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RANDOM PROCESSES IN THE NERVOUS SYSTEM

by

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In an article on the subject of *The Brain,* which appeared in the May 1971 issue of the Netherlands journal *Geestelijke Volksgezondheid,* De Froe, after a general approach, poses the question: ‘what actually goes on in our minds?’.

What strikes one when reading De Froe’s paper is that when he describes the functions and tasks of the brain he refers to this organ in the plural. This seems odd, even though the plural form is commonly used in everyday language. We mostly talk about ‘brains’ and sometimes about ‘the brain’, but always, and especially in the latter case, with a sense of respect. One can find this out for oneself by saying the words ‘brains’ and ‘the brain’ aloud. One will then notice that ‘brains’ should really be written with a capital ‘B’ and that ‘the brain’ should be capitalised in full, thus ‘Brains’ and ‘THE BRAIN’. Incidentally, De Froe starts his paper with the phrase *pluralis majestatis.* Later on, remarkably enough, the or ‘in which all of us and many animal species possess is, as it were, ‘addressed’ and referred to in the third person plural of majesty rather than ‘discussed’. Listen to De Froe when speaking also on behalf of others he provides some of the answers to his earlier question:

> ‘The brains are much smarter than we are. *They* know more and do more’.

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and: ‘The brains receive and relate information. *They* remain continuously active night and day’.

Yet this approach is only a few decades old, as the historical review with which De Froe opens his article clearly shows. It seems to me that the sense of respect arose from the scientific research done on the brains. And certainly not only because this research provided a substrate for the concepts ‘soul’ and ‘spirit’; it arose also because of and perhaps especially because of the almost inconceivable multiplicity and complex nature of the functions of the nervous system revealed by this research. It is possible though that this feeling about the function of the brain is even older. After all it has been voiced before in the writings of earlier authors. De Froe tells us that the anatomists of the past found a source of amusement in giving names conveying sexual allusions to certain parts of the brains: ‘One might put it that they were practising pornography in this field.’ In view of the sacred nature of pornographic words, it seems to me that by using them in that way these investigators already had some ideas of the brain’s true function.

Although we think we already know a good deal about the structure and functioning of our brain, enough at least that any increase in our knowledge evokes the feeling of respect I have referred to, this knowledge is still extremely fragmentary. Everyone who does research in this field, on the basis of whatever discipline, knows that he is concerned with only a small piece of an immeasurable jig-saw puzzle. A puzzle so large, but whose solution(s) is (are) so promising, that I share with many others the opinion that this research is at least as much worth promoting as was (and still is) the case for nuclear physics. To give an example: on the basis of Pavlov’s work on conditioned reflexes (1903) it seems now (1974) that we may learn to manage ourselves better than we were willing to believe until recently and that in the future we will be able for instance by conditional training of functions of our body that are still considered not to be under our volitional control to cure ourselves of certain diseases now requiring complicated treatment with drugs...

The danger of the usual line of approach today is that too often we compare the functioning of our brain, and therefore of ourselves, with ‘the computer’. For the uninitiated a magic apparatus which can calculate ‘everything’ and can do ‘everything’, on the basis of fixed rules. We thus run the risk of coming to consider our brain as an extremely complicated automaton, but nevertheless as an automaton, in other words a thing that works on the basis of fixed rules and whose workings after further unravelling of what is hidden in the future are known and therefore predictable, so that the picture of absolute control, the ‘Big-Brother-is-Watching-You’ horror looms up. Refined psychological and electronic control would make of man a robot in the hands of a few. However, this phenomenon is anything but futuristic; it has existed for centuries. In the last world war hundreds of millions became robots in the hands of a single man. And numerous, often terrifying examples of influences at work today, ranging from fairly .subtle to relatively coarse, are supplied by the recent history of, for instance, the role of the mass media in local and international events.

