Neuronal dynamics and conscious experience: an example of reciprocal causation before epileptic seizures.

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Article publié dans *Phenomenology and the Cognitive Sciences* 1:169-180 (2002)

> « He was thinking, incidentally, that there was a moment or two in his epileptic condition almost before the fit itself, when suddenly amid the sadness, spiritual darkness and depression, his brain seemed to catch fire…his sensation of being alive and his awareness increased tenfold…his mind and heart were flooded by a dazzling light…culminating in a great calm, full of serene and harmonious joy and hope, full of understanding and the knowledge of the final cause. The fit (which followed) was of course unendurable. »
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> *Fyodor Dostoyevsky*, "*The Idiot*" (1868)

Clearly, the issue of neurophenomenology (Varela, 1996) is not only philosophical but empirical and experimental. Our purpose in this article is to illustrate concretely the efficiency of this approach in the field of neurosciences and, more precisely here, in epileptology. In particular, a number of recent observations have indicated that epileptic seizures do not arise suddenly simply as the effect of random fluctuations of brain activity, but require a process of "pre-seizure" changes that start long before. This interesting observation have been reported at two different levels of description: on the one hand, the epileptic patient often experiences some <u>warning symptoms</u> that precede seizures from several minutes to hours in the form of very specific lived events. On the other hand, the analyses of brain electrical activities have provided strong evidences that it is possible to detect a <u>pre-seizure state in the neuronal</u>

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dynamics several minutes before the electro-clinical onset of a seizure. The discovery of this possibility of seizure anticipation has been mainly motivated by new advances in mathematical methods for analyzing complex systems. According to this new approach called neurodynamics (Varela, 1999; Freeman, 2000; Abarbanel and Rabinovich, 2001), the brain activity can no longer be regarded as a purely random phenomenon but reflect the self-organization and emergent structures at multiple levels of integration, including that of conscious cognitive acts in relation to local neural activity. Based on this radical approach (Thompson and Varela, 2001), we review here some of the ongoing work of our research group concerning seizure anticipation. In particular, we discuss experimental evidences of 'upward' (local-to-global) formation of conscious experience and its neural substrate, but also of the 'downward' (global-to-local) determination of local neuronal activity by situated conscious activity and its substrate large-scale neural assemblies. This causal role of conscious experience may lead to new kinds of therapy for epileptic patients.

1. Neurodynamics: a mathematical description of brain dynamics

The active brain is inherently unstable with both temporal and spatial degrees of freedom. At the macroscopic level of description, brain dynamics exhibits a succession of transient spatio-temporal patterns of activity that mediate with adaptive perceptual synthesis and sensorimotor integration. Neural synchrony is an important candidate for such large-scale integration, mediated by neuronal groups that oscillate in specific bands and enter into precise phase-locking over a transient period of time (Varela et al., 2001). Furthermore it has been shown that large-scale integration implicates not only the establishment of dynamical links, but also their dismantling to give way for a next cognitive moment (Rodriguez et al., 1999). Indeed, much evidence shows that synchronous patterns are continually created, destroyed and subsequently recreated on multiple spatial and temporal scales in the nervous system. A central question is whether the spontaneous fluctuations of these patterns reflect a hidden dynamical structure. In the last decade, new answers were proposed to this problem (see Elbert et al., 1994 for a review). It was suggested that one difficulty to analyze complex signals was the result of examining the time series in terms of static rather than dynamic behavior. Indeed traditional analyses decompose the components of a complex activity and thus reflect a limited amount of information (one-dimensional). In contrast, the dynamical view suggests that a time series may reflect an unambiguous relation between present and future states and take into account all other variables participating in the dynamics of the system (multi-dimensional). This approach has drastically modified the manner in which physiological processes are viewed and described (see McKenna et al., 1994 for a review). For example, some neuronal processes formerly perceived as random, are now viewed in terms of lawful nonlinear pattern. Given that a complex dynamic system (such as the human nervous system) can involve an enormous number of interrelated dependent variables that are impossible to measure directly, the main problem is how to analyze a multidimensional dynamics knowing only a few variables that can be measured. In fact, it can be mathematically established (Taken, 1981) that, if we can measure any single variable with sufficient accuracy, for a long period of time, then it is possible to make quantitatively meaningful inferences about the underlying dynamical structure of the entire system from the behavior of this single variable. The geometrical properties of the trajectories evolving in this phase-space can be then expressed quantitatively using nonlinear measures. This neurodynamical approach provides a practical toolkit for the analysis of complex behaviors at different levels of organization of the nervous systems from single neurons to neuronal ensembles (Abarbanel and Rabinovich, 2001).

