Dynamic Treatment of Pain

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Institute of Computer Science
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Abstract:

The unilateral dorsal root section of sensory nerves is used as the deafferentation pain model to study the single neurons dynamics of the medial thalamic nuclei of laboratory rats. It is argued that the dynamic description by means of time mappings of interspike intervals of firing neurons is more appropriate as the standard stochastic description in the form of firing rates. Then new approach based on the chaodynamic methods is applied to analyze possible differences in the neuronal dynamics between normal and deafferented rats. It is found there are principal differences in the neuronal dynamics detected here by various patterns of the reconstructed chaotic attractors. In the control rats the firing patterns of single neuron are represented in the form of homogenous attractors, in deafferented rats in the form of non-homogenous attractor patterns with the some structure. Besides one can distinguish by this method also differences in the neuronal dynamics of single neurons of deafferented animals with the typical automutilative behaviour indicating painful states and cases without a pain. The perspective of this method is a possible prediction of pathological changes of the activity of appropriate single neurons dynamics. As the method of chaodynamics is universal a potential exploitation is not only in the case of nociception, but also in other pathologies of brain, like epilepsy, depression, psychosis.

Keywords:
nociception, single neuron dynamicsc, interspike intervals, chaodynamic methods, chaotic attractors reconstruction.

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1 Introduction

Pain is a complex experience that involves not only the transduction of noxious environmental stimuli, but also cognitive and emotional processing by the brain (Julius & Basbaum, 2001). This makes a pain very complex phenomenon. And in spite of very exciting time in the field of pain research, when major advances are occurring at almost every level of analysis, from the transduction of noxious stimulus in a primary afferent neuron to the impact of such stimulus on cortical circuitry, the general paradigm of pain is still missing. A progress has been made in identifying cortical loci that process pain massages, but far greater advances have been made in understanding the molecular mechanisms whereby primary sensory neurons detect pain-producing stimuli, a process referred to as nociception. In this sense major advances in the development, cellular, and molecular biology and integrative neurosciences can be also related to the neurobiology of pain (Dubner & Gold, 1999).

These insights have arisen predominantly from the analysis of sensory systems in mammals, as well as of studies of invertebrates. Electrophysiological studies have, in fact, shown the existence of primary sensory neurons that can be excited by noxious stimuli. So in this respect, acute pain can be regarded as a sensory modality much like vision or olfaction. But pain is unique among sensory modalities in that electrophysiological recordings of single primary sensory fibres have been made in awake humans allowing simultaneous measurement of psychophysical responses when regions of the head and body are stimulated. Fibres that innervate such regions arise from cell bodies in trigeminal and dorsal root ganglia (DRG), respectively. But we are not going into details of the pain pathways here.

Instead, the main goal of the paper is to analyze a role of time in neuronal processing in general and in a pain, in special. But it is rather surprising this problem in general has been attached only recently (Hopfield, 1996; Koch, 1997; Rieke, at al. 1997; Rao & Sejnowski, 2001). Our dynamic treatment of pain is as far as we know even the first attempt in this direction.

Concerning the role of time in neuronal processing there are two main aspects to the issue. First, the relationship between a timing of an event in the external world, i.e., stimulus and the timing of the representation of that stimulus at the level of firing neuron. Second, an accuracy and importance of the relative timing of spikes among two or more neurons (Koch, 1997). Here, our concern will be mainly concentrated on the first aspect, i.e., the extent to which the exact temporal arrangements of spikes of firing neurons matter for the neuronal information processing in the case of normal physiological conditions and in the case of pathological situations with a pain.

To make such analysis possible we do use the model of deafferentation pain (Campbell, et al., 1999). Details are given in section 2. Besides the reasons to exploit single neuron dynamics for this purpose are specified, too (see the section 3). Then it is argued that a single neuron with the sigmoidal transfer function can behave chaotically (Andrey, 1998).

But as such systems are in general ergodic the dynamic description by means of time mappings of interspike intervals of firing neurons is more adequate as the standard stochastic description in the form of firing rates. The argumentation for the dynamic description in the case of painful states is given in section 4. The experimental setting for the study of deafferentation pain in the laboratory rats is sketched in section 5. Besides, the chaodynamic methods used to analyze possible differences in the neuronal dynamics between normal and deafferented rats are described in this section, too. In the next section the obtained experimental results are analyzed by such chaodynamic methods and some universality of dynamics of single neurons of deafferented rats with the typical automutilative behaviour indicating painful states and cases without the pain is obtained. It seems the painful states can be indicated or materialized in the changing of dynamic neural coding in the adequate single neurons firings of spikes. This is summarized in section 7. Finally in the Conclusions (section 8) some perspective applications of the method of chaodynamics in other pathologies of brain are shortly mentioned, too.

2 Deafferentation pain

Pain usually results from the continual stimulation of nociceptors, producing continual transmission in nociceptors pathways. This process is referred to as nociceptive pain (Campbell, et al., 1999).

Deafferentation pain is then the causative lesion which affects the peripheral nervous system. As a model for deafferentation pain the cervical dorsal root rhizotomy in rats has been used in recent years. Also unilateral dorsal root section in rats is then used as the model of central pain (Basbaum & Jessel, 2000). During the deafferentation of dorsal roots of sensory nerves, the syndrome of changing sensitivity is developed. It starts by licking, scratching and biting and is finished by the automutilating behaviour. This is considered to have a close relation to the pain originating in central structures because there are no more inputs available from the peripheral nerves after deafferentation. These characteristics are very important as they will allow us to specify cases of deafferented rats with the pain and those with no painful behaviour.

Now, principal questions can arise. Namely, what are changes one can observe after the unilateral rhizotomy of dorsal roots is realized? At what levels? So the natural question is to ask also what is a role the pain can play in qualitative or even quantitative changes in the measured thalamic neuronal dynamics. Or put it in an opposite way, how is the pain materialized in the neuronal dynamics or by other words, what is a code for the pain if there is one, at all? As will be shown in the paper to detect such differences in the neuronal dynamics of normal and pathological situations with a pain it will be sufficient to exploit a single neuron dynamics representation. Well, this brings some troubles on the technical part of analysis - the measurement on single neurons, but it is much more efficient and convenient on the theoretical side of analysis. In this connection it is worth to mention that neurons are very complicated, nonlinear systems. So the description and analysis of single neurons is in principle much easier as for groups of neurons. There are other reasons to accept the strategy of single neurons dynamics representation and experimental realizations.

