Artificial neurons in oncological pain: 
the potential of Scrambler Therapy to modify a 
biological information

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Abstract

Thirty-three terminal cancer patients suffering from extremely severe drug-resistant pain were treated with Scrambler Therapy, a new bioengineering-based method for treating oncological/neuropathic pain. Preliminary tests of the method’s effectiveness were performed by measuring pain intensity (visual analogue scale (VAS)) before and after each treatment session, and the duration of absence of pain in the hours following each single application, as well as by recording the variation in painkiller consumption. Each patient subsequently continued to receive treatment until the end point was reached, verifying whether the method retained the effectiveness displayed during the reference period. The VAS statistics before and after each treatment session, and of the baseline VAS prior to treatment and at the end of the reference cycle were subjected to a paired t-test (statistical significance). Both VAS references indicated a significant decrease in pain intensity, with \( p < 0.0001 \). The entire sample responded positively to the treatment throughout the statistical reference period and continued with unchanged effectiveness until the end point was reached. Seventy-two percent of the patients suspended treatment with painkillers during the first applications, while the remaining 28% considerably reduced the dose they were taking prior to Scrambler Therapy. No undesirable side effects emerged and compliance proved to be optimal.

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1. Introduction

The pain system, like the entire tegumentary system, is characterized by a high level of information content which forms its essence. Specific receptors, normally subdivided into two classes—mechanoceptors for mechanical stimuli and multimodal receptors for those that respond indifferently to all painful stimuli; they are biological elements that are able to convert a chemical, physical or mechanical event into specific pain information. Many substances have the capacity to dynamically modulate the response to pain by sensitizing or desensitizing the receptors and the conduction/processing pathways during the ascending phase. The complex modifications activated by the nervous system in response to a painful stimulus are thus the focus of a wide variety of organic reactions designed also to reestablish conditions of homeostatic equilibrium that the pain information signals as being in danger or disturbed. In most cases, this equilibrium can be rapidly restored thanks to a series of reactions involving much of the biological system as a whole. In this case, the pain information, its purpose achieved, returns to a silent state. However, there are situations in which this has not happened, either due to the impossibility of removing the cause of the biological damage, or due to intrinsic damage to the pain system itself (neuropathies) as a result of damage to/compression of the nerve fibres [2]. In such a context the onset of very extensive, complex reactions may be observed, themselves capable of modifying the original information triggering the pain phenomenon (sensitization–autonomization) thus setting up an iterative process that, in the case of chronic pain, and of neuropathic and visceral pain in particular, tends to render all known therapeutic strategies gradually (or completely) ineffective [3–5]. The useful fact that emerges from all these scenarios is the central role of control exerted by information over the chemical–structural variations of the system. I mention en passant the fact that by information we mean the measurable and mathematical expressible component of a news item or rather the measurable elimination of the uncertainty of an arbitrary event [6]. In this case, information is represented by the sequence of pulses generated by the activated nociceptor, pulses that “describe” the type of pain, attributing to it specific properties such as, for example, the intensity or the type of sensation experienced. Overall, this represents a good description of a cybernetic process, that is, one of communication (pain information) and regulation (chemical feedback to modify perception and adaptive reactions). It may thus be reasonably assumed to be possible to control the lower levels of complexity of the pain system (the chemical reactions regulating the coding of pain information and the subsequent feedback) by manipulating the “information” variable alone at higher levels of complexity [1]. An arbitrary system level must in this case be such as to be able to make up for the incomplete knowledge characterizing the role of the chemical molecules involved in the pain phenomenon, which may conveniently be represented by means of the black box technique. This involves using a model in which the input and output are known but not the internal translation process that takes place inside the “box”. It must also take place at a stage at which information expression is sufficiently “visible” for it to be investigated analytically and be interpreted univocally. In view of the assumptions, so that it can be treated easily enough using comparatively inexpensive technology in order to develop the method, this information content has been defined and investigated at the level of
complexity (emerging properties different from the individual variables interacting in this particular state of the system) expressed by the biopotentials generated by the receptors depending on the nociceptive stimulus. The research procedure adopted therefore allowed a comparatively complex system model to be constructed which could be defined in purely conceptual rather than experimental terms, in which the biological variables were translated into cybernetic variables, extrapolating the role and the modality of the pain information regardless of the biochemical aspects and its etiopathogenesis, using systems theory and information theory to rationalize the research procedures. The hypothesis of operating by blocking nervous transmission was immediately rejected although it is actually one of the more commonly adopted solutions. By its very nature the nervous system reacts to and processes information. Theoretically, the absence of information can only increase the entropy (information disorder) of the channel involved, and very probably will produce adaptive reactions increasing the sensitivity to the painful stimulus. The approach actually adopted to respect the initial theoretical criteria (use of information as the active principle) was to replace the “pain” information with artificial “non pain” information, in full respect of information theory, to which the reader is referred for further information. Essentially, an artificial neuron was developed that behaves as a “Pain Scrambler”, that is, as a system capable of interfering with pain signal transmission by “mixing” another signal into the transmission channel (the nerve fibres) for the purpose of masking the original information by modifying its content (from pain to non-pain), although allowing it still to be recognized as ‘self’ by the nervous system. The process is outlined in Fig. 1.