2. Examples of upward and downward causation in epilepsy.

Focal epileptic seizures originate in specific parts of the cortex and either remain confined to those areas or spread to other parts of the brain. The clinical manifestations of the seizures are related to the area of the cortex in which the seizures start, how widely they are propagated and how long they last. Since the first observations of Hughlings Jackson (1888), it is clear that a local epileptic activity often creates experiential events in the patient's mind. Typically, experiential phenomena occur at the beginning of a seizure and are a part of the patient's aura. Experiential responses that occur in epilepsy often involve the visual and auditory modalities in the form of illusions or, more importantly, hallucinations (Gloor, 1990). In the latter, the patient may see a scene, a face, or hear a voice or a piece of music being played. The content of these hallucinations usually appears familiar to him, although he may not always be able to identify it specifically. Olfactory and gustatory hallucinations are less common and their true experiential character is debatable, since they are usually not described by the patient as a specific olfactory or gustatory sensation. Memory phenomena of two kinds occur, in particular in temporal lobe seizures. First, there may be actual recall of past event or situation, usually more vivid and intrusive than a commonplace recollection or secondly, there may be a feeling of recognition, of familiarity or reminiscence. If the feeling of familiarity occurs in isolation, it is often inappropriately attached to the present, creating the illusion that the present is like the re-enactment of a past situation or event, the so-called "déjà-vu illusion". The patient is, however, always aware and usually struck by the illusionary nature of his experience. Penfield (1938) made the important discovery that these mental phenomena can be reproduced by electrical stimulation of the temporal lobe in epileptic patients during surgical procedures performed for the relief of their seizures. It follows that a local neuronal activity at the level of an epileptogenic zone can produce upward effects, acting eventually on the global level of a moment of consciousness.

The converse also seems to be the case, though less documented and controversial: for example, a subject can voluntarily affect a local epileptic activity, as indicated by numerous patient reports and a few clinically reported cases. Penfield and Jasper already in 1954 described a parietal seizure blocked by the initiation of a complex mathematical calculation, and later Morrell (1989) made a similar observation in a child with acquired aphasia. In a more indirect way, Fenwick (1981) reported a bio-feedback experiment where a patient was able to watch online the count of epileptic spikes arising from the temporal structures. She was asked to try by an act of will to reduce the number of spikes. The patient gradually learned to reduce the number of spikes compared with the control period. She soon became adept at this and was able to practice this outside the hospital with a subsequent reduction of her seizure frequency. One can assume that such intervention is possible because the epileptogenic zones are embedded in a complex network of other brain regions that actively participate in normal large-scale interactions. From these observations, it follows that the global pattern of integration (the result of upward causation) can produce downward effects, acting eventually on the local level of epileptogenic zones, whose activity can thus be taken as an indicator of the downward influence. Our own work demonstrated this effect in the case of a patient with an unusually focal and stable occipito-temporal epileptic discharge (Le Van Quyen et al., 1997a-b). The patient showed no evidence of cognitive impairment, and was willing to participate in simple cognitive testing consisting of a visual and auditory discrimination following an odd-ball protocol. For the visual task, the subject was asked to press a button when the target stimulus (a reversed Kanizsa triangle) appeared, in contrast to two other stimuli (a Kanizsa triangle and a real triangle). The temporal intervals between successive discharges were analyzed. At first glance, these intervals seemed like a pure oscillation with an added noise. A closer inspection, however, showed that the distribution of these intervals hid a finer dynamic pattern recovered in a phase-space (here a first-return map). Analysis revealed various clusters of unstable rhythmicities having an underling short-time causality: a tendency in successive time steps to follow recurrent trajectories that approach the clusters along a specific direction and remain nearby before they diverge away along another unstable direction. Furthermore, changes in the internal structure of the epileptic spike patterns co-varied with the specific mental state the subject is undergoing, as can be seen from a histogram of their occurrence in each case. This finding is already remarkable, but even more so is the finding that the shift of rhythmicities along the diagonal is about 20 msec, which means that the modulation is carried by activities in the gamma frequency range (30-70Hz). All of this suggests that the local activity under study is transitorily modulated by the gamma activity associated with the subject's cognitive states. These findings strongly suggest that the act of perception contributes, in a highly specific manner, via the phase synchrony of its associated neuronal assembly, to pull the epileptic activities towards particular unstable periodic orbits. This 'downward' (global-to-local) causation (Thompson and Varela, 2001) opens possibilities for a 'cognitive' intervention and control of epileptic seizures.

