Optimization of the Vagus Nerve Stimulation Parameters with CI-Methods

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Abstract

In order to improve the Vagus Nerve Stimulation (VNS) statistical efficacy increase for certain parameter vectors was investigated. Such vectors are used in real cases. Although immediate tests on humans are not possible it was possible to find rats as adequate substitute models. The rats were stimulated with a protocol of 81 parameter vectors. Their physical response was recorded. Each rat is different but it is assumed that for some vectors similar response will occur. If only enough rats were recorded then a statistically safe prediction could be made about what parameter vectors will result in effects mostly desired by the therapist. It is the primary goal of the project to find similarities in different response cases for some of the typical vectors and eventually provide deeper insights on the treatment. The project faces extremely large data amounts from data acquisition. Methods of Computational Intelligence (CI) are used for the conversion of data to knowledge. After conventional data pre-processing evolutionarily designed artificial neural networks are used in order to evaluate available data and to help medical staff verify their medical thesis.

1. Introduction

The VNS is the only electric therapy method used widely in order to minimize the frequency of seizures in refractory epilepsies but its efficacy varies greatly and some of the reasons are well known; others are not. The efficacy of the stimulation improves over time and becomes best roughly after a year of application. The efficacy of the stimulation also degrades over time and becomes worst after many years when the vagus nerve's surface suffers from electric cicatrice. [2][3] These long term effects are accompanied by some short term deviations that seem to be affected by the choice of the parameters. The question arises whether the method can be improved by a more intelligent choice of the parameters.

There are five parameters, which can be set on the stimulator. The first parameter defines the stimulation duration (T_{on}). The second parameter defines the pause between stimulations (T_{off}). The stimulation consists of square signals that occur periodically at the frequency (f). The temporal width of the square pulses is defined by the pulse-width parameter (P). The current output is defined by the current-strength parameter (A).

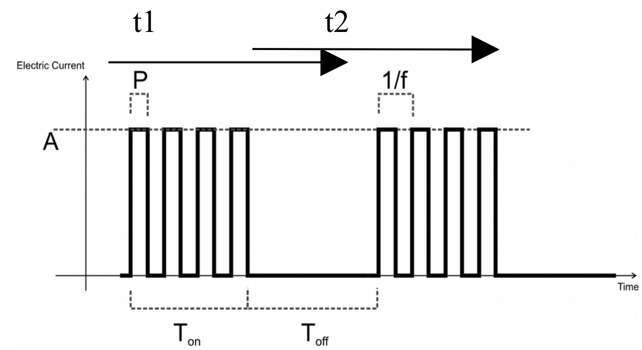

Image 1. Parameter vector (P, A, f, Ton, Toff) defining stimulus. In the programs T_{on} and T_{off} is referred to as ON and OFF. The timers t1 and t2 indicate time since stimulation started (t1) or since when stimulation ended (t2).

The stimulators today offer dozens of choices for each of the parameters. A combinatorial experimenting is not possible due to the large amount of combinations. Assuming that each of the device parameters had just 20 possibilities, then such an experiment would offer 3.2 million combinations for exploration.

$$c = 20^5 = 3200000$$

It is an exhaustible amount when considering that the current project's recording protocol has relied on just 81 parameter vectors which already are difficult to record and to analyze. With CI methods we were able to tackle this complexity.

In human body there are two Vagus nerves. The stimulation electrode is wrapped around one of them and then the attached stimulator sends electric impulses to the nerve in a manner specified by the parameter vector. The parameters are programmed with a handheld device and they are transmitted via an antenna to the stimulator residing beneath the patient's skin.

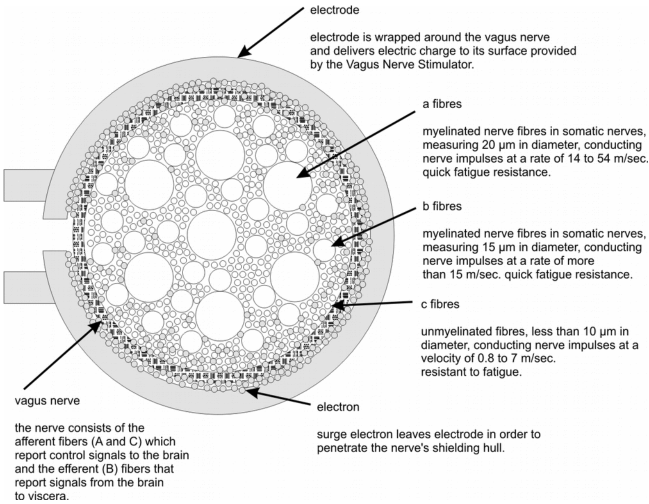

Image 2. The electrode is wrapped around the Vagus nerve. Electric impulses inject electrons into the nerve. [5][6]

The idea behind the stimulation is to interrupt the afferent and efferent communication of the organs. It is expected that such an interrupt will enforce a change in oxygen absorption and distribution. Electrons saturate the nerves' surface suppressing eventual potentials for a neural spike. By far not all of the fibres can be blocked this way and the electrons can cause a signal themselves. Such signals can be harmful and painful. Parameters of this kind are being avoided in the project.