I do not deny that the investigation of the nervous system might increase the possibilities for mass influences even further, but I continue to be sceptical about the great claims made in this respect. The psychological approach to and the control of large masses by means of the communication media has become an inseparable part of our society, and I feel that improvements in this field are more likely to be quantitative than qualitative. Also we have become all too accustomed to the chemical and biological influences on man. But I believe that progress *in biological* research and in particular with regard to the functioning of the nervous system will provide each of us, as individuals, with more weapons to resist undesired influences on the group and the individual. If, for instance, this research should enable a human being to suspend his sense of pain at will (a conceivable -development, in my opinion) or to shut off his consciousness under heavy psychological pressure, torture or third-degree interrogation would become useless. Or, to take a more positive example: if man could learn to use his brain more effectively he would be armed better against influences which he rejects, and he could make himself more conscious of the ‘good’ and ‘bad’ aspects of an influence. And also he could make himself more conscious of his function as a social being. You may call this science fiction or even say I am biased (although I do not think I am), but you will, I hope, be able to share my feeling of anxiety that, after a period in which science and technique have made massive destruction and massive manipulation possible, these sciences are on the threshold of developments which can promote individual resistance as well as individual progression and social consciousness, and that research in this field is currently being impeded. When man is no longer unconditionally susceptible to stimuli applied by others and to threats of hunger, torture, unwanted operations, blackmail, solitary confinement, and a speedy or slow violent death threats over which he has no control then in my opinion, he need not be and cannot be involuntarily manipulated because he is too complex to be absolutely controlled in the mass by a few. Aldous Huxley's Brave New World describes a world filled with subhuman structures, not with people.

The very complexity of our brain in itself means that the thesis that when everything is known everything will consequently be predictable and controllable is untenable. The fact that complexity increases unpredictability is also used in practice to create what are called random processes. If, for instance, one puts a series of five regular pulses of different frequencies into an electronic instrument which produces a pulse when it receives two or more pulses within a certain short period, the new pulse series can only be distinguished from a random series with great difficulty and at great expense. And here we are only concerned with a simple process. For much more complicated processes it is not realistic to assume that they could all be recognised in all detail at the same time and therefore that they could all be controlled. In 1948 already, Wiener stated that the ultimate model for a cat is of course another cat. In that case it makes no difference whether the latter was born or should it ever become possible made in a laboratory. In both cases it would be possible to rear the animal to be so stupid that many of its reactions would be predictable; but what we have get then is not a cat but a dumb creature having only its appearance in common with other cats. I am, therefore, inclined to reverse the conclusion: as soon as manipulation makes some living being 'completely' or to a great extent manageable, it no longer belongs, except for its external characteristics, to the class to which it originally belonged.

In short: great complexity and randomness are separable in theory but not in practice. In this context I am not concerned with absolute defini tions of the concept random. When *within a given system* (organism, group of organisms) a process occurs whose effects are not predictable *in detail for that system* and cannot be influenced in detail *by that system,* I call this a random process *within that system.* Even if such a process should be completely recognisable and predictable for an *outsider* and therefore not random for him, that process is nevertheless a random process because the outsider's knowledge is *irrelevant* for the system in question.

Another popular idea is that we function according to fixed rules. This thesis too is untenable. I shall try to explain why.

Most organisms live at temperatures between 0° and 40° Celsius, far from the absolute zero point, which means that the molecules in our body perform the random motions, which, after their discoverer, are called Brownian movement. As a result of these movements, particles of matter for instance the sugar molecules in our blood will move from areas with a high concentration of this kind of particle to the areas where it is used and where its concentration is consequently low. This current of particles created by Brownian movement and at concentration differences, i.e. diffusion, is essential for our functioning and therefore forms a condition for life itself. Without these random processes life is impossible.