3 Single neuron dynamics representation

All primary sensory nociceptors make synaptic connections with neurons in the grey matter (dorsal horn) of the spinal cord. Subsets of dorsal horn neurons, in turn, project axons and transmit pain massages to higher brain centers, including the reticular formation, thalamus, and ultimately the cerebral cortex (Basbaum & Jessel, 2000).

But we can use the important result obtained already by Adrian (1926). It tells that individual sensory neurons produce stereotyped action potentials (AP), or spikes. The mechanism is that incoming stimuli either produce such APs, which then propagate long distances along the cell's axon, or they do not. There are no intermediate signaling mechanisms. This means that a single neuron can provide information to the brain through the arrival times of the spikes. Here we realize the old wisdom that one can anytime learn something of classics. Because it is precisely the case as recent work shows that the sequence of APs from single neurons provide an efficient representation of even complex dynamic inputs (Eichenbaum, 1993; Wallis, et al. 2001; Fairhall, et al. 2001). One can say this is one of two extreme views on information coding in the cortex in general. One view we just present here espouses a systematic organization imposed of a hierarchy of "filters" or "detectors" that encode stimulus features and complex events by the activity of single neurons as mentioned above. For a completness one should note that the contrasting view espouses a fully distributed representation that encodes each item by distinct spatio-temporal activity patterns of homogenous arrays of neurons (Eichenbaum, 1993). Let us add here that in principle these opposing views may in fact be reconcilable in the real brain. But we are not going to details here. Instead we will concentrate on the first view, i.e., we decide for a single neuron representation, contrary to an ensamble or population coding in our treatment. Alas, it must be say here that such the idea is in fact not new one. As was stated by Palm (1986): The idea of representation of relevant propositions about the outside world in single neurons has been the basis for a leading experimental paradigm in neurophysiology from 1950's up to present days. As a confirmation of that, see, e.g., Mc Kenna, et al. (1992).

4 Dynamic vs. stochastic description - the case of pain

In the preparation for an appropriate strategy to describe pain by means of specific properties of spontaneous neuronal dynamics we have argued so far that the single neurons representation is of

possible use. Now it is known neurons can operate in distinct ways, depending on the duration of the interval T_Σ over which they effectively summate incoming synaptic potentials (König, et al., 1996). According to this rule one can make the following classification. If this T_Σ is greater than the mean interspike interval (ISI) of firing neurons, by other words, if changes in single presynaptic APs are very small ($\Delta V_i \ll 1$) then summation acts in such a way that firing should depend mostly upon the averaged frequences $\overline{\nu}$ of long trains of incoming pulses (single presynaptic APs), not on their exact timing. Here we have the firing rates model and one speaks about so called stochastic paradigm with an ad hoc Poissonian distributions, and so on (Rieke, et al., 1997). So far this has been mainly (or even only) accepted scenario (Stowell, 1996). If just opposite is true, i.e., T_Σ is shorter as the mean ISI then neurons act essentially as coincidence detectors with the analogy to the synfire chains model of Abeles (1982). Besides there exists another mode of neuronal dynamics in the form of bursts (Lisman, 1997) which is difficult to classify according to the T_Σ of above analysis. But such bursts may play the role in pain (Vaculín, et al. 2000; Radhakrishnan, et al., 1999).

Now, it is interesting to note that the question Abeles asked (Abeles, 1982) about the role of the cortical neuron should be "integrator or coincidence detector" has not been answered fully yet. But it is well possible that the question is ill-posed one. Then it seems natural to ask what is a generator of spikes? Is it not possible to make a reconstruction of such neuronal dynamics? From a very general point of view one could think about a stochastic source of ad hoc random process of firing spikes. And one has a classic stochastic paradigm of coding as mentioned above (Rieke, et al., 1997). This approach is very popular till present days. On the other band with the advent and progress of chaos theory one has been tempting to exploit it in the qualitatively new approach to the coding problem. The point is that the source of spontaneously firing spikes would be of dynamic nature possessing a chaotic dynamics. Then one speaks about temporal or dynamic encoding (Judd & Aihara, 1992). But it was proved both experimentally (Aihara, 1995) and also analytically (Andrey, 1998) that even single neurons can really behave chaotically. So one can use methods of chaodynamics (Andrey, 1986) to analyze further such spontaneous firing of neurons. Before going to apply such methods to characterize experimentally recorded spontaneous neuronal activity of single neurons of medial thalamic nuclei in the laboratory rats it should be stressed here that this new angle of view of dynamic approach is very useful. It allows to unify the above presented classification of firing patterns into one picture. In this sense one can comprehend two above mentioned cases as a developed chaos for the firing rates model an a low chaos for other case. The bursting firing of spikes can be then considered as the intermittent chaos. Let us note we do not take into account the problem of synaptic noise here. This is very complicated matter, still open and we will mention about it later on in the discussion (Faure & Korn, 1997).

So far we have argued that the role of chaos may be very important in neural systems (Freeman, 2000; Rabinovich & Abarbanel, 1998; Andrey,1998). As was said before this fact is in agreement with the idea of temporal coding. That is very interesting as it is natural to take into account the timing between spikes as the changes of amplitudes of firing spikes are negligible. That is very specific feature of spikes. But because one can suppose that the dynamics of firing neurons is chaotic then according to ergodicity of such systems it is equivalent for a description of information processing in such systems to use, e.g., the dynamic changes of spike amplitudes or equivalently time mappings of inter-spikes intervals (ISI) between firing spikes of experimental recordings on single neurons of laboratory rats. But this is nothing else as the temporal coding or by other words the use of AP timing for stimulus representation (Hopfield, 1995; Koch, 1997; Aihara, 1995).

At this point we arrive to the main problem of the paper. Experimentally observed recording of APs arrival times of nerve cells resulting from spontaneous activity of single neurons are analyzed by methods of chaodynamics (Rokyta, et al., 2001) for physiological normal and pathological states with a pain. But the analysis of real cases will be made in the next sections.

