and the results stressed the importance of fronto-temporal-parietal associative cortices within the "awareness-regions" model and also suggest a relation between excess of slow wave activity and diminished level of awareness in brain injury population (Leon-Carrion et al. , 2008).

6. Nonlinear dynamics analysis (NDA) and unconsciousness

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 characterize 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 synchronization 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).

6.1. Principles of different NDA methods

6.1.1. Lempel-Ziv complexity (LZC)

Lempel and Ziv proposed a useful complexity measure that characterizes 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 characterizing the depth of anesthesia (Zhang et al. , 2001).

LZC analysis is based upon a coarse-graining of the measurements, such that the EEG time series must be transformed into a finite symbol sequence. To do this, we used a simple binary sequence conversion (zeros and ones): Data values below or equal the mean of the given sequence were assigned the symbol "0," and the values above the mean were assigned the symbol "1". This algorithm gives the number of distinct patterns contained in the given finite sequence S=s1, s2, …, sn.

Once digitized, the EEG sequences were scanned according to the method of Kaspar and Schuster (Kaspar and Schuster, 1987). The corresponding complexity measure, c(n) increased by 1 unit when a new subsequence pattern was found in the process, and the next symbol was regarded as the beginning of the next subsequence pattern. The pattern searching continued until the last symbol was scanned. For instance, a time series of EEG signal (6.65, 2.63, 7.15, 1.04, 1.68, 5.55, 3.67, 4.51,…) whose average was 4.11 could be converted into a binary sequence, 10100101…; c(n) of the binary sequence was 4, since different patterns observed in it were 1, 0, 100 and 101. More details of the LZC calculation can be found in the literature (Kaspar and Schuster, 1987, Zhang, Roy, 2001).

In order to obtain a complexity measure that is independent of the sequence length, c(n) was normalized. For a binary conversion, Lempel and Ziv (Lempel and Ziv, 1976) demonstrated that:

$$\lim_{n \to \infty} c(n) = b(n) \equiv \frac{n}{\log_2(n)}$$

such that c(n) could be normalized via b(n):

$$LZC = \frac{c(n)}{b(n)}$$

LZC usually ranges between zero and one. It is a nonlinear dynamic measure indicating the rate of appearance of the new patterns in a time series. A larger LZC implies a greater chance of the occurrence of new sequence patterns and thus a more complex dynamical behavior (Li et al. , 2008). LZC can be viewed as independent of number of samples when n is large (Zhang, Roy, 2001).

In Fig. 1, we present the four LZC analysis steps. The first step consisted in a pre-processing of the signals: artifact-free epoch selection and band-pass filtering. In the second step, the EEG data was transformed into a binary sequence through so-called coarse-graining procedure. The third step was subsequence pattern finding, used to estimate the complexity of the binary sequence – c(n). Finally, the normalized LZ complexity of the signals was calculated.
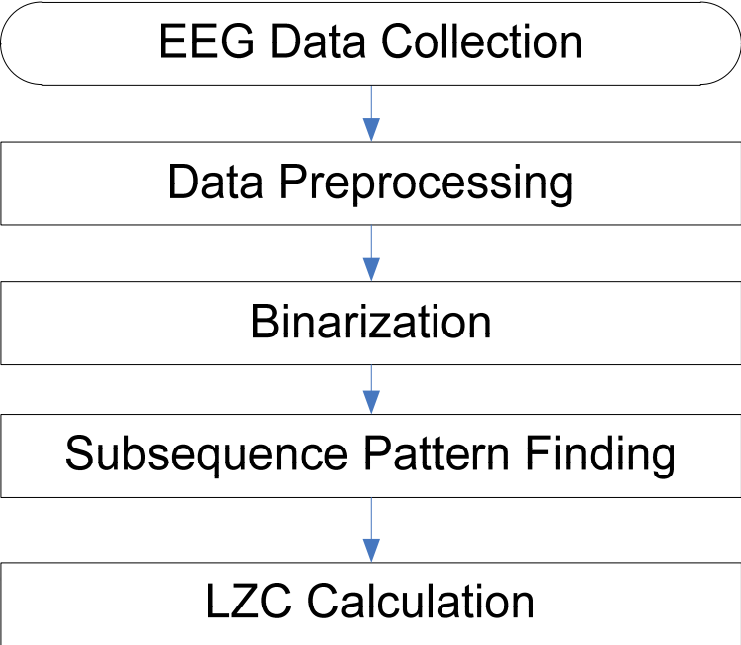
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        ┌─────────────────────────────────┐
        │      EEG Data Collection        │
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        │          Binarization           │
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        ┌─────────────────────────────────┐
        │   Subsequence Pattern Finding   │
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        ┌─────────────────────────────────┐
        │         LZC Calculation         │
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Figure 1. Block diagram of the steps followed in the LZC analysis: signal pre-processing, binarization, subsequence pattern finding and LZC calculation.