It is extraordinary that this thesis must be restated today. In earlier centuries, and at present among so-called 'primitive' societies in other words among peoples (still?) not infected by the Western ideology irregularity, unpredictability, was one of the most important indications of the presence of life. All irregular phenomena were deified, that is, ascribed to (a higher form of) life. Unpredictable behaviour and life were also seen as closely related in the western world. So much so that even Brown had great difficulty in accepting that the irregular dancing movement of small particles suspended in a liquid, his own discovery, was not caused by life in these particles. Today, on the contrary, we associate life too much with the activity of automatons. Here I run the risk of being misunderstood, because it is indeed so that automation theory or, taken more widely, systems theory is of fundamental importance for the study and understanding of organisms and ultimately of ourselves. But I have asked myself at times how a hypothetical extra terrestrial visitor to the moon would see the Surveyor or the Lunogod. Something settles on the moon and starts to move, looks around, shifts its position, remains motionless throughout the moon-night, becomes active when it ends, and feeds itself on sunlight. After further consideration our guest realises that the range of possibilities is limited but that nevertheless the action pattern is not, or not entirely, predictable. Finally, the object ceases to move altogether, it 'dies'. He would now find that it comprised a complicated system of wires and parts, a kind of nervous system, and he may have noted that it was in contact with beings somewhere else, for instance on the earth. Was it alive? In his position my answer would have been in the affirmative.

Unpredictability, irregularity, is also a characteristic of creativity. Try seeing this in reverse. When a certain production process is predictable in every detail we do not speak of creativity but of productivity. As a possible source of creativity, De Froe refers to the clash between the world of dreams and the world of knowledge. Here too, the aspect of unpredictability is concealed as it is in other aspects of creativity. It is also concealed in the complexity of our nervous system.

If we take a look at our nervous system, we know now that the basic elements in this system are the nerve cells. These cells operate on the basis of a difference in electric voltage over the cell membrane caused by a difference in the concentration of ions inside and outside of the cell. This potential difference is of essential importance for the sensitivity of these cells to stimuli, for their capacity to pass messages along. Both diffusion and the transmission of messages reduce the concentration differences, but these are restored by the metabolic processes occurring in the cells. This requires the presence of fuel molecules, and molecular collisions. Both processes occur as a result of the thermal random movements. The continuous inflow and outflow of electrically charged particles, the ions, even in the resting state, also has the effect that the difference in electric voltage over the cell membrane fluctuates continuously, albeit only slightly, around a mean difference in electrical potential. This random fluctuation of the electrical potential, which is caused directly (and indirectly) by the diffusion, is called electrical membrane noise, because it occurs over and is related to the cell membrane.

The investigation of membrane noise helps us to understand the structure and the function of these membranes. This is not the place to go into the subject in detail; it will suffice to note that when the electrical potential over the membrane of nerve cells changes, the character and intensity of the noise changes too. It is conceivable that differences between nerve cells are at least partially dependent on differences in the character and intensity of these random processes.

This can be extremely important. When a nerve cell receives stimuli just strong enough to cause it to fire (i.e. to send an electric signal along the cable belonging to this cell, to other nerve cells, or to muscle or gland cells) it sometimes happens that the cell does not fire even when all of the stimuli are identical. The sensitivity of the cell to stimuli . fluctuates in a random way. And this fluctuation is related to the membrane noise referred to. A firing of the cell consists of a short impulse with an amplitude of about 0.1 Volt, which is transmitted along the nerve fiber. An impulse of this kind is called an action potential. And here we learn that the small random movements of molecules can lead to an element of unpredictability in the occurrence of these large signals.

In some sensory mechanisms the nerve cells continuously produce long series of action potentials on a random basis. Therefore, we cannot predict when such a cell will fire, and we can only observe that the cell *produces on average a certain* number of action potentials per second. For a few sensory mechanisms (e.g. in the eye) it is clear that *this is* due to random processes inherent in the stimuli themselves, for instance the variation in the stream of light particles falling on these sensory cells.

In other cases the membrane noise can be responsible for the random firing. The irregular activity of these cells remains (to a certain degree) irregular but the average frequency of the signals per second is dependent on the strength of the stimulus. The stimulus strength modulates this random process, and we know now that the modulation of a random process of this kind forms a highly efficient mode of signal transmission.

The use of models has made it possible to demonstrate that membrane noise contributes to the development of extremely sensitive elements in which the average firing frequency is a measure for the intensity of the stimulus. Without the presence of random processes (noise) this sensitive signalling could not take place. It is clear that the small random phenomena occurring at the molecular level have very important consequences for the firing of nerve cells.