5 Materials and Methods

To study the dynamics of neurons of thalamus and cerebral cortex of experimental rats in normal physiological states and in the pain, experimental recordings of spontaneous unit activity, or action potential (AP) of firing neurons, have been exploited. After surgical operations and standard anes-

thezitation the spontaneous discharges of single axon ending in the injured site were recorded in the standard way by microelectrodes. Then discharges are input to an A/D converter and on-line recorded by a computer with an adequate sampling frequency. After a standard filtration of noise and making a surrogate data analysis one gets spontaneously recorded AP trains of spikes in the form of time series data. At this point one could follow the standard or now almost classic way of analyzing the spikes dynamics, namely by constructing histograms, Fourier analysis or studying averages firing frequency rates. This approach is based on the stochastic paradigm, when it is assumed that a firing of spikes is an ad hoc random process (see, e.g., Rieke, et al. 1997).

But with an advent of deterministic chaos, qualitatively new possibilities to analyze time series data have arrived. So (recently) one can analyze above mentioned experimental data of spikes firing single neurons by methods of chaodynamics (Andrey, 1986). To do this one needs to suppose that another scenario, namely the dynamic paradigm with the pulse or temporal view upon neuronal firing is going to play an important role. In such case the arrival times of individual APs can encode the significant information. So instead of averaged firing rates a timing between spikes plays the role of dynamic parameter. Besides then is a good reason to assume single neurons have a strong potentiality to behave chaotically (Andrey, 1998; Judd, Aihara 1993). But in general one can say chaos is irregular in time and can have structure in phase space (Abarbanel, 1996). And precisely this is the case here.

So we are in a position to apply some chaodynamics methods to analyze our experimental data now. As amplitudes of spikes do not change so much, in an excellent agreement with what was said before, to analyze the dynamics of neuronal activity one would exploit a time dynamics of APs trains of firing spikes. More precisely we will use time intervals between spikes as the new time mapping to characterize the dynamics of firing neurons. We can do this in a rigorous way because of ergodicity of chaotic systems. Besides, such time mapping is nothing else as well known interspike intervals (ISI) description. To proceed we do extract ISIs from the above preprocessed experimental data of APs trains or spikes in the standard way. In this way we do get a new time series that can be thought of as a sequence of observations $S_n = s(x_n)$ performed with some measurement function s(.). Now, any real system can be modeled by an adequate dynamical system. Since the usually scalar sequence S_n, in our case just ISIs, in itself does not properly represent the commonly multidimensional phase space of the dynamical system one has to employ some techniques to unfold the multidimensional structure using the available data (Abarbanel 1996, Schreiber 1999). To make a phase space reconstruction the method of delays is often used. Vectors in a new space, the embedding space, are formed from time delayed values of the scalar data:

$$Y_n = (S_{n-(m-1)\tau},\ \ S_{n-(m-2)\tau}, , S_n) \tag{5.1}$$

The number m of elements is called the embedding dimension, the time τ is referred to as the delay or lag. Embedding theorems by Takens and Sauer (Schreiber, 1999) guarantee that if the sequence S_n does indeed consist of scalar measurement of the state of dynamical system, then under above mentioned conditions, the time delay embedding provides a one-to-one image of the original set $\{x_n\}$, provided m is large enough. There is a large literature on the "optimal" choice of the embedding parameters m and τ. It turns out, however, that what constitutes the optimal choice largely depends on the application. The reconstruction is the important tool for the visual inspection of data. Commonly, two dimensional projections of three - dimensional renderings are enough to catch the point and can even be used to guess a good choice of the delay time for higher dimensional embeddings. Concerning this matter we can also say that a time delay must be some multiple of the sampling time since we only have data at those times. Besides we want the time delay τ to be large enough that S_n and $S_{n+\tau}$ to be rather independent but not so large that they are completely independent in statistical sense. We tried different values of time delayes in our reconstructions.

At this point we are prepared to determine some other characteristics of dynamics of firing single neurons such as Lyapunov exponents, fractal diamensions or Kolmogov-Sinai entropy. But the point is here that it is technically rather difficult to get adequate long experimental recordings of firing neurons in vivo.

Nevertheless the application of the above described reconstruction techniques to the time recordings of firing neurons of normal states of experimental rats and to states after deafferentation allows for surprising possibility to classify such states in a different way as was done so far by using only "classical

methods" as histograms, Fourier transforms of spectra, and so. The details will be described in the Discussion (section 7).

We have used the software package for the methods of chaodynamics worked out as M-tool-boxes under MATLAB at the Institute of Computer Science, Prague and partly also TISEAN Package of Max Planch Institute for Physics of Complex Systems, Dresden.

6 Experimental data of single neurons firing recordings and chaodynamic analysis of results

To analyze the thalamic neuronal dynamics in physiological and pathological states of pain after a deafferentation the male Wistar rats weighing 280 to 400 g were used. The same anaesthesia for both the deafferentation and the proper recordings was used. The section of left dorsal roots proximal to the spinal ganglion to prevent the development of neuron was executed on cervical dorsal roots C5 to C8. Then dorsal rhizotomy was made completely on C5-Th1. After the operation the animals were kept separately in individual cages and were continuously observed. During and after the deafferentation of dorsal roots of sensory nerves, the syndrome of changing sensitivity is developed at some animals.It starts by licking, scratching and biting and is finished by the automutilating behaviour (Albe-Fessard & Rampin, 1991). Immediately after an onset of such autotomy behaviour the extra cellular single unit recording was performed. For more technical details see Vaculín, et al. (2000). On-line recordings of measured data of spontaneous unit neuronal activity (APs firing) of nuclei in the medial thalamus (Central lateralis (CL) and parafascicularis (pF)) were performed. The data were digitalized in a standard way.

At this stage we are prepared to use the experimental data to study possible differences in the dynamics of appropriate thalamic neurons in normal and pathological states after the deafferentation. But in accordance with what has been said above one can classify laboratory rats we used into three groups: the group I - rats with the above deafferentation and the autotomy behaviour (18 neurons); group II - rats with the deafferentation without such automutilating behaviour (10 neurons) and finally group III - control animals without any deafferentation and of course without a pain (4 neurons). But this is in a sense only a subjective classification, especially that of after deafferentation states.

