Complexity Loss in Physiological Time Series of Patients in a Vegetative State

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Abstract: Consciousness has not yet been satisfactorily defined because of its puzzling nature which involves the perception of the environment (perceptual awareness) and of the self (self-awareness). Current available methods fail in establishing prognosis in patients with vegetative state (VS): to our mind, this failure stems from the heterogeneous localization of brain damages causing VS and from available approaches tending to investigate self-awareness separately from perceptual awareness, whereas consciousness should be explored as a single and indivisible whole. Moving from the assumption that consciousness depends on the normal activity of wide neural networks, that may be regarded as complex systems whose outputs show a nonlinear behaviour, we propose a nonlinear approach applied to electroencephalographic (EEG) signal, aimed at exploring residual neural networks complexity in patients with VS. For this objective the EEG recording of 10 patients previously admitted to our department were retrospectively analyzed and compared with those of ten matched healthy control subjects. Approximate Entropy (ApEn) was calculated from the average values of time series with fixed input variables. Mean ApEn values were lower in patients then in controls ($t_{18}=12.3$, $p < 0.001$). ApEn is able to discriminate patients from controls thus supporting the hypothesis about a decreased neural networks complexity in VS.

Key Words: approximate entropy, vegetative state, nonlinear, complexity, coma

1 PREDICTING OUTCOMES IN PATIENTS WITH DISORDERS OF CONSCIOUSNESS

What is most inscrutable for us human beings is human beings both with regard to ourselves and our fellow creatures (Scriven, 1965). It is common notion that the keystone to human unpredictable behaviour is consciousness and, in particular, its puzzling nature with subjective and unconscious correlates. Despite this, all attempts that throughout the ages have been made to satisfactory define consciousness were unsuccessful because of its elusive essence that cannot be localized within circumscribed brain areas as confirmed by the

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heterogeneous localization of brain damages underlying disorders of consciousness (DOC) and by the absence of specific neuroradiological patterns associated with the loss or the recovery of consciousness. Consequently, diagnosis and prognosis of these disorders still remain an intriguing challenge for clinical practitioners with consequences that can be imagined at medical and social level.

Patients in a vegetative state (VS) are awake but not aware. VS may be described as a condition of prolonged absence of consciousness whose outcomes are difficult to be assessed. This is not only because of the wide variety of brain damages described in these patients, with far-reaching histopathological and anatomical picture, but also because of the lack of a univocal definition of consciousness itself (Adams, 2000; Zeman, 2001). Consequently, recognizing unambiguous signs of conscious perception of the environment (perceptual awareness) and of the self (self awareness) in patients with DOC in order to establish their prognosis is still very difficult. Currently available methods still fail in establishing prognosis in patients with DOC: to our mind, this failure stems from available approaches tending to investigate self-awareness separately from perceptual awareness, whereas consciousness should be explored as a single and indivisible whole.

The present paper summarizes the results of a pilot study aimed at exploring which additional information may be achieved in patients with VS by nonlinear measures applied to EEG signal. We investigate whether the EEG signal nonlinear dynamics is modified in the above patients with respect to healthy control subjects.

**Functional Neuroimaging Approach to Perceptual Awareness**

Several efforts have been recently made towards exploring perceptual awareness by revealing correlations between brain activation patterns and features of conscious experience in patients diagnosed as being vegetative or minimally conscious. For this aim, an increasing number of researches are using functional magnetic resonance and positron emission tomography to detect the neural substrates of awareness in patients with DOC (Qiu, 2007). According to the above approach, the comparison of patterns obtained in patients and healthy subjects respectively may provide speculative information on the wide networks underlying consciousness and practical suggestions on the prognosis of patients. In this respect, several observations have been recently reported: when asked to imagine playing tennis or moving around her home, a patient in VS showed respectively the activation of the supplementary motor area and the activation of the parahippocampal cortices, the posterior parietal lobe, and the lateral premotor cortices (Owen, 2007).

Other researches were performed in a series of patients alternatively diagnosed as being in vegetative or minimally conscious state (MCS), with a view to check any difference in brain activation patterns between the two groups: when patient’s own name was uttered by a familiar voice, patients in a condition of persistent VS showed the activation of the primary auditory cortex
alone; unlike the previous cases patients in MCS or subsequently emerging to a
MCS showed an increased activity in the primary auditory cortex and in
hierarchically higher order associative temporal areas during the same
stimulation paradigm (Di et al., 2007). The above patients activated the same
cortical areas as did healthy control subjects thus suggesting the following
ambiguous paradigm: processing an environmental stimulus within the same
areas of healthy control subjects might imply their being conscious of it.
However, according to our opinion, activation of some specific isolated brain
areas does not unequivocally imply their involvement in the unknown neural
network underlying consciousness (Sarà, 2008). Moreover, the reported
activation may be regarded as an implicit preconscious neural response until
proved otherwise.

In fact, processing a stimulus does not necessary amount to being
conscious of it since consciousness exists in the relationship between an
organism and environmental stimuli in a feel of feeling continuous experience
underlying subjectivity (Damasio, 1999; Sarà, 2008). Indeed, stimuli processing
is a serial phenomenon in that it can be divided into successive temporal and
anatomical stages ranging from the initial stimulation of receptors to the final
cortical perception: along this neural composite pathway establishing where the
unconscious processing ends and consciousness starts is not easy. This
observation is further confirmed by a growing body of controversial data about
brain activation patterns associated with conscious and unconscious processing:
Some studies suggest that unconscious subliminal stimuli can be deeply
processed and activate similar brain areas as do consciously perceived stimuli
(Melloni, 2007), whereas others suggest that conscious processing mostly
depends on specific parietofrontal activity (Dehaene, 2006). Moreover,
functional neuroimaging applications provide information about the activation
of specific isolated areas without focusing on their specific functioning
modalities and interconnectivity.

As a consequence of the above controversial statements, approaching
consciousness by functional neuroradiological studies alone may not allow us to
assess patients in a standardized manner. Moreover, the problem of functional
neuroimaging approach to detect re-emergence from coma also lies on its
dependence on a proper reaction of patients to specific verbal requests: patients
asked to perform a cognitive task (i.e. imaging playing tennis) are considered as
having cognitive performances that cannot be a priori established.

Clinical Approach to Self-awareness

The most employed tools to evaluate patients with DOC are the Level
of Cognitive Functioning (LCF) Scale and the Coma Recovery Scale-Revised
(CRS-R), that are validated and standardised neurobehavioural instruments
specifically designed for use in these patients. The LCF scale is based on the
classification of patients in eight levels reflecting various degree of cognitive
functioning ranging from the lack of any response to the presence of purposeful
and appropriate responses. The CRS-R is able to measure across the span of
improvement to track an individual from coma to consciousness recovery
(Giacino, 2005). It is divided into 6 subscales addressing auditory, visual, motor,
oromotor, communication and arousal processes with the lowest item on each
subscale representing reflexive activity and the highest one representing
cognitively mediated behaviours.

LCF and CRS-R scoring are based on the observation of specific
behavioural responses to sensory stimuli arising from the external word.
However, in our opinion, this evaluation shows some limits because it provides
information that are confined to a neurobehavioral perspective, thus failing to
explore subjectivity. In fact, consciousness does not only consist in perceiving
the external world and voluntary interacting with it (perceptual awareness) but
also in being aware of the self (self-consciousness). Therefore, evaluating
consciousness just by clinically monitoring the behavioural response to
environmental stimuli may not be enough: if a patient exhibits no movement
during the behavioral examination, we are not enabled to conclude that he is
unconscious.