6.1.2. Approximate entropy (ApEn)

Entropy, when considered as a physical concept, is related to the amount of "disorder" in the system. Approximate entropy can quantify the irregularity of data time series, i.e., 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 anesthesia demonstrate that the subject is awake, whereas low levels of entropy correlate with deeper unconsciousness (Anderson et al. , 2004, Bruhn et al. , 2003, Hans et al. , 2005, Vakkuri et al. , 2004).

Approximate entropy is a measure of system complexity that was proposed by Pincus and Singer (Pincus and Singer, 1996). It is computed as follows:

$$ApEn(m,r,N) = \lim_{N \to \infty} [\phi^m(r) - \phi^{m+1}(r)]$$

$$\phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln C_i^m(r)$$

where C is the correlation integral.

The absolute value of approximate entropy is influenced by three parameters: the length of the epoch (N), the number of previous values used for the prediction of the subsequent value (m), and a filtering level (r). The noise filter defines the tolerance r that discerns "close" and "not close" subvectors of length "N." "r" measures the amount of noise in the data that is filtered out in the ensuing calculation.

ApEn calibrates an extent of serial interrelationships, quantifying a continuum that ranges from totally ordered (zero) to completely random (infinite). It assigns a non-negative number to a time series, with larger values corresponding to more complexity or irregularity in the data (Pincus, 2001). With increasing irregularity, knowing past values will not enable reliable prediction of future values, and approximate entropy will increase. Thus, decreasing irregularity (decreased ApEn) will cause lowered complexity in the time series, i.e. reduced nonlinear cell-dynamics or interaction of cortical networks.

6.1.3. Cross aproximate entropy (C-ApEn)

Cross approximate entropy (C-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). It is a recently introduced technique for analyzing two related time series to measure the degree of their asynchrony. C-ApEn is very similar to ApEn in design and intent, differing only in that it compares sequences from one series with those of the second (Richman and Moorman, 2000).

Given two time series of N points,

$$\{u(j); 1 \le j \le N\} \quad \text{and} \quad \{v(j); 1 \le j \le N\}$$

form the vectors

$$x_m(i) = \{u(i+k) : 0 \le k \le m-1\}$$
$$y_m(i) = \{v(i+k) : 0 \le k \le m-1\}$$

in which, u and v are the time series, m is the dimension of the vector, r is the same threshold used in the definition of ApEn, and N is the length of the time series. The distance between two such vectors is defined:

$$d\left[x_m(i), y_m(j)\right] = \max\left\{\left[u(i+k) - v(j+k)\right] : 0 \le k \le m-1\right\}$$

$C_i^m(r)(v \| u)$ is defined as the number of $y_m(j)$ within r of $x_m(i)$ divided by N-m+1, such that

$$\phi^m(r)(v \| u) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln\left[C_i^m(r)(v \| u)\right]$$

Lastly, the estimated approximate entropy of finite series is:

$$Cross - ApEn(m,r,N)(v \| u) = \phi^m(r)(v \| u) - \phi^{m+1}(r)(v \| u)$$

While the single-channel ApEn measures the temporal complexity of the EEG, the two-channel C-ApEn reflects the spatial decorrelation of cortical potentials from two remote sites (Hudetz, 2002). Since conscious cognitive processes depend on functional brain regions networks, C-ApEn could reflect the general state of functional connectivity of the brain that supports conscious processes.

What does raised C-ApEn mean about inter-cortical functional connectivity? This question is of great importance. According to Hudetz and Sleigh's explanation, EEG entropy should not be viewed simply as an indicator of disorder, but as a measure of the number of possible microstates a cortical neuronal network may access. The greater the number of microstates, the higher the informational content they represent (Hudetz, 2002, Sleigh et al. , 2001). Therefore, C-ApEn may be interpreted as a measure of the number of states independently accessible by the two cortical areas. Thus, an increase in C-ApEn during painful or auditory stimuli may indicate not only an increase in the number of independent microstates available for the two cortical areas, but also increased inter-cortical communication or information flow (Wu et al. , 2011b).