So to proceed further the dynamics of single neuron firings should be analyzed in a possibly rigorous way. To this end we know from the considerations of section 4, the dynamic treatment is more appropriate here. To be more precise for the dynamic description one needs interspike intervals (ISI) time mappings as was mentioned in the previous section 5. Such ISI maps were extracted from original recordings of neuronal unit activity in anaesthetised (Narkamon + Xylazin) rats. This was done for all 32 neurons recordings of APs firings. Details will be published elsewhere (Rokyta, et al., 2001).

So under above assumptions we are prepared to apply some chaodynamic methods to analyze further our experimental data now. The goal is to look for possible qualitative or even quantitative differences in thalamic neuronal dynamics of single neurons of laboratory rats with and without deafferentation. We will follow the way of a phase space reconstruction of dynamics, or by other words, the underlying strange attractors by the method of delays as was described in the section 5.

Let us denote firing times of given neuron as $t_i, i = 1, 2, ...$ From the firing times t_i, the interspike intervals (ISIs) are defined naturally, as

$$S_i = t_{i+1} - t_i, \;\; i = 1, 2, ... \tag{6.1}$$

So one can use the series $\{S_i\}$ of ISI's to reconstruct the attractor. In other words, there is one-to-one correspondence between m-tuples of ISI's and attractor states, which associates each vector $(S_i, S_{i-1}, , ..., S_{i-m+1})$ of ISI's with the corresponding point $x(S_i)$ on the attractor, as was described in the section 5. We have performed such reconstructions for ISI's time mappings for all 32 neurons measured. But here we only present the most typical cases for the above mentioned three groups of tested animals. The more detailed analysis also from the biological angle of view will be published elsewhere (Rokyta, et al., 2001).

Fig. 1 shows the extracted ISIs time mapping of single neuron firing spike trains (we do not show here) for the deafferented old animal with automutilative behaviour of group I rats. Then the reconstructed chaotic attractor of the time series of Fig. 1 with the delay $2\tau(k = 2)$ is shown in the Fig. 2. In comparison with Fig. 10 where the same is done for ISIs mappings in the case of recordings of single neurons firings spike trains of the control animal without any deafferentation of group III, one can see principal differences indicating the different neuronal dynamics of neurons of medial thalamic nuclei. It should be mention that all recordings were performed on single neurons from the same loci of the brain of experimental rats. While in control animals without the deafferentation the chaotic attractor is rather homogenous in the structure, in the deafferented animals the reconstructed attractor is more dense occupating the smaller space with the typical shape of triangle with the concave edge.

Surprisingly enough in the case of young animals with the deafferentation and the mutilative behaviour we get the very different dynamics of single neurons firings represented by a specific shape and structure of reconstructed chaotic attractor of adequate ISIs time series. This can be recognized at the Fig. 4. The shape of attractor in this case is very different both from the case of control animals (Fig. 10) but also from the previous case of old animals from the same group I. Here the attractor is also endowed with the some substructure in comparison to the previous case of old animals (Fig. 2). We did not plan to make special experimentations on young animals and this exciting result was obtained in a sense as the byproduct (see Rokyta, et al. (2001)). So we do intend to make more measurements on young animals to confirm this important finding.

Now in the case of single neurons firing spike trains for the deafferented animals without automutilative behaviour the reconstructed chaotic attractors show Figs. 6 and 8 for the young and old animals, respectively. The first of all we do not observe such impressive differences in the shape and structure of reconstructed chaotic attractors between young and old animals as in the case of deafferentation with the mutilation (Figs. 2 and 4). Instead the attractors have similar topology for young and old rats here. But the shape is different as those of reconstructed attractors of deafferented old animals with the automutilative properties, namely here (Figs. 6 and 8) we have the attractors with the convex shape. By oter words the curvature of attractors in the case of deafferentation with and without the automutilative behaviour is just opposite. This is very interesting problem not only biologically but also from the dynamical point of view. But we do not have any answer yet. Besides by the more detailed inspection of Figs. 6 and 8 one can find out even the differences in the space and the geometry of attractors in the case of young animals (Fig. 6) and the old ones (Fig. 8). At this point one need to exploit other invariants of chaodynamics. We do intend to make a further analysis in this direction (Andrey, 2001).

Here we again find out the principal differences in the neuronal dynamics of single neurons for the case of deafferented rats without the automutilative behaviour (group II) represented by reconstructed attractors (Figs. 6 and 8) in comparison to the control animals (group III) with the attractor of Fig. 10.

As mentioned above we presented here only typical cases of reconstructed dynamics of single neurons firing spikes by means of reconstruction of adequate chaotic attractors of ISIs mappings extracted from recordings of single neuron firings of medial thalamic nuclei of laboratory rats. We considered three groups of such animals: the deafferented rats with the mutilative behaviour (18 neurons) - group I; the deafferented rats without the automutilation (10 neurons) - group II; and finally control animals without any injure and pain (4 neurons) - group III. The more detailed analysis with the stress upon biology of the above analyzed findings as well as the detailed description of experimental settings with the specification of measured loci and the recording technique used will be published elsewhere (Rokyta, et al., 2001).

7 Pain's characteristics and discussions

We have attempted to apply methods of chaodynamics to reconstruct underlying chaotic attractors of single neurons interspike intervals series recorded from experiment. Let us mention here that similar attempts have been made recently, in investigating the role of chaos in neural systems but not all of them used single neurons recordings (Rabinovich & Abarbanel, 1998; Di Mascio, et al., 1999; Stoop, et al., 2000). But to our knowledge this study is the first one in applying the chaodynamics to the dynamic treatment of pain in the qualitative manner by means of reconstruction of underlying chaotic

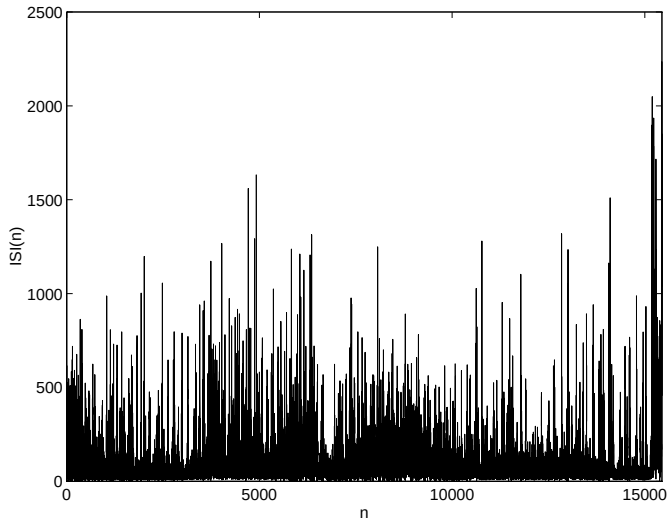

Figure 6.1: Extracted interspike intervals of single neurons firing spike trains for the deafferented old animal with automutilative behaviour of Group I.