Matters are further complicated by self-consciousness being difficult to
be objectively evaluated because of its subjective and multi-faceted nature with
six different proposed senses (proneness to embarrassment, self-detection, self-
monitoring, self-recognition, awareness of awareness and self-knowledge)
which are closely integrated but not comparable (Laureys 2007; Zeman, 2001).
Consequently, exploring consciousness in noncommunicative severely brain
damaged patients by monitoring perceptual awareness alone seems inadequate
as does evaluating it by considering self-recognition alone (i.e. mirror self-
recognition or specific reactivity to one’s own name) as recently proposed by
others (Laureys, 2007): We are convinced that the six senses cannot be explored
as distinct because a patient who follows himself in the mirror is not necessarily
able to recognize consciously his own body as his own or to experience
embarrassment because the awareness of others is directed on him. As a matter
of fact, all difficulties in clinically evaluating consciousness arise from a
conceptual basis we define as the “paradox of the parts of an unknown whole,”
which leads us to wonder whether it is possible to study the distinct parts of a
whole that we have not yet described in its entirety. The speculations concerning
the relation parts to the whole cannot be beneficial unless we say something
about its unitary nature, no matter how homogeneous or incomplete it may be.
We thus believe that the search for consciousness does not necessarily require
the recognition of several micro-consciousnesses with neural correlates
separately being identified (Zeki, 2003). If, for example, we differentiate the
self-recognition from the self-knowledge (i.e. one’s knowledge of oneself) we
must, however, admit that both share the property of belonging to a single
“body” we call consciousness about whose unitary nature we know nothing.
Therefore approaching consciousness by breaking it up may be useful only if we
refer to conscious healthy subjects, in which case, despite consciousness cannot
known in its entirety, we will at least be able to state that it is present. Otherwise
the segmentation of consciousness into separate senses might end up worsening
its assessment in subjects with VS or MCS. In fact, if we stated that a patient recognizes himself in the mirror we would necessarily be confronted with two hypotheses: (a) that the “isolated sense” of self recognition has the properties of the whole consciousness which would amount to having as many consciousnesses as the isolated senses or (b) that that sense refers to and depends on “consciousness as a single entity.” To our mind, these two hypotheses are mutually exclusive with obvious unviable consequences at epistemological level, since: in the former case there would exist as many consciousnesses as the suggested arbitrary subdivisions, whereas, in the latter case, studying a single one would not be enough to state that the subject is more or less conscious. By way of conclusion, quantifying consciousness from a mere clinical point of view seems to be equally questionable, since it raises several epistemological questions.

Neurophysiological Approach

To the best of our knowledge, only a few studies have reported on the neurophysiological characterization of patients with VS and MCS: a marked inter-individual electroencephalographic and evoked potentials variability reflects the wide heterogeneity of these patients, thus suggesting the low predictive value of neurophysiological findings for a return to consciousness (Guerit, 2005; Kotchoubey, 2002; Kulkarni, 2007). Interest has been recently aroused by the possibility that a transient long distance synchronization across widely separated regions of the brain in the gamma frequency range may be a signature of conscious perception (Melloni, 2007). However, until now standard neurophysiological data cannot be strongly related to conscious experience and their presence does not unequivocally predict a recovery of consciousness or allow to differentiate between vegetative and minimally conscious patients. Additional information may be provided by quantitative EEG analysis as revealed by our recent findings suggesting that cortical sources of alpha rhythms are related to awareness in patients with persistent VS (Babiloni et al., 2009).

COMPLEXITY CONNECTIVITY AND FUNCTIONAL ISOLATION

Theory

By definition, the loss of connectivity within a complex system reflects the functional isolation of its single parts (Pincus, 1994). Most natural systems have to be regarded as complex systems whose outputs show a chaotic behaviour consisting of sudden, disproportional and unpredictable changes. Sustained fluctuations of autonomic functions such as temperature, blood pressure and heart rate can be described as chaotic phenomena: their behaviour is well described by nonlinear models and depends on the integrity of the complex system itself. Healthy complex systems are characterized by a sufficient functional connectivity with good lines of communication within their parts and normal nonlinear outputs. On the other hand, diseased systems show a reduction of connectivity with crucial biologic messages being either slow to
transmit and receive or unable to arrive: the reduced connectivity of these systems leads to a greater autonomy and isolation of their parts resulting in a reduction of nonlinear parameters due to a greater regularity of their specific outputs. Nonlinear analysis estimates complexity by means of several methodological approaches studying self-similarity (i.e. Correlation Dimensions and Detrended Fluctuation Analysis), the degree of unpredictability (Approximate entropy, Shannon entropy and Kolmogorov entropy) and the local predictability of a system in the phase space (Lyapunov exponent; Ott, 2002; Schuster, 1995). Approximate entropy (ApEn) is the nonlinear parameter most widely used to quantify the unpredictability of time series such as physiological outputs and to determine the complexity of changing systems (Pincus, 1991, 1994). It has been regarded as a local detector of the degree of connectivity between the system taken into account and its functional environment.