Medical expertise predicts that the best therapy is given when strong changes in the ventilation rate (VR) are observed whereas heart rate (HR) changes occur as little as possible. It cannot be said for sure, that the assumed medical thesis is correct. The project is laid out in a way allowing other theories to be tested. This happens in the final stage of the project where medical staff can interrogate the system for parameters that seem to statistically meet some specified criteria. Thanks to the methods of computational intelligence many parameters can be tested and identified as best without having applied them on a real model before. This saves time and a lot of tests on animals. Theoretically VR and HR might not be the all in relevant features; therefore another five effects were investigateed due the course of the project:

- Ventilation Amplitude (VA)
- Inhilation Time (VI)
- Exhilation Time (VX)
- Minute Ventilation (VT)
- Ventilation Slope (VS)

2. Methods

2.1 Tools

Matlab was defined to be the project's main tool. Many parts of the software were created for the special purpose of this project in Matlab. Data recording is done with Spike2 [7].

2.2 Data Acquisition

The data used in the project is recorded from healthy rats. Epileptic rats' illness interferes with the recording process. Before recording, a rat must be sleeping or one cannot separate stimulation effects from effects occurring during consciousness. Epileptic rats suffer seizures relatively frequently which are making the rats run through various levels of wake state. A day of recording is not unusual until all 81 parameter vectors were recorded. Hence long natural sleep periods are required and healthy rats fulfill this requirement since they are active at night.

At first, the rat must be equipped with sensors. During a surgery the animal is prepared for the Vagus Nerve Stimulation. The electrode is wrapped around the nerve manually. During this surgery also the electrodes for the electrocardiogram (ECG) and the electric artifact from the stimulator are implanted. After quick recovery the rat's response to the stimulation can be recorded. The ventilation data is recorded from a barometric box (plethysmography). The rat is feeling comfortable at all times. Any noise is avoided, only the stimulation changes interfere with the rat's sleep. This way the rat likes to sleep most of the time, which is a necessary requirement for the recording process.

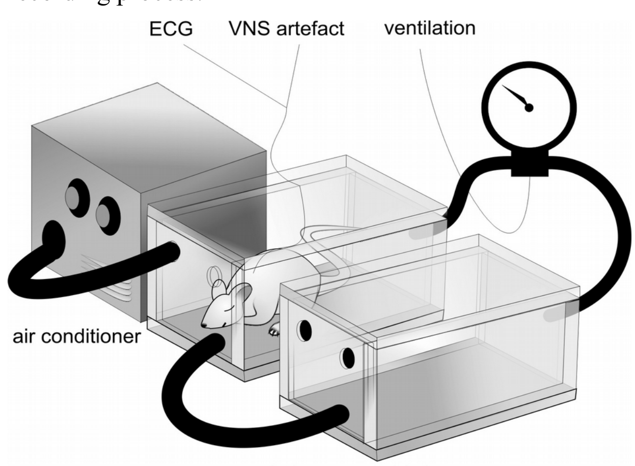

Image 3. The recording environment during data acquisition. Three signals are being recorded: ECG, VNS artifact and the ventilation volume changes.

In order to complete a record each rat is stimulated with a set of 81 different parameter vectors. A total time of seven to nine hours of recording is easily achieved. The recording is done with 19" rack mounted amplifying A/D converters. The three signals electrocardiography (ECG), Vagus nerve stimulation artifact (VNS) and the barometric changes in the box due to ventilation (V) are attached to that device. The device transfers data to the computer through a USB communication channel where it is recorded with the Spike2 data acquisition software. This software doesn't allow interrupting the record and then continue in the same file.

Each break would result in a new file. Stopping, saving the file, waiting and starting anew is an awfully error prone and time consuming process which would stretch the total time of work easily by two hours. Overwriting a file would produce errors that can not be recognized neither by a human nor by a computer. Hence the data acquisition is done in only three parts where the necessary time for the operation of the computer is low and errors can be mostly avoided. The resulting spike files typically contain 2½ hours of recorded data each and are roughly the size of 200 MB.

For each rat there is typically more than 500 MB of data recorded. The project aims at recording more than twenty rats for the database resulting in more than 10 GB of raw data to be scanned.

2.3 Data Pre-Processing

The data is not free of errors and is not suitable for computational analysis; therefore manual filtering is done in order to distill the relevant features. The features are corrupted by bad contacts on the electrodes, electrode misplacement, cross talking on the lines or simply by the rat toying around with the wires.

The filtering is not trivial and requires human's creative capabilities and a priori knowledge about the experiment in order to recognize parasitic effects and take proