Neural sequences: experimental evidence and deductive principles

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Summary

Comprehensive study of brain performances implies reference to sequences of repetitive functional elements (events). In this particular experimental field, these are sequences of psychomotor reactions and particularly verbal reactions with different modalities of stimuli and pre-established intervals before responding. The organization of these sequences or temporal cycles is based on different sets of stimuli and series of processes that are measured through parameters related to trials that activate the central mechanism of working memory. Monitoring of sequences in rehabilitation training is performed through analysis of the course of the intermediary oscillations between the onset and the end (conventionally established) of treatment. Knowledge of these oscillations provides useful information on the nature of facilitating or fatiguing effects of training procedures.

KEY WORDS: sequences, training in neurorehabilitation, verbal reactions, working memory.

Introduction

Over the past fifteen years, our systematic verbochronometry research in normal and neurologically impaired subjects has allowed us to analyze, in the context of neurorehabilitation training, fluctuations in verbal reaction parameters during paradigmatic twelve-reaction stochastic sequences and during more prolonged sequences of self-rated reactions (1,2). In the present paper we focus on sequences, and specifically neural sequences, looking at the intimate structure of series of reactions, at the intrinsic interdependence of successive reaction parameters, at the neurological and psychological origins of these sequences, and at the modalities by which they can come to modify brain function and structure in learning processes. On the basis of these data one can gain prognostic clues useful for evaluation and reliable criteria for planning training.

This is a rather new line of research in the neurosciences which began to emerge in its own right when, in the field of physics, Heisenberg's uncertainty principle (or principle of indeterminism), which is supported by the quanta theory, and Zadeh’s fuzzy theory opened up important new perspectives in the philosophy of science. In fact, a predominant trend in scientific studies throughout the last century was the search for the least element. In physics: the quantum. In biology: the cell. In motor science: the motor unit. In neurology: the neuron. In cognitive psychology: Bergson’s "intuitive moment". In psychological experience: the present according to St Augustine. In introspective philosophy: the Self (3,4). This interest in single elements is still prevalent in many disciplines: theoretical physics, analytical anatomy, analytical physiology, neurohistology and introspective analysis of time (according to Bergson’s "intuitive moment"), and certainly this research led to fundamental technical progress making it possible to master these areas of study. However, this interest in single elements can be likened to the interest that a naïve archeologist might feel when he finds he is able to identify the single bricks of a hidden building: his discovery, while fascinating, is of limited value because he remains far from understanding the true essence of the building.

A similar criticism can be applied to human behavior. An existence, if limited to a single moment in time, a single instant of self-awareness, would be an existence entirely devoid of meaning. Life is a sequence of passages of which we must be aware in order to be able to learn to live and to accept dying (5). Indeed, when a line of research is confined to a single element (or event) this creates difficulties for anyone wishing to investigate reality as a whole, in all its complexity:

i) The study of quanta involves the dimensions of space and time, their connections and the development of new related features;
ii) The many single details of a cell tell us very little about how living cells exist and about their relationship with the physical-chemical environment from which they draw nourishment and to which they react;
iii) The motor unit remains inert matter if we do not study it as a living entity – as part of an agonist-antagonist-synergist kinetic set that is activated in pursuit of a target;
iv) Similarly, we need to consider the neuron not in isolation but in the context of neurological events that can occur only in an ensemble of neurons through a sequence of excitations and inhibitions, post-excitatory potentials and post-inhibitory potentials occurring through neuronal synapses;
v) To reduce cognitive psychology to intuitive moments is like starting the analysis at the end, thereby leaving out all the sequences of compulsory and voluntary...
processes that interact in a flow of subliminal additions, integrations, differentiations, comparisons and correlations of different representations;
v) Similarly, St Augustine’s concept of present is the result of an abstract overview of sequences of recorded and stored information, linked to current representations and to those of future probable sequences, assembled in a moment of meditation.