2. Two levels of description of the route towards an epileptic seizure.

Traditionally, the epileptic seizure has been the major focus of interest for diagnosis, treatment and research in the field of epilepsy. Much useful information can be gained, however, from studying events that precede the seizure. Indeed, there is evidence from several different sources that epileptic seizures not occur like a bolt from the blue and cannot be regarded in isolation:

• Pre-ictal experiences: The mental state of the patient (emotion, stress, sleep or lack of sleep, sleep-wake cycles, menses) and external environment (intermittent photic stimulation) are known to be favorable or facilitate seizures (Engel, 1989). The term "seizure threshold" is used to explain this propensity to seizures determined by predisposing and facilitating factors, i.e. they do not necessarily evoke seizures, but may increase the likelihood of attacks by sensitizing the brain to some stimulus for the period in which they operate. Lennox (1946) first proposed some of these factors in his "Reservoir Theory". Briefly this theory implies that the input of various metabolic, emotional and other factors fill a reservoir until it overflows (i.e. seizure threshold is reached) and a seizure ensues. Recognition of these state-dependent predisposing or precipitating factors provide evidences of the close interrelation between seizure activity and behavior. Nevertheless, how these interrelations interact to produce a seizure are not yet investigated. For this purpose, several recent attempts have been made to systematically describe the charting events surrounding the time of the seizure. For example, a multicenter study has recently investigated the frequency of the occurrence of warning symptoms (Rajna et al., 1997). Unexpectedly, about 50% of the patients experienced warning symptoms before a smaller or greater part of their seizures. These symptoms (also called prodomes) include depressive disorder, irritability, sleep disorders, nausea, headache. There was usually a long interval above 5 minutes (in 42% of the cases) between the warning symptom and the onset of the seizure. Despite the importance of these findings, no systematic strategy has yet been used for identifying warning events from the patient's experience. The analysis of the preictal experience has relied until now almost entirely on the use of questionnaires, which are not sufficient to obtain precise and reliable first-person descriptions (see next section).

• Pre-ictal Neuro-Dynamical changes:

The analysis of dynamical changes in the electroencephalographic activity (EEG) preceding an epileptic seizure allows the characterization of a pre-ictal state several minutes prior to seizure onset (see Le Van Quyen et al., 2001b for a review). Babloyantz and Destexhe (1986) were the first to demonstrate that the generation of ictal activity in the brain corresponds with a specific dynamical state which is clearly different from normal ongoing activity. A more precise analysis of the transition from interictal state to the ictal state has been explored by our group in the last few years (Martinerie et al., 1998; Le Van Quyen et al.,1999; Le Van Quyen et al., 2001a). In a population of 47 patients, we demonstrated that in most cases (90%) changes toward long-lasting states occurred before the seizure (mean 5 minutes) and were more pronounced compared to maximal changes occurring during interictal states, thus enabling us to define a preictal state. Lehnertz and Elger (1998) confirmed these findings in a comparable group of patients. Taken together, these converging evidences suggest that the seizure might be interpreted as the "tip of the iceberg" in the sense that it is just the climax of a process of changes that starts long before. These findings are promising to characterize in formal terms the pre-ictal state, and thus establish the necessary conditions for the occurrence of a seizure. More precisely, we can distinguish two main dynamical scenarios according to which the brain can pass from a normal to an ictal mode of behavior. In *scenario 1*, the dynamical system representing brain activity is subjected to gradual endogenous or exogenous changes before a transition to seizure takes place, at a time scale much longer that the actual seizure onset. These changes can lead to closing the distance, in an topological sense, between the interictal and an ictal dynamics. In *scenario 2*, we assume that the changes of the system's parameters affect directly the current dynamics. The last can deform either gradually or suddenly into a low-dimensional dynamics and when this deformation becomes substantial a clinically manifest seizure will take place. It is much too early to predict which of these two scenarios are more closer to the reality. Of course, longer time-scales may be useful for better characterization and understanding of mechanisms of generation and timing of epileptic seizures. Furthermore, given the importance of these results for the patients themselves, it must be verified whether the preictal neurodynamical changes are or are not accompanied by experiential phenomena, which need an explicit first-person account.