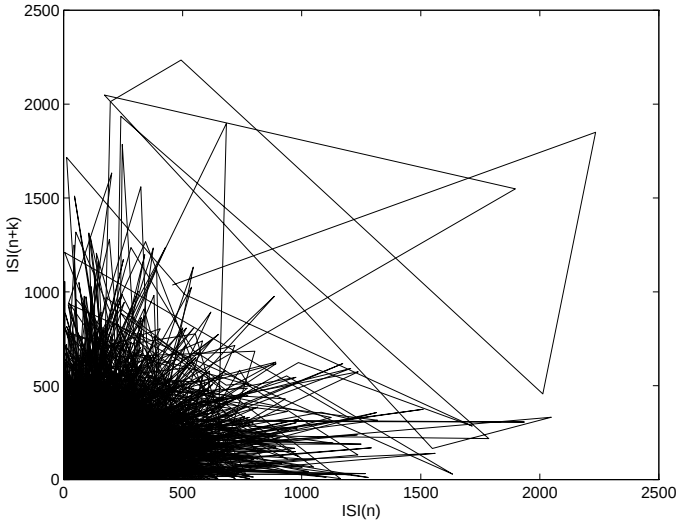

Figure 6.2: Reconstructed chaotic attractor of interspike intervals of single neurons firing spike trains for the deafferented old animal with automutilative behaviour of Group I.

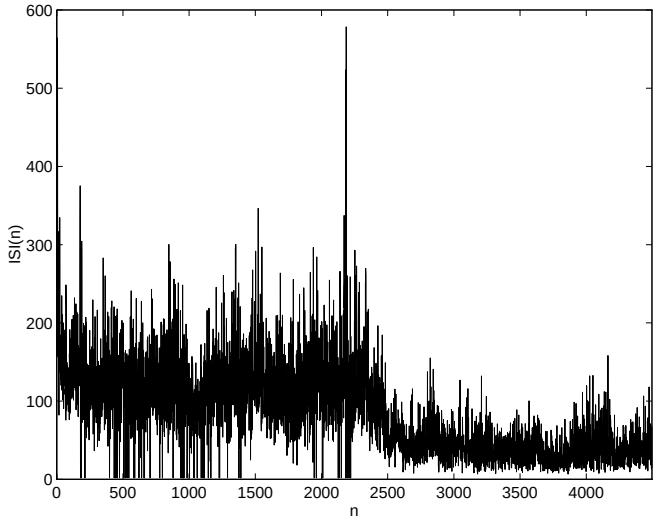

Figure 6.3: Extracted interspike intervals of single neurons firing spike trains for the deafferented young animal with automutilative behaviour of Group I.

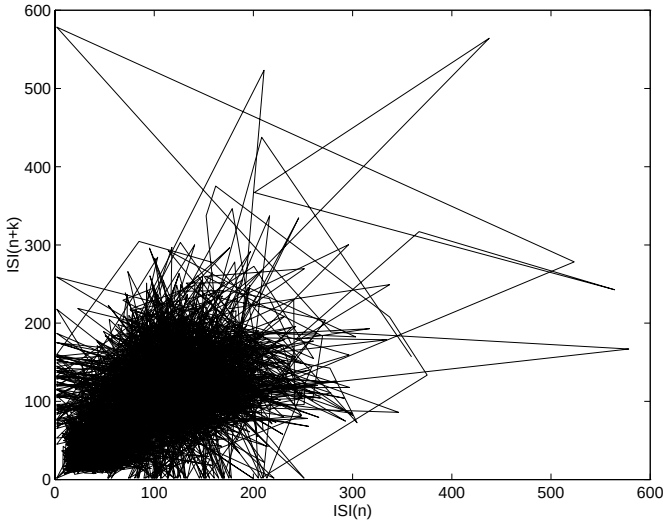

Figure 6.4: Reconstructed chaotic attractor of interspike intervals of single neurons firing spike trains for the deafferented young animal with automutilative behaviour of Group I.

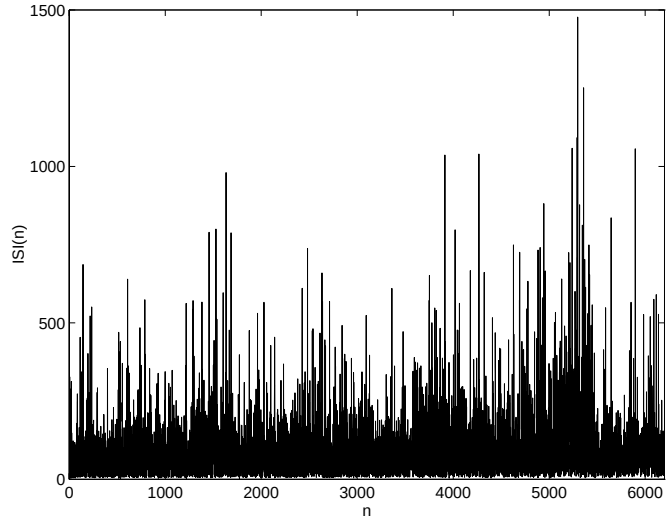

Figure 6.5: Extracted interspike intervals of single neurons firing spike trains for the deafferented young animal without automutilative behaviour of Group II.