These six critical points substantiate the idea that a unique and ultimate guiding thread is to be found in sequences of elements (events). On the other hand, to understand a primary sequence in its entirety it is necessary to identify changes in the parameter values during the sequence, shifts from intrinsic stochastic constraints, and the interference of direct control on the part of the subject, all of which are outside human perception. The underlying original sequence of events is a whole, not split by the cognitive nucleus of the Self into a subject-object dualism. It can be compared to a net whose knots (the equivalents of Selves) are the intersections of interfering and intersecting sequences that branch off rather in the way the trees do, or lighting. To make this model of reference more adherent to the real situation, we must add to it an essential dynamic character: in this complex system (the net) there exist many stationary states whose nature and number depend on intrinsic parameters of control. At higher values of these parameters the system presents bifurcation points. The lines in the net are irregularly zig-zagging, and states of disorder with non-linear patterns can emerge. In accordance with this scheme of a dynamic, complex system, brain performances, too, are characterized by arborizations, recurrent feedbacks, non-linear trajectories, sometimes of a chaotic nature. These features have been studied particularly in the sequences of speaking, in the passages from intention to the intermediate unconscious processes, sometimes of a chaotic nature.

Recurrent effects in neural sequences

Neil Kirby in 1980 (7), in an important paper published as a chapter in Welford’s book Reaction Times (8), sought to investigate the origin of the oscillations-in-time of single or choice reactions occurring in sequences prolonged until 1000 reactions. He interpreted the repetitive and alternating effects as depending on a double matrix: (i) cerebral processes with excitability modifications following previous excitations; (ii) psychological factors of expectancy and prediction that imply activations of short term memory and working memory.

De Brabander (9) and Davidson (10) applied to the study of sequences the theories of complex systems and chaos in line with the principles of entropy. Important neurophysiological and neuropsychological investigations of reaction sequences have been carried out by Hikosaka et al. of the Universities of Tokyo and Kyoto and the Institute of Bethesda (11). A first batch of experiments on the learning process of several programs of trials at different levels of intensity was performed in monkeys; a second one was completed in humans and involved the examination of reaction times [according to our methodology of Multiple Delayed Reaction Verbochronometry (MDRV) and 100 Self-Rated reactions (SR100) trials]. Hikosaka et al. think that these oscillations could depend “on a variability of processes similar to those occurring within a narrower range at much shorter periods of time in 12 reactions of a single trial, and at a slightly more prolonged performance in trials of sustained attention with self-rated intervals of stimuli, responsible for perseverations and pauses”.

With regard to the large bivalent oscillations occurring during learning processes, Hikosaka et al. ascribe these to the fact that “a sequential procedure is acquired through the functions of two brain systems that operate each independently of the other, in parallel nets, one occurring in a spatial, the other in a motor dimension”. Moreover Bekker et al. (12) investigated the electrophysiological correlations of mental processes in protracted sequences.

Training of working memory processes

Serial reactions involving working memory processes have been applied in neurorehabilitation since 1999, starting with Klingberg’s work at the Karolinska Institute with children affected by attention-deficit-hyperactivity disorder (13).

Over the past two years our group at the IRCCS S. Maugeri Foundation in Veruno (Novara, Italy) has been applying training of working memory in a larger field of neurological disorders. Our work started in 1985 with the application of diagnostic-functional assessment tests based on series of verbal reactions (14). The verbal channel was chosen, instead of the usual hand-key pressing modality, for practical and theoretical reasons: the correspondence between the stimulus and the response is more direct; the range of possible choice of stimuli and modality of reactions is wider owing to the uniquely human – copiousness of speech, and the technical system required was simpler and more flexible. The subjects’ performances consisted mainly of delayed reactions that imply the involvement of processes of working memory. These performances are task-independent: therefore the recourse to the verbal channel would not imply a limitation of the examination to the field of speaking, but also involves the other psychomotor channels as exclave-executing systems (14).

The series of reactions, on the part of the subject, are of three different types: i) 12 examiner-rated (Er) reactions, ii) 100 self-rated reactions (SR100), iii) 2000 reactions of both types carried out in different periods, twice weekly for a month (4) during training of working memory.

The 51 normal control subjects examined were 22 males, 29 females; age: 18-82 years; education: 4-30 years. The 61 patients were: 42 males and 19 females; age: 29-87 years; education: 5-18 years; 32 were affected by Parkinson’s disease, seven by essential tremor, four by cerebral vasculopathy, five by confusional syndromes due to cranial trauma, three by mental deterioration, three by chronic fatigue syndrome, and seven by heterogeneous psychoneurotic syndromes.
We have established that in sequences of 12 reactions a certain deterministic intrinsic auto-organization occurs that makes the oscillations of their parameters (mainly time reactions) converge to produce a significant mean value.

On the other hand, the measurement of the whole intermediary course of more protracted series of reactions sheds light upon the occurrence of markedly irregular intermediary fluctuations in reaction parameters, with many unpredictable orders and directions. In SR120, the course of the sequences following the first set of twelve reactions presented marked deviations from the previous oscillations (within 12α); we were thus able to consider separately the first 12 reactions (12α) and the subsequent groups of 12 reactions (12α). By measuring the deviation in the 12α group appearing between the first interstimulus interval (ISI) and the subsequent ISI (∆α) and the deviation between the mean value of 12α and that of the subsequent 12α groups, we identified some segments in the sequences that appeared chaotic and others that appeared more regular. The distribution of the ISIs in 12α in the 51 normal subjects, ranging from 150 to 900 ms, showed a bimodal shape with a first curve from 100 to 500 ms, and a second from 500 to 900 ms.

Sharp deviations were observed in the course of the sequences. We found that the ∆ISI 1-12 values (i.e., the difference between ISI values at the first interval and at the 12th interval) presented a bimodal shape, respectively from 50 to 100 ms (more ordered sequence) and from 100 to 200 ms (seemingly chaotic sequences), with prevalence of impulsive subjects in the first group, and of reflective ones in the second.

The main result of this research is that complex series of variations occur in the parameter of a reaction with respect to the previous one: groupings of values of adjacent reactions (chunking) can be identified, as well as oscillatory irregular decreases and increases, sometimes converging towards a mean value, sometimes diverging and showing marked deviations from the initial values (14).

This range of variations was originally classified as an expression of stochastic functions inherent in the series of tests with a number of reactions sufficient to detect a significant mean value. But the real extent of the fluctuations, revealed by the measurements of the intermediary oscillations during long sequences, is much wider than the span considered for the measurement of the mean value of time reactions, and appears to reflect a behavior common to most physical phenomena. Thus, our research revealed a large series of sequences of both chaotic and deterministic modality, and we tried to detect the influence of intrinsic and extrinsic factors in the production of this oscillatory behavior (4).

Fluctuations in complex systems

The term used in dynamic complex systems to indicate the occurrence of variations or oscillations in the behavior of parameters of a quantity under examination is “fluctuations”. Fluctuations, even minor ones, may be sufficient to produce a perturbation of the system that induces in it a transformation towards a stable state different from the current one. In this framework, fluctuations are important factors for the evolution of a system. In deterministic (it is understood that, thanks to the concatenations between causes and effects, we can predict exactly the behavior of nature. However, in the behavior of dynamic complex systems a latent aleatory character emerges (15): “Very small, differences in the initial conditions can produce very great differences in the final phenomena”. This is deterministic chaos (4).

Today, the student of neural sequences can profit from many investigations into not only the number and degree of sequences related to many kinds of performances, but also their neural substrates. Some of them are characterized by a high degree of freedom as in the case of scratching; others are more organized and purposeful, like the movements of hens towards grains of wheat, or of a man taking an object; these are sequences charged with praxic integrations. Other movement sequences, e.g., the flight of a fly, contain an intermediary degree of freedom (16,17). Yet, in all these sequences a mixture and combination of variations in brain excitability and variations of the information from the environment seem to be responsible for complex trajectories.

Transfer processes and pulling effects

Transfer processes

Transfer processes in neural sequences can be explained, preliminarily, through a simple allegorical example.