This leads me to another remark which seems appropriate in this article. The concept of noise which was originally probably applied more often in a romantic or poetic context the hum of bees, the murmur of a brook has now acquired a negative association. Noise limits our capacity to observe. That this is so will be confirmed by almost anyone who has listened to a radio or watched television when the signal carrying the program was very weak. At one time visual noise (interference) in the form of fog or a snow flurry was more likely to evoke a positive reaction than is the case now with our modern means of transportation (except among those who travel by train). It seems to me that the present negative attitude is dangerous and can blind the investigator to the *useful* functions of noise and of other random processes exemplified by those I have discussed above. Now voices are being heard again which in the case of restricted admission to ‘positive’ (advanced education) or ‘negative’ (military service) situations, prefer the drawing of lots among equal candidates to systematic rules that involve elements of injustice just because they are systematic. The use of chance as an element of justice is often condemned, but is very old. Many cases are to be found in, for example, the Bible.

In 1952 Fatt and Katz came to the theoretical conclusion that the membranes of very small parts of cells produce more noise than those of larger parts of cells. This hypothesis was later confirmed by experimental research. Because a great deal of research is done on nerve cells which are large and therefore easier to approach, the membrane noise present in these cells may not play a very important role. It is to be expected that these phenomena will be more distinct when small cells are investigated as well, and small cells occur much more frequently than large cells.

In large cells, however, the influence of the small terminal areas of the preceding cell can be distinguished. In 1952 Fatt and Katz also found that signals occur in large cells that originate from the small terminations of the preceding cell without the arrival of a pulse in the latter cell. This spontaneous, irregularly occurring phenomenon they called synaptic noise. A synapse is the place where the processes of two nerve cells are in contact with each other for the transmission of signals. The termination of the preceding cell (the presynaptic part) is usually very small. It contains small vesicles filled with a chemical substance (the transmitter substance). The membrane of this termination (the presynaptic membrane) lies close to the membrane of the cell to which the message is to be transferred (the postsynaptic membrane). These and other investigations showed the following. The content of one of the small vesicles can empty spontaneously into the space in the synaptic junction. This substance attaches itself to the postsynaptic membrane and is then degraded. Meanwhile, however, it has made this membrane locally permeable for certain ions. As a result, the membrane potential is changed at this site. This change spreads over the cell but becomes weaker with increasing distance. Thus, when it reaches the next decisive surface area this change in voltage difference will be weaker the further away the synapse in question is located.

Now, there are two kinds of synapse: one in which the transmitter substance changes the voltage difference in the direction of the threshold potential (exitatory synapses) and one causing a change away from the threshold (inhibitory synapses). When the sum of all these effects becomes so large that the threshold value is exceeded, the cell will fire. The average spontaneous activity of these synapses is so low that a spontaneous firing of these large cells is extremely unlikely, although this may be completely different for small cells.

When an action potential arrives at the terminal area of a nerve cell, the chance that a vesicle will empty at that place is greatly increased, once every two or three times the situation is realised. If many action potentials arrive simultaneously at an equal number of terminations, about half or a third of these terminations will transmit the signal, which in turn increases the chance that an action potential will be fired by the decisive area of the cell.

It is evident from all this that the signal transfer is based on the modulation of random processes in the synapses. An action potential increases the chance of the expulsion of a unit (quantum) of transmitter substance.

We do not know much yet about the random processes underlying the synaptic transfer probability. In all likelihood fluctuations in the permeability of the presynaptic area to calcium ions play a role, possibly in interaction with the membrane noise of these elements.

It follows from foregoing that random processes play an important role both in the signal-transmitting part of the nerve cell and in the cell membrane itself. A role which we can expect to become clearer when the more numerous, smaller nerve cells which are more difficult to study are investigated as well. Meanwhile, it has become clear that signal transfer occurs by means of the modulation of random processes. Since almost all of the synapses in the nervous system show the structure described here, the inevitable conclusion is that the nervous system functions on the basis of random processes.

In this connection we can ask ourselves two things. First: how is it possible that a system whose elements actually function on the basis of random processes nevertheless works so well and is sometimes even so very exact? And secondly: what function may be ascribed to random processes in this system?