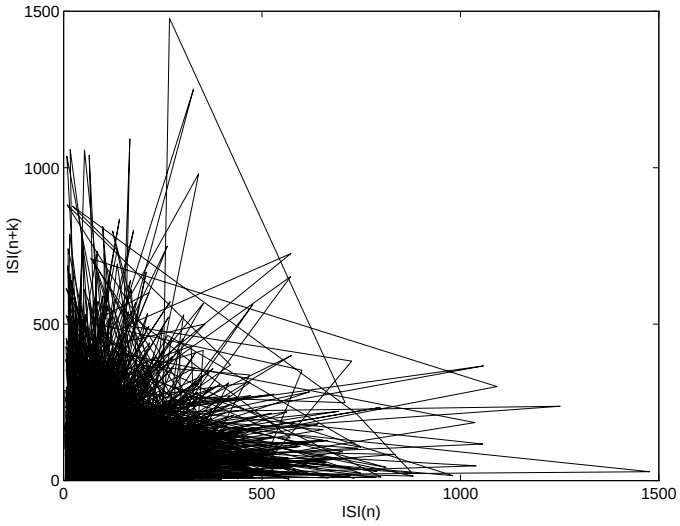

Figure 6.6: Reconstructed chaotic attractor of interspike intervals of single neurons firing spike trains for the deafferented young animal without automutilative behaviour of Group II.

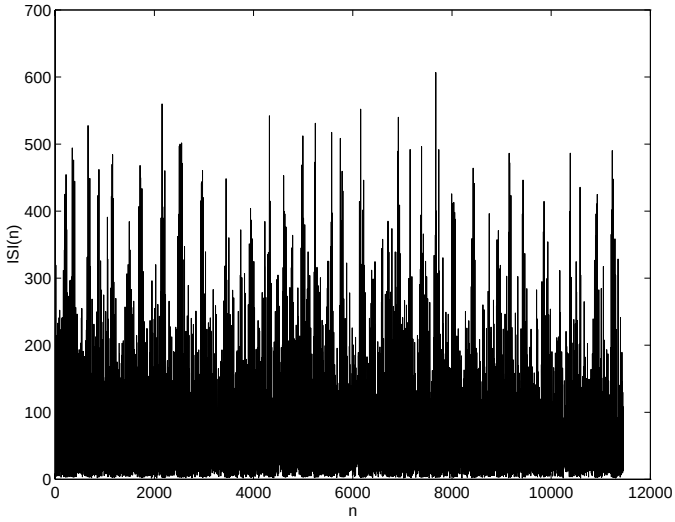

Figure 6.7: Extracted interspike intervals of single neurons firing spike trains for the deafferented old animal without automutilative behaviour of Group II.

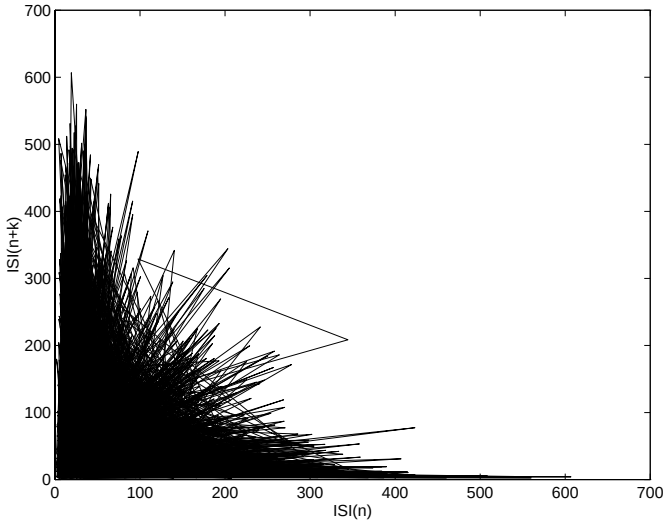

Figure 6.8: Reconstructed chaotic attractor of interspike intervals of single neurons firing spike trains for the deafferented old animal without automutilative behaviour of Group II.

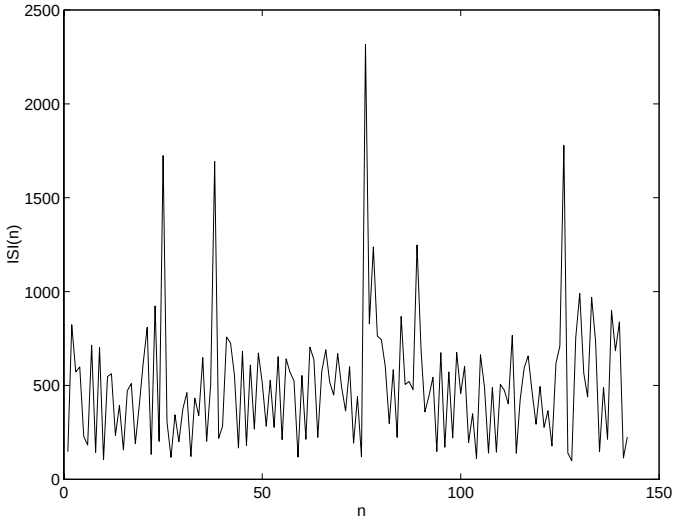

Figure 6.9: Extracted interspike intervals of single neurons firing spike trains for the control animal of Group III.

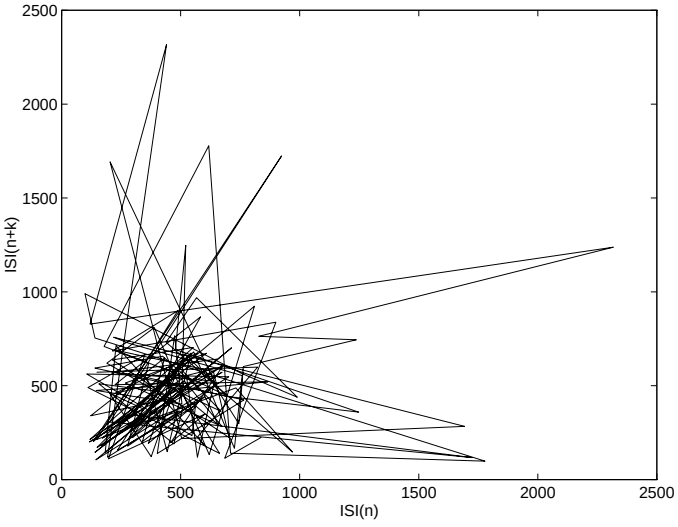

Figure 6.10: Reconstructed chaotic attractor of interspike intervals of single neurons firing spike trains for the control animal of Group III.

strange attractors. From the above section where experimental data were treated in this way one can deduce that the pain is represented by the neuronal dynamics with in a sense reduced the chaoticity of underlying time mappings of ISIs. This seems to be in agreement with previous findings for the similar phenomenon in other brain pathologies, e.g., in the case of epilepsy (Lehnertz, 1999) or Alzheimer patients (Jelles, et al., 1999). But one must be a little careful as the EEG recordings are analyzed there. N.B., the application of chaodynamics to such macroscopic, in a sense, thousands of parallely firing neurons, EEG recordings, is very disputable.