Hypothesis

Consciousness depends on the normal activity of wide neural networks, that may be regarded as complex systems whose outputs show a degree of unpredictability empirically quantifiable by means of a nonlinear approach. It is the central hypothesis of this paper that disorders of consciousness might be the result of the above neural networks derangement with an ensuing decrease in complexity and inter-connectivity between parts and an higher degree of functional isolation of each of them; this, in its turn, would bring about a decline in the chaotic behaviour of their outputs (i.e. fluctuations of heart rate or electroencephalographic features), with monotony taking the place of unpredictability.

We propose that the residual complexity of neural networks underlying consciousness may be evaluated by investigating the chaotic behaviour of several physiological outputs showing a nonlinear pattern. In this respect, we recently described a reduction in nonlinear behaviour of heart rate in 10 patients in VS compared to healthy matched control subjects: patients showed lower mean ApEn values with respect to control subjects and, among patients, those with lower ApEn values either died or remained in VS (Sarà 2008). This suggests that nonlinear analysis applied to ECG signal is able to discriminate not only patients from controls but also patients who recover from those remaining in VS.

METHOD

Participants

Out of 15 patients admitted to Post-Coma Intensive and Rehabilitation Care Unit and previously investigated by means of ECG nonlinear analysis, an EEG recording was available in 10 (6 males and 4 women; mean age 42.2, SD 17.1, range 21-73). At the time of EEG recording all included patients were free of any acute comorbidity such as respiratory failure, infections, fever or hypothermia and severe dysautonomia. Moreover, they had no history of epileptic seizures and were not treated with neurotropic drugs such as tricyclic
antidepressants, anticholinergics, benzodiazepines, barbiturates and neuroleptics. The control group consisted of 10 healthy subjects who were recruited from a pool of volunteers and matched by age and sex with the patients group (6 men and 4 women; mean age 41.6, SD 16.3, range 24-72).

Procedure

For each included patient we retrospectively analyzed an EEG recording with a duration of at least 5 minutes. EEG had been recorded from each subject using the Electroencephalographic monitoring system (E.B. NEURO, Florence, Italy). The registration protocol included the montage of 19 scalp electrodes positioned according to the International 10-20 system (channels Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz and Pz), with all electrodes referenced to the chin. During registration, patients were in a resting state, awake and with closed eyes.

Ten healthy subjects matched by age and sex were subjected to EEG recording under the same conditions (also immobilized in bed) and used as controls. EEG data from patients and controls were thereafter processed with a lowpass hardware filter at 100 Hz. Then they were sampled at 256 Hz, with a 12-bit A-to-D precision, and processed with a high-pass filter at 70 Hz. The recorded EEG data were analyzed and fragmented off-line in consecutive epochs of 5 seconds. An average number of 30.0 ± 18.5 artefact-free epochs (mean ± SD) were selected from each electrode and each subject and copied as ASCII files for offline analysis on a personal computer (Workstation Hewlett Packard, Dual processor). The offline analysis was implemented in MATLAB language (release 6.6, The Mathworks, Natick, MA).

Approximate Entropy

ApEn was computed by using the following equation:

$$ ApEn(N, m, d) = (N - m + 1)^{-1} \sum_{i=1}^{N-(m-1)} \ln C_{i}^{m}(d) - (N - m)^{-1} \sum_{i=1}^{N-m} \ln C_{i}^{m+1}(d) $$

(Pincus, 1994). To compare ApEn values of patients and controls, Student t-test was applied. Degrees of freedom were not adjusted for heterogeneity of variances, because Levene’s test did not indicate a clear departure from homoscedasticity. In addition, mean values and the corresponding 95% confidence intervals were plotted to show the size of the differences between the two groups.

Approximate Entropy quantifies the complexity (or irregularity) of a signal, and offers robustness in case of short and noisy data (Pincus, 1991). This robustness to infrequent, even very large or small artefacts, in contrast to variability measures, is a useful statistical property for clinical applications. ApEn is scale invariant and model independent, evaluates both dominant and subordinated patterns in data, and discriminates series for which clear feature recognition is difficult. ApEn is defined as the logarithmic likelihood that the patterns of the data that are close to each other will remain close for the next
comparison within a longer pattern: the greater likelihood of remaining close, regularity, produces smaller ApEn values, and conversely. In Eq. 1, runs of patterns in time series are compared; if runs remain close in successive observations, regularity is high and thus complexity of the series is low, resulting in smaller ApEn values. For computation of ApEn, given N data points, two input parameters should be set: the run length m (that is an adimensional number) and the filter level d (that is a percentage).