3. The First and Third: A necessary circulation.

The findings of preictal neurodynamical changes are particularly interesting since they lead us to address the following question: is it possible to collect precise descriptions of the subjective experience of epileptic patients during the minutes and hours preceding seizures? It is particularly difficult for an epileptic patient to describe his preictal experience, for the following reasons: 1) The patient may have most of his seizures during sleep. 2) The patient may experience warning signals but doesn't remember them because of postictal amnesia. 3) Antiepileptic drugs may reduce the patient's ability to perceive subtle sensations preceding seizures. 4) The perception of warning signals often triggers an emotional reaction of stress and panic, which in turn hampers the perception of warning signals. 5) The language usually used in the medical circle for describing seizures is underlain by the assumption that seizures cannot be anticipated nor influenced by the patient : this does not encourage the awareness of anticipating signals nor the will to describe them.

These reasons make preictal experience even more difficult to describe than more common subjective experiences. Furthermore, it would be very naive to believe that describing subjective experience in general is basically an easy task. A large part of our experience is pre-thought, unconscious. This explains the paucity of initial verbal self-reports on any subjective experience. For a person to be able to describe his experience, he must become conscious of this pre-thought knowledge. Moreover, this awareness necessitates a special training and/or a mediation. Therefore, in order to help the patients to become aware of their preictal experience and to describe it, we use the following complementary methods:

1) Relaxation techniques: We are exploring the possibility of training patients in various relaxation techniques in order to reduce the fear which clouds their perception of warning signals just before seizures.

2) Self-report : After each seizure, the patient is invited to complete a log form, containing questions which draw his attention to the different aspects of his preictal experience.

3) Interview: The specific technique we use helps the patient to explicitate his experience. This process of explicitation unfolds in three stages :

- guiding the patient towards the concrete evocation of a particular preictal experience from the past, by helping him to rediscover, in a very precise manner, the images, sensations, sounds... that are associated with his experience, until he feels that he is "reliving" it. At this stage, a few patients are afraid that the evocation of a past seizure might trigger a new seizure: in our experience, this happened only once, with a patient suffering from a "reflex epilepsy" (a particular type of epilepsy which is precipitated by specific external or internal stimuli).
- helping the patient to slow down the "film" of his experience, in order to become aware of his internal process and aspects of his experience which until then were pre-thought. At this stage, it may be useful to show the video recordings to the in-patients whose EEG-Video is recorded, in order to help them to recall their internal sensations. After analysis of the EEG, the moment of the preictal neurodynamical change should be indicated to the patient, to help him to focus even more precisely upon his sensations at this particular moment.
- enabling him to put into words his experience, with the help of a particular form of questioning. After this description, the next important step is analyzing each description in order to extract from it a synthetic representation of the dynamical micro-temporal structure of the experience, and also of the dimensions of the experience which are not temporal.