In fact one can be even critical to ad hoc applications of methods of chaodynamics to analyzing EEG recordings. The reason for this is apparent if one realizes that the dynamics of single firing neurons can be very complex, and as was shown even chaotic. Then the point is that it is almost impossible to predict something about behaviour of interacting chaotic oscillators, in general. And in concrete, e.g., the calculation of dynamical dimensions of particular EEGs need not necessarily lead to direct conclusions about the underlying dynamics. In other words, there are too many factors in such game which can influence even the quality of behaviour of such systems we know almost nothing about.

In this context our strategy to study the spontaneous single neurons activity of the medial thalamus nuclei of laboratory rats seems to be based on fixed grounds. Also the method of chaodynamics used seems to be very reasonable. From the results obtained in such way one can deduce many consequences going in the opposite direction, from the reconstructed strange chaotic attractors back to the possible dynamic mechanisms of nociception representation (or realization) in the brain, e.g., by specific changes of adequate neural codings for the realization of pain (Rokyta, et al., 2001a). But this is another story and it will require a lot of pains and effort that open problems still prevailing would be surmounted.

8 Conclusions

This article is the first attempt to study the deafferentation pain executed by the unilateral dorsal root section of sensory nerves of laboratory rats as the dynamic process by means of time mappings of interspike intervals of single neurons firings recordings. The new approach based on chaodynamic methods is applied to analyze possible differences in such neuronal dynamics of normal and deafferented rats with and without automutilative behaviour. It is found there are principal differences in the neuronal dynamics of such states detected here by various but typical and almost universal patterns of the reconstructed chaotic attractors of measured ISIs of firing single neurons. Besides we have some preliminary results indicating there are some specific features distinguishing the thalamic neuronal dynamics of young and adult animals. But to make some definite conclusions the more experiments are needed. We do plan to follow this direction of very exciting findings closely related to the problem of developmental issues for a coming time.

The method used seems to be perspective as it can provide a possible prediction and classification of pathological changes of the appropriate single neurons dynamics in a very general sense. By other words, as the method of chaodynamics used here is universal the potential exploitation is not only in the case of nociception, but also in other pathologies of brain, like epilepsy, depression, psychosis. Alas, here again the experimental recordings of single neurons firing spikes trains are strongly recommended.

And in the opposite direction, from such detected changes of underlying dynamics one can deduce some plausible consequences in the form of new views and solutions to the well known old problems and paradigms. Concretely here, the new formulation of dynamic neural coding which is not in the contradiction with the existing classical dogma of stochastic coding (in the form of firing rates) but rather it is complementary to it, is possible.

Appendix

In this appendix we give the analytic proof that the sigmoidal form of transfer function is important and sufficient condition for a single neuron to have the chaotic behaviour.

To do this we use the generalized McCulloch-Pitts neuron model (McCulloch &Pitts, 1943) in which instead of the unit step function the sigmoidal transfer function will be exploited (Andrey, 1991). Then we have for a given single-node neuron dynamics

$$y(t_{n+1}) = \sigma[h(t_{n+1}) - \Theta] \tag{8.1}$$

$$h(t_{n+1}) = \sum_{i=1}^{N} w_i x_i(t_n) \tag{8.2}$$

where

$$\sigma(\xi) = \frac{1}{1 + e^{-\lambda\xi}} \tag{8.3}$$

Here $x_i(t_n)$ is the action potential (AP) or the spike of the i-th neuron at time $t_n, i = 1, ..., N$, adding up potential to the given neuron. By other words it is the presynaptic potential; w_i are weights between presynaptic neurons and the given neuron; h is the local field; Θ is the axon hillock threshold or bias; σ is the sigmoidal transfer function with the slope λ and $y(t_{n+1})$ is the output or the firing spike of given neuron at the time t_{n+1}. For simplicity we put $\xi(t_n) = h(t_n) - \Theta$, and call it the effective field.

Now, let us suppose, the interspike intervals (ISI) defined in (2) are very small. So one can perform the Taylor expansion of (3)

$$y(t_{n+1}) = y(t_n) + \frac{dy}{d\xi}d\xi = y(t_n) + \frac{dy}{d\xi} \cdot \frac{d\xi}{dt} \cdot \Delta_n t + ... \tag{8.4}$$

where $\Delta_n t = t_{n+1} - t_n = s_n, i = 1, 2, ...$ Now we can use the nice property of sigmoid (5), namely

$$\frac{d\sigma}{d\xi} = \lambda\sigma(1 - \sigma) \tag{8.5}$$

After substituting from (7) for $\frac{dy}{d\xi}$ into (6) as well as for $\frac{d\xi}{dt}$ of (3) and (4) and neglecting higher terms $(\Delta_n t)^k, k \geq 2$ we get

$$y(t_{n+1}) = y(t_n) + 4ay(t_n)(1 - y(t_n)) \tag{8.6}$$

where

$$\begin{aligned} a &= \frac{\lambda}{4}(\xi(t_{n+1}) - \xi(t_n)) \\ \xi(t_{n+1}) &= \sum_{i=1}^{N} w_i x_i(t_n) - \Theta. \end{aligned} \tag{8.7}$$

Introducing the substitution

$$z(t_{n+1}) = 4ay(t_{n+1}) - \frac{1 + 4a}{2} \tag{8.8}$$

into (8)we get finally

$$z(t_{n+1}) = c - z^2(t_n) \tag{8.9}$$

where

$$c = 4a^2 - \frac{1}{2} \tag{8.10}$$

is the parameter of the obtained logistic equation (11) and the a is given by (9).

But it is well known (Schuster, 1984) that the logistic equation (11) possesses the chaotic behaviour for some values of parameter $c > c_{crit}$, where for (11) $c_{crit} \doteq 1.8284$.