Although m and r are critical in determining the outcome of ApEn, no guidelines exist for optimising their values. In principle, the accuracy and confidence of the entropy estimate improve as the number of matches of length m and m+1 increases. The number of matches can be increased by choosing small m (short templates) and large r (wide tolerance). However, there are penalties for criteria that are too relaxed (Pincus, 1991). Pincus (2001) has suggested estimating ApEn with parameter values of m=1, 2 and r=0.1, 0.15, 0.2 and 0.25 times the SD of the original data sequence. Normalizing r in this manner gives ApEn a translation and scale invariance, in that it remains unchanged under uniform process magnification, reduction, or constant shift to higher or lower values (Pincus, 2001). Moreover, several studies (Pincus, 1991; Pincus & Keefe, 1992) have demonstrated that these input parameters produce good statistical reproducibility for ApEn for time series of length N=400.

![Mean values (with 95% confidence intervals) of ECG and EEG ApEn in patients and controls.](image)

**Fig. 1.** Mean values (with 95% confidence intervals) of ECG and EEG ApEn in patients and controls.
The ApEn computation allows us to estimate the degree of functional isolation of interlinked subdivisions within a complex system. ApEn quantifies the functional isolation of each subdivision independently of the fine anatomical structure governing the whole system itself. Consequently, investigating the neural networks functional isolation from a dynamic output signal perspective might allow us to predict consciousness recovery in severely brain injured patients, even if we know nothing about the anatomical features and localization of damaged consciousness.

RESULTS

Data from nonlinear EEG analysis sounds similar to what previously suggested from ECG nonlinear analysis. Mean ApEn values were lower in patients than in healthy control subjects both for ECG and EEG analysis (ECG: mean 0.68, SD 0.26, vs 1.10, SD 0.17; EEG: mean 0.65, SD 0.08 vs 0.97, SD 0.03). The difference between the two group was statistically significant (EEG: \(t_{18} = 12.3, p<0.001\); ECG: \(t_{28} = 4.6, p<0.001\)). This suggests that ApEn is able to strongly discriminate patients with persistent consciousness impairment from healthy control subjects.

DISCUSSION

Because consciousness has to be regarded as a whole with features that cannot be predicted by the behaviour of its parts taken separately, it is not advantageous to break it up into separate clinical domains in order to facilitate its assessment at patients’ bedside. From now on, we propose to consider “healthy consciousness” as a non divisible entity that requires the mutually advantageous conjunction of environment and self awareness which both depend on the integrity of a sufficient neural connectivity. Similarly, residual consciousness in patients with DOC has to be considered as a non divisible entity which is the result of their residual connectivity. We suggest an alternative approach to indirectly explore consciousness in order to avoid any misinterpretation arising from imprecise definition of consciousness itself and from unsuccessful attempts to localize it. According to this model the prognosis of patients with DOC may be assessed by quantifying the residual neural networks’ complexity through a measure of the residual degree of their chaotic behaviour. For this purpose we suggest the use of a nonlinear approach to quantify the regularity and predictability of their physiological outputs and to determine the residual complexity of diseased neural systems. This suggestion moves from the assumption that neural networks have to be considered complex systems as much as any other natural system. Consequently, the consciousness impairment in patients with severe brain injury may reflect the degree of decreased neural networks connectivity with an higher functional isolation within residual survived brain areas. Our hypothesis is also consistent with recent findings that identified the highest cognitive functions in the functional expression of several interconnected areas and found in connectivity and complexity the prerequisites to relate stimuli processing and conscious elaborating (Dietrich, 2003; Goldberger, 2002; Sporns 2000, 2002).
Other studies suggested that patients with DOC might suffer from a disconnection syndrome within a wide frontoparietal network functionally connected with thalamic structures and that the residual integrity of this system may be used to predict a clinical improvement in these patients (Laureys, 2005). However, it sounds unconvincing to talk about a localization of consciousness within such wide neural networks including long-range cortico-cortical (between midline-posterior and latero-frontal areas) and cortico-thalamic (between midline-posterior cortices and non specific thalamic nuclei) connections. These doubts are after all endorsed by the heterogeneous localization of brain damages underlying DOC and by a large body of evidence suggesting that frontal networks are not necessary for basic awareness (Dietrich, 2003). Consequently, the main concern in predicting the chances of recovery of consciousness does not lie in demonstrating the restored activation of specific areas within the above system by means of their activity but with identifying the functional expression of the whole connectivity which is the prerequisite of complexity. Therefore, our assumption is that in patients with DOC it is possible to detect a loss of connectivity, leading to functional isolation, the consequence being a decrease in the nonlinear behaviour of their outputs with monotony taking the place of unpredictability. Since nonlinearity is closely connected with the complexity and intrinsic connectivity of all natural systems (Pincus, 1991, 1994), we suppose that the wide derangement in neural networks occurring in patients with DOC, by reducing their connectivity and increasing their isolation, may be detected by a decrease in the nonlinear behaviour of their physiologic measurable outputs. Our hypothesis could be tested by using some nonlinear parameters suitable to quantify the unpredictability of fluctuations in a specific time series in order to discern the complexity of systems and their changes when affected by a disease.