Note should be taken of the many similarities but also the important differences compared with traditional scrambler techniques, used mainly to “protect” confidential information from possible interception during the transmission, with conversion back to
the original signal on reception. In our specific case, the ultimate aim is obviously
different, and there are additional conditions and aims to be respected in view of the
particular type of application involved. In this sense, it is significant that the information
produced by the “mixing” is not just any kind of information but has the property of
being recognized, as far as possible, as ‘self’ and as non-pain. Otherwise, the system
would be totally ineffective. These conditions were obtained by simulating sequences of
biopotentials artificially generated by digital synthesis and having the following
characteristics.

1.1. Compatibility with the transmitting and receiving channel

Construction of a set of wave forms (basic coding) that, when assembled in real time by
means of suitable control algorithms, can simulate as exactly as possible the geometric
trend specific to endogenous biopotentials.

1.2. Compatibility of the information content

Dynamic generation using artificial neurons of “packets” (strings) of information
recognized as “non-pain”, the content of which is varied over time by means of suitable
algorithms used to recognize the simulated signal as ‘self’ and to reduce the adaptation of
the perception as a function of the noise, and the amplitude of which is such that it may be
decoded as the dominant stimulus by means of the overmodulation of the endogenous
biopotentials. The latter condition has given rise to the theoretical expectation of a
favourable readaptation of algogenic sensitivity. It is hypothesized that the learning
mechanism of the pain system, now “remodelled” to suit the non-pain Scrambler
information, as a result of the well-known adaptive properties that lead to a sensitization
to intense and frequent pain stimuli, results in a gradual raising of the subjective pain
threshold.

1.3. Global optimization of the simulation with the characteristics of the biological system

Increased compatibility of the simulated signal with the nervous system with the
inclusion in the principal information during simulation of the stochastic fluctuation of the
noise figure of the nervous transmission network.

2. Materials and methods

The supporting technology (Scrambler Therapy ST5) was developed as a prototype to
allow the required clinical trials to be conducted to evaluate the method. It consists of a
multiprocessor apparatus able to simulate five artificial neurons that allow five pain
areas in the same person to be treated simultaneously. The treatment is fully automated,
including the dynamic parametrization required for the correct functioning of the
method. This criterion, rendered inevitable by the active principle involved, ensures a
very high degree of repeatability of the experimental data as it is not necessary to select
the operating parameter manually except for the simple regulation of stimulus intensity, which is manually set at the perception threshold. Each treatment session lasts 45 min on average; the required frequency is changed to suit the subject concerned, and after the initial attack therapy, may even consist of a single treatment every 24 h. Application is by means of disposable surface electrodes applied in the skin areas corresponding to the pain areas. Thirty-three patients, all suffering from intense drug-resistant pain and at an advanced stage of oncological disease with widespread metastases, were recruited for the trial.