Clearly, it would be futile to stay with first-person description in isolation. As introduced by F. Varela (1996), this research seeks articulations by <u>mutual constraints</u> between the field of phenomena revealed by experience (first-person) and the correlated field of phenomena established by the neurodynamics (third-person). In particular, we need to build appropriate links with the geometry of the phase space landscape and, in particular, with the domain of stable/unstable regions which push or pull the trajectories along a variety of specific causal paths. The particular path that a dynamical system follows is determined by its current state in conjunction with its global intrinsic dynamics. This is not merely a formal description (as shown in section 2), but exhibits exactly the kind of simultaneous unfolding that phenomenological observation suggests (Varela, 1999): first, there is “local-to-global” determination as a result of which every novel path has its own feature, lifetime and domains of interactions. Second, there is “global-to-local” determination whereby global intrinsic characteristics of a system govern or constrain future behavior. They are typically manifest through changes in “control parameters” and boundary conditions, rather than through the interaction dynamical variables. These control parameters constrain or prescribe the behavior of individual paths, “enslaving” them to specific regions in the phase-space As described above, there are two main dynamical scenarios according to which the brain can pass from a normal to an ictal mode of behavior. The crucial question is now: how can this preictal dynamics be understood as a moment of consciousness? One way this can be done is by having a transient state mobilizing numerous, widely distributed, and constantly interacting functional areas of the brain (Thompson and Varela, 2001). The assumption is that such dynamic integration underlies both the unitary and the transient character of moment-to-moment experience (what Husserl called ‘the living present’). One currently explored proposal is that such large-scale integration could be mediated by neuronal groups that exhibit a wide range of oscillations (theta to gamma ranges, 6-80 Hz) and can enter into precise *synchrony* over a limited period of time (a fraction of a second). These large-scale synchronous patterns are thus like keys that combine with the system lock to open the door of a moment of consciousness. The scientific investigation of possible “conscious regions” in the state space is still in its infancy and needs further developments.

5. Future perspectives: seizure control through “mental causation”

In spite of recent developments of new antiepileptic drugs, 30-40% of patients with epilepsy do not become seizure-free. The perspective opened by the ability to anticipate a seizure several minutes in advance would provide a time window during which therapeutic measures may be taken to avoid the risk of seizure occurrence. In this context, an important therapeutic measure could be <u>self-control</u>: a patient could learn to discriminate early signs of the pre-ictal activity and subsequently generate cognitive/behavioral responses to inhibit the epileptogenic processes. Indeed some patients may be able to abort their own epileptic seizures by various techniques. Mental actions (i.e. concentrating intensively) or physical actions (i.e. applying a specific stimulus such as rubbing the body part involved in ictal onset), can occasionally be effectively employed to improve epileptic seizure control. This approach is illustrated by the classic case of Efron (1957). His patient had complex partial seizures with a long olfactory pre-seizure state. A strong olfactory stimulus, such as perfume, could abort her seizures. A few months later, this stimuli could be conditioned to a bracelet and the sight of the patient’s bracelet was substituted for the strong smell. Finally, a second order conditioning was possible: just thinking about the bracelet was effective in aborting seizure. This study marked the beginning of our understanding of how conditioning mechanisms could be systematically used to alter and inhibit the development of an ongoing seizure. A recent study has shown that detailed self-observation which aimed at identifying warning signals and the development of proper countermeasures achieved a significant reduction of seizures and can contribute to improving long-standing intractable epilepsies (Schmid-Schönbein, 1998). In parallel to the discrimination of early signs of epileptogenic activities, biofeedback procedure can also be used to produce specific changes in EEG patterns activities, such as reduction of abnormal low frequencies (Birbaumer et al., 1990) or facilitation of intermediate rhythmic frequencies (Sterman et al., 1981).

6. Conclusion

Our understanding of the mechanism that underlies the generation of seizures has progressed to the point where it is clear that most seizures are unlikely to have a random basis. Seizures cannot be regarded in isolation but require a process of changes in brain dynamics that starts long before its manifestation. These observations reaffirm the point that epileptic seizures do not occur in a behavioral vacuum and, indeed, warning experiential events are well-known to occur during the pre-ictal phase and at the very beginning of the seizure. These experiential phenomena raise interesting questions concerning brain mechanisms involved in the production of human experiences. Nevertheless, a first-person methodology appears here crucial to describe these experiences in a rigorous way. Furthermore, the efficiency of this approach needs a continuous circulation between the field of phenomena revealed by the patient’s experience and the correlated field of phenomena established by the neurodynamics. Finally, if conscious experience is an emergent phenomenon, then we can accordingly hypothesize that it is downwardly causally efficacious with respect to neural activity, and therefore that we should be able to observe the effects of a moment of consciousness and its substrate large-scale neural assembly at the level of the local properties of neural activity. Indeed we have already reported that a particular cognitive task can manifest a specific effect in the local activity given by an epileptic discharge, when seen at a sufficient level of detail. Nevertheless, this dynamical view of epilepsy as being a reciprocal causation between a human experience and the brain functioning require further careful conceptual and empirical investigation.

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