The answer which can be given to the first question is that in the nervous system large numbers of elements are used to achieve the same effects. To ensure accuracy, the data are sent across parallel channels to numerous comparable cells, or to fewer, but very large cells. By way of an example, we may consider the regulation of our muscular activity. Nerve fibres run from large nerve cells in the spinal cord to the muscle cells, where each fibre ramifies and sends a branch to each of a number of muscle cells. Each of these subgroups of muscle cells must be activated when an action potential arrives via its nerve fibre. A single synapse is not sufficient to exceed the threshold value of the muscle cell; this requires the activity of many synapses. But each of these synapses has only about one chance in two of firing. This means that if there were present only that number of synapses needed to reach the threshold of the cell, only about half would be active and a contraction of the muscle cell would hardly ever occur. In reality there are a few hundred synapses in the contact region between nerve fibre and muscle cell. When the nerve fibre is active this means that on average, for instance, 100 synapses become active, so many more than are necessary that it is a rare occurrence for a (mammalian) muscle cell not to be activated when an action potential is sent to it. The same holds for the large nerve cells in the spinal cord. Many fibres coming from various parts of the nervous system and carrying even more synapses, terminate at such large cells. The number of synapses on one such nerve cell has been estimated at 10,000 or more. In other words: functional security is based on the activity of large numbers of comparable elements. It is, however, adapted to the demands put on the relevant part of the nervous system. For example, the knee-jerk reflex (a sharp tap on the patellar ligament causes the muscle to contract) is unequivocally variable under conditions of constant stimulation. A process like the measurement of elapsed time in our cerebellum probably possesses greater precision and therefore involves many more nerve cells.

Such large numbers of nerve cells are also useful in connection with another random process. After early childhood the total number of nerve cells in the body does not increase. But destruction occurs. When this destruction is not systematic, its effect will not be noticeable for a very long time. Estimates are given in the literature that in man about 100,000 nerve cells disappear every day on average at arbitrary places. But in relation to the total of about 10 billion nerve cells, the loss is relatively limited even over a period of 100 years. Demonstrable damage is usually systematic.

For the second question, regarding the function of random processes in the nervous system, it is impossible to give a complete answer if only because so much remains unknown. A few functions have already been mentioned: the increase in the sensitivity of threshold elements to stimuli with a longer duration; the irregular pulse series of spontaneously active cells, which are modulated by the stimuli: here, a random process creates a ‘carrier wave’ for the transmission of data. Still other functions are conceivable. Networks of neurons can show a discontinuously changing output signal in response to an input signal with a continuously varying intensity. In such cases the presence of noise will result in an output signal which changes continuously with the input signal. Another possible function is that when information is transported in parallel cables (nerve fibres) coupling could occur between the cables, which would influence the transmission of information unfavourably. These phenomena do not occur when the series are irregular in character. It is safe to expect that more functions will be found when research workers become prepared to consider not only the limitations that random processes can give but also their possible functions.

What seems to be the most important function within the scope of this paper concerns the entire organism as well as the concepts of freedom and creativity. The aspects of the functioning of the nervous system mentioned here imply the existence of the possibility to react ir, unexpected ways. Such a form of reaction is therefore new, can be harmful but can also be beneficial. In the latter case this contributes to the phenomenon we call creativity and which has already been referred to in connection with the complex structure of ourselves. This kind of aspect is also inherent in the concept freedom if one of the aspects we include in this concept is the ability to react in unexpected ways. Both the complex structure and the presence of random processes therefore guarantee the actual and persisting presence of processes and conditions we indicate by the in fact undefinable concepts creativity and freedom.

Literature:

For a detailed bibliography we refer to the following articles:

A. A. Verveen and H. E. Derksen, *Fluctuation phenomena in nerve membrane.* Proc. IEEE, 1968, 56, 906-916.

A. A. Verveen and L. 3. DeFelice, *Membrane noise.* Progress in Biophysics and Molecular Biology, 1974, in press.

A.A. Verveen, 1974. Random processes in the nervous system..
Methodology and Science, **7:** 80-91.