So we have shown that the firing of single neurons with the sigmoidal transfer function contains inherently deterministic chaos. (The more detailed analysis with the discussion of the possible biological meaning of the parameter a given by (9) as well as that of logistic equation (11) with the

parameter c depending upon other characteristic properties of the given neuronal dynamics process will be published elsewhere (Andrey, 2001).

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References

Abarbanel, H.D.I. (1996). Analysis of observed chaotic data. Springer Verlag, New York.

Abeles, M. (1982). Role of the cortical neuron: integrator or coincidence detector? Isr. J. Med. Sci. 18, 83-92.

Adrian, (1926). The impulses produced by sensory nerve endings: Part I. J. Physiol. (Lond) 61, 49-72.

Aihara, K. (1995). Chaos in axons. In: The handbook of brain theory and neural networks. M.A. Arbib (Ed.). The MIT Press, Cambridge, MA.

Albe-Fessard, D. & Rampin, O. (1991). Neurophysiological studies in rats deafferented by dorsal root sections. In: Deafferentation pain syndromes: Pathophysiology and treatment. B.S. Nashold, Jr. & J. Ovelment-Lewirr (Eds.), Raven Press, New York, 125-139.

Andrey, L. (1986). The relationship between entropy production and KS - entropy. Progr. Theor. Phys. 75, 1258-1260.

Andrey, L. (1991). Simple biological neural networks and stability criteria for equilibrium memories. Neurocomputing, Vol. 3, No. 1, 221-230.

Andrey, L. (1998). Potentiality of complex behaviour in single neurons. In: Chaos and noise in biology and medicine. (Ed. by Barbi, M. & Chillemi, S.). World Scientific, Singapore.

Andrey, L. (2001). In preparation.

Basbaum, A.I. & Jessel, T.M. (2000). In Principles of neuroscience (Eds. Kandel, E.R., et al.). Mc Graw-Hill, New York.

Campbell, J.N., et al. (1999). In Textbook of pain (Eds. Wall, P.D. & Melzack, R.), Churchill Livingstone, Edinburgh.

Di Mascio, M., et al. (1999). Reduced chaos of interspike interval of midbrain dopaminergic neurons in aged rates. Neuroscience, Vol. 89, No. 4, 1003-1008.

Dubner, R. & Gold, M. (1999). The neurobiology of pain. PNAS 96, 14, 7627-7630.

Eichenbaum, H. (1993). Thinking about brain cell assemblies. Science 261, 983-984.

Fairhall, A.L., et al. (2001). Efficiency and ambiguity in an adaptive code. Nature 412, 787-792.

Faure, P. & Korn, H. (1997). A nonrandom dynamic component in the synaptic noise of a central neuron. Proc. Math. Acad. Sci. USA, 94, 6506-6511.

Freeman, W.J. (2000). Neurodynamics. Springer-Verlag, London.

Hopfield, J.J. (1996). Transforming neural computations and representing time. PNAS 93, 15440-15444.

Jelles, B., et al. (1999). Decrease of non-linear structure in the EEG of Alzheimer patients compared to healthy controls. Clinical neurophysiology 110, 1159-1167.

Judd, K.T. & Aihara, K. (1992). The role of dynamics in information processing by the brain. Concepts in Neurosciences 3(2), 123-133.

Judd, K.T. & Aihara, K. (1993). Pulse propagation networks: A neural network model that uses temporal coding by action potentials. Neural Networks, Vol. 6, 203-215.

Julius, D. & Basbaum, A. (2001). Molecular mechanism of nociception. Nature 413, 203-210.

Koch, Ch. (1997). Computation and the single neuron. Nature 385, 207-210.

König, P., et al. (1996). Integrator or coincidence detector? The role of the cortical neuron revisited. Trends Neurosci. 19, 130-137.

Lehnertz, K. (1999). Non-linear time series analysis of intracranial EEG recordings in patients with epilepsy - an overview. Internat. J. Psychophysiol. 34, 45-52.

Lisman, J.L. (1997). Bursts as a unit of neural information: making unreliable synapses reliable. Trends Neurosci. 20, 1, 38-43.

McKenna, T., et al. (1992). Single neuron computation. Boston, MA: Academic Press. 19, 130-137.

McCulloch, W.S. & Pitts, W. (1943). A logical calculus of the ideas immanent in nervous activity. Bull. Math. Biophys. 5, 115-133.

Palm, G. (1986). Brain theory. Springer-Verlag, Berlin.

Rabinovich, M.I. & Abarbanel, M.D.I. (1998). The role of chaos in neural systems. Neuroscience, Vol. 87, No. 1, 5-14.

Radhakrishnan, V., et al. (1999). A comparison of the burst activity of lateral thalamic neurons in chronic pain and non-pain patients. Pain 80, 567-575.

Rao, R.P.N. & Sejnowski, T. (2001). Spike-timing-dependent Hebbian plasticity as temporal difference learning. Neural Computation, Vol. 13, No. 11, 2221-2237.

Rieke, F. et al. (1997). Spikes. Exploring the neural code. The MIT Press, Cambridge, MA.

Rokyta, R., et al. (2001a). In preparation.

Rokyta, R., et al. (2001). The thalamic neuronal dynamics in physiological and pathological states evoluated by chaodynamics methods. The talk given at the 31st Annual meeting, Society for Neuroscience, San Diego, CA.

Schreiber, T. (1999). Interdisciplinaory application of nonlinear time series methods. Physics Reports. Vol. 308, No. 1, 1-64.

Schuster, H.G. (1984). Deterministic chaos. Physik-verlag GmbH, Wienheim.

Stoop, R., et al. (2000). When pyramidal neurons lock, when they respond chaotically, and when they like to synchronize. Neuroscience Research, Vol. 36, No. 1, 81-89.

Stowell, H. (1996). Naming the neuron in vain. Neural Networks 9, 4, 723-725.

Vaculín Š., et al. (2000). Dorsal rhizotomy changes the spontaneous neuronal activity of nuclei in the medial thalamus. Physiol. Res. 49, 279-283.

Wallis, J.D., et al. (2001). Single neurons in prefrontal cortex encode abstract rules. Nature 411, 953-956.