Nonlinear parameters have been already used in a wide variety of contexts including the evaluation of heart rate dynamics in physiologic and pathologic states (Ryan, 1994), the evaluation of hormonal signaling generated by interlinked systems (Liu, 2005) and the assessment of anesthesia of different depth (Esmaeili, 2007). With respect to anesthesia, the possibility of using ApEn for monitoring wakefulness fluctuations has been widely investigated: ApEn may be employed as an indicator to evaluate anesthetic drug effects and the depth of the achieved anesthesia (Jordan, 2008). In this respect, nonlinear measures are more reliable than all linear parameters deriving from EEG power spectrum analysis (Otto, 2008) and, among nonlinear measures, ApEn has to be considered as having the maximum accuracy to discriminate the various states of anesthesia (Esmaeili, 2007).

Conversely, no data are available about the potential of ApEn to reflect consciousness gradations and transitions in patients with VS who, by definition, are awake but not aware. Our experience suggests that ApEn, both applied to EEG and ECG signal, show a strong sensitivity and specificity in discriminating patients from healthy control subjects and in identifying patients at higher risk of remaining in a condition of persistent VS. Thanks to its discriminant validity in comparing the neural networks complexity, ApEn may be proposed as a reliable
indicator in more systematic studies, allowing us to avoid the reject of working hypotheses that are actually true (type I error) or the legitimation of hypotheses that are actually false (type II error).

In our hypothesis ApEn may be used to discern residual complexity and connectivity in patients with DOC in order to establish their short and long-term prognosis more precisely. If this hypothesis were correct, patients showing a greater signal regularity in several physiological outputs (i.e. heart rate and electroencephalographic activity) would show a relatively lower residual functional connectivity between neural networks with a higher likelihood of unfavourable outcomes. Conversely, patients showing a greater unpredictability of their outputs should have more chances to recover consciousness. More systematic studies employing larger samples will investigate the prognostic validity of ApEn and its potential to predict outcomes in patients with VS.

The increasing number of individuals with DOC as a consequence of severe and widespread brain injury requires more reliable and objective methods to predict their prognosis. Our hypothesis might suggest an alternative model to assess consciousness at patients’ bedside by quantifying its functional prerequisites and dynamical correlates. This approach might provide a comprehensive view on how to evaluate residual neural complexity in non communicative severely brain damaged patients, thus bypassing the difficulties arising from the paradox of “the parts of an unknown whole” and from the wide variability of lesions underlying DOC. In this way we might improve our ability to indirectly explore consciousness and to predict outcomes in patients with VS and MCS.

By way of conclusion, we believe that approaching consciousness per se may encounter several difficulties because of its puzzling nature, whereas examining patients with DOC from a dynamical point of view may help us to understand the wide range of consciousness gradations daily observed in clinical practice.

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**REFERENCES**