6.2. Clinical application of NDA correlated with unconsciousness

NDA also can quantify the depth of anesthesia and sedation, and has been shown to be a sensitive and agent-specific correlate of the central effects of anesthetics. Researchers have demonstrated that LZC and ApEn can distinguish between awake and anaesthetized state of human subjects (Anderson, Barr, 2004, Bruhn, Bouillon, 2003, Ferenets et al. , 2006, Ferenets et al. , 2007, Hans, Dewandre, 2005, Kumar et al. , 2007, Noh et al. , 2006, Vakkuri, Yli-Hankala, 2004, Voss et al. , 2006, Zhang, Roy, 2001). In sleep research ApEn was statistically significantly lower during Stage IV and higher during wake and REM sleep (Burioka et al. , 2005, Papadelis et al. , 2007).

6.3. Application of NDA in assessing unconsciousness

Wu et al. studied 21 patients in PVS, 16 in MCS and 30 normal conscious subjects (control group) with brain trauma or stroke. 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 (C-ApEn) were calculated

for all subjects. The results showed that 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. The author considered that with EEG nonlinear analysis, the degree of suppression for PVS and MCS could be quantified and the changes of brain function for unconscious subjects could be captured by NDA. The possible mechanism might be that recovery of unconsciousness and the degree of suppression of unconsciousness are mediated through the brain cortex; NDA can reflect different levels of consciousness by measuring the complexity of the neuron networks in the brain cortex (Wu, Cai, 2011a).
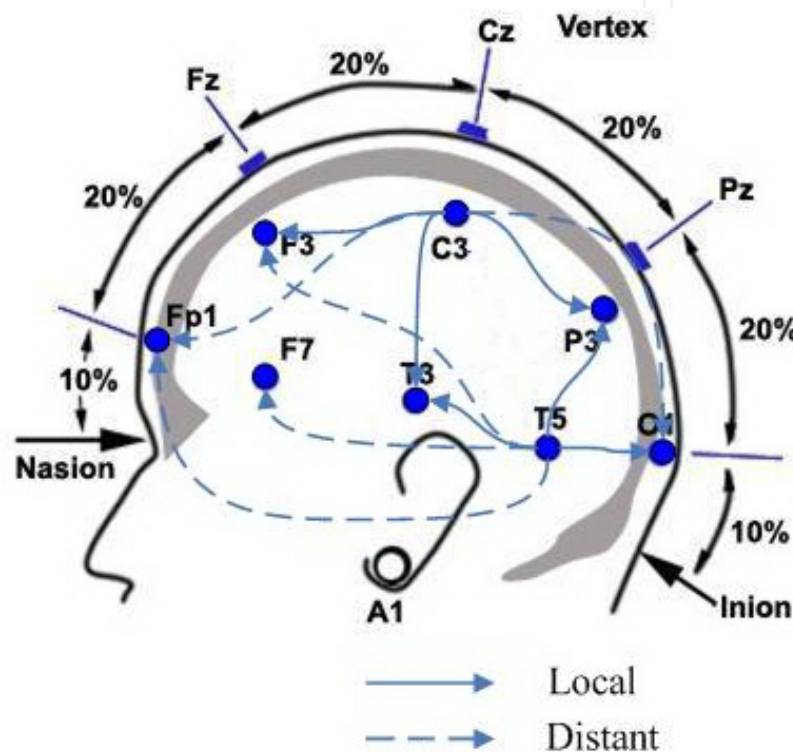

Figure 2. Schematic diagram of local and distant C-ApEn pairs.

Further study with C-ApEn was carried out to investigate the cortical response to painful and auditory stimuli for subjects in PVS and MCS, and measure the interconnection of the residual cortical functional islands. The results showed that interconnection of local and distant cortical networks of patients in PVS was generally suppressed, and painful or auditory stimulation could hardly cause any activation of associative cortices; instead, interconnection of local cortical networks of patients in MCS improved significantly; the only significant difference with the normal conscious subjects existed in the unaffected distant cortical networks. The author also present some question: does raised C-ApEn of patients in VS and MCS under various stimulation conditions mean a better prognosis? Could C-ApEn be used as a feedback index of such resuscitation therapies as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) that could increase the excitability of cortical regions of interest? Further research is needed to answer these questions (Wu, Cai, 2011b).

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