Inclusion criteria:
- oncological pain
- very high baseline VAS in drug treatment

Exclusion criteria:
- pacemaker user
- neurolithic blockage of celiac plexus
- other neurolesive pain control treatment

The treatment protocol entailed abandoning or reducing the basic pain control therapy in the case of effective pain reduction by Scrambler Therapy. For statistical purposes, the trial programme was based on a cycle of 10 therapy sessions with a frequency of one every 24 h, that could be increased depending on the patient’s needs according to the duration of the analgesia after each single treatment. At the completion of the 10 sessions, each patient was allowed to continue the applications until the end point. Pain intensity was evaluated using the visual analogue scale (VAS). This linear scale consists of the visual representation of the pain amplitude as perceived by the patient. The amplitude is represented by a line having no reference marks. One extremity indicates absence of pain and the other the worst imaginable pain. The scale was indicated before and after each treatment session by the patient marking the pain level experienced on the scale. This type of test can easily be repeated over time, has the advantage of simplicity, is widely used, is language-independent and is easily understood by the majority of patients. Furthermore, each patient was requested to keep a diary in which they noted the duration, expressed in hours, of the absence of pain after each treatment session, the intensity of the pain when it reappeared, and the consumption of painkillers if used. The statistical significance of the VAS complied was measured using the paired t-test.

3. Results

VAS trends before and after each treatment session in the cycle are shown in Fig. 2. The figure shows how the baseline VAS preceding the treatment has a mean value for the whole group of over 107 points out of a maximum of 120 (maximum imaginable pain), and that this decreases rapidly after the first treatment session. The statistical significance is found to be $p<0.0001$. If we observe the trends for subsequent treatment, we find that, despite the reduction or elimination of the supporting pain-killing drugs taken at the beginning of the trial, the baseline VAS drawn up prior to
application is increasingly low, which indicates not only a persistent absence of pain, but a readaptation of the pain system, which is in agreement with the theoretical assumptions. Several slight fluctuations corresponding to the eighth and tenth treatment sessions are apparently due to complications in the oncological conditions of one of the patients, which contributed to raising the general average by a few, practically negligible, points.

Fig. 3 shows the difference between pain intensity prior to Scrambler Therapy treatment at full painkiller dosage and baseline pain intensity in the absence of treatment at the end of the cycle, and the absence of or marked reduction in painkilling drugs. Also, in this case, the statistical significance evaluated by the paired t-test was found to be $p < 0.0001$. It should be noted that a baseline VAS of < 10 out of 120 is considered as pain slight enough to be considered in practice as vague perception of annoyance.

Fig. 3. Basic VAS.
4. Discussion

In recent years, our physiopathological and biochemical knowledge concerning pain has increased considerably, without however being accompanied by a corresponding increase in the effectiveness of pain management therapies in the case of severe pain such that of visceral pain, or of oncological pain in general. Perhaps the most important experience emerging from the research leading up to the conception of Scrambler Therapy is the possibility of obtaining truly significant results through a change in approach and perspective in analysing a problem and that medical science can benefit extensively from the advancement in knowledge which can lead to clinical applications when analytical multidisciplinary approaches are followed. I consider that several ideas emerging from the study of Scrambler Therapy can be usefully applied in other fields. It must be emphasized that the decision not to interrupt the perception of pain by blocking the pathways but rather to control its properties by manipulating a system metavariable currently seems to be a solution that is as innovative as it is successful and which perhaps represents the beginning of a new era in previously untreatable pain therapy.

The preliminary results obtained using Scrambler Therapy are extremely encouraging, both in terms of enhanced pain control after each treatment session, and in view of the possible maintenance of effectiveness over time. In the latter case, in agreement with theoretical predictions, a gradual reduction is found in baseline VAS as well as an unchanged effectiveness until the end point is reached. All patients responded fully to the protocol and none reported undesirable side effects, and compliance was excellent.

The following conclusions may be drawn from these preliminary results:

- Scrambler Therapy produced a surprising statistically significant ($p < 0.0001$) pain control response.
- During the applications, all the patients reported a very rapid (in the order of a few seconds) disappearance of the perception of pain, the absence of which was increasingly prolonged for many hours after the end of the session as the number of treatment sessions increased, which indicated a favourable remodelling of the pain system.
- No undesirable side effects were reported.
- All the patients displayed excellent compliance with the treatment.
- The support of painkillers rapidly proved unnecessary in 72% patients, and was reduced to very low levels in the remaining 28%.

This extremely positive outcome is an encouragement to perform more extensive trials of Scrambler Therapy to obtain further knowledge. In view of the completeness and extent of the results, it may reasonably be assumed to be a very productive approach, and thus, in the near future, it will be possible to treat with ease and without side effects oncological pain, the intensity and difficult management of which has always been considered a focal point of the disease, where significant efforts should be made to improve the patient’s quality of life, which often amounts to prolonging the life itself.
References