Around the time I was engaged in measurements of the intermediary oscillations in the training of verbal reactions and was just starting to see the emergence of rules governing the sequences, I happened to take my little grandson Thomas [about whom I wrote in my book Italians and Germans (18)] to a children’s play park. When we got there, little Thomas ran over to three rocking toys fixed on powerful iron springs inserted in the ground (Fig. 1). These toys were shaped to look like animals: one resembled a horse, relatively small; the second a hen, relatively large with respect to the third, which looked like a dog. The three “animals” could be made to swing by a relatively weak push; after a first, single push they could swing for quite a long time; their oscillations were repetitive, stereotyped and showed different amplitudes, proportional to the force of the push. The child sitting on

Figure 1 - Little Thomas’s three spring-toy animals.
them could stop or amplify these oscillations at will. The three “animals” were oriented towards an ideal center, about a meter from each of them. Had they been able to move in the direction in which they were facing, they would have met in the middle, at which point their oscillations would have interfered with one another in various ways. Anyway, given that the toys were fixed to the powerful springs in the ground, the axis of all the oscillations remained topologically immovable; these were repetitive, essentially stereotyped sequences fixed in their local space: they moved about their axes but remained in a single, stationary point; there was no transfer. This situation can be likened that of perseverations, i.e. iterative sequences occurring without any participation of the subject who remains inattentive and absent-minded, moved by series of extrinsic events like the periodic motions of the springs. On the contrary many kinds of oscillation, even in the physical world, are characterized by processes of transfer, which is a connatural property of their kinesthetic essence extending in space. Biological sequences are more specifically qualified by processes of transfer, but in a quite different context: the transfer is realized thanks to neural mediation; repeated changes in oscillations produce modifications of ensembles of neurons in the brain. Changes in oscillations of neural performances, i.e. new orders of neuromotor executions, form corresponding neural patterns that connect, in space, newly shaped substrates of different sequences. It is worth underlining the modality of the transfer, which is independent of the psychological attitude of the subject: we are talking about biophysical and biochemical processes that take place within the structure of the nervous system; the transfer is an unconscious mechanism even when the subject intentionally carries out the sequence with the purpose of acquiring new abilities. In a subsequent phase the creative activity of an imaginative and reflective subject, acting as an organized guide, can give rise to other nearly infinite sequences which can, in turn, produce new transfers.

**Pulling effects**

Starting from these processes of neuroplastic transfer we can analyze briefly a further fundamental phenomenon of neural sequences, the pulling (or dragging) effect. A pulling effect can occur between two sequences endowed with transfer ability. As an example we may take psychomotor reactions performed in association with gait sequences, a situation that is at present under experimental investigation at our institute in Veruno. A second kind of pulling effect can occur between one of the above-mentioned sequences and those produced by vital energy (or “orné”). Biological energy is expressed by the impulse to move (the restless being) that characterizes the first years of life in particular and that has its source in the brainstem reticular system of Moruzzi-Magoun. This system was identified as a multi-faceted vigilance generator active in different emotional-affective and instinctive experiences. The pulling effect makes this complex system resonate but it does so only when there is still a glimmer of élan vital still surviving in the brain. If this goes out, as in the different anhedonia syndromes, ranging from depressive psychoses and cyclical psychoses to the most severe cases of chronic fatigue, no pulling effects can occur: in these conditions, all attempts to appeal to the subject’s capacity for psychological reaction will come to nothing; the appealing sequence produces no transfer, like a message sent out in the wildest desert.

These conditions represent the second case, after that analyzed with reference to transfer processes: in both conditions the cerebral support emerges as an absolute necessity in the evolution of functional sequences (i.e. it permits the acquisition of previously learned ability). An interpretation of these phenomena from a physical point of view was advanced by José Alvarez Lopez (19) through recourse to the concept of entropy and particularly the negative entropy (negentropy) specific to vital processes that export entropy in order to maintain their own entropy at a low level. Further interpretations can be found in the recent paper by Patricia Churchland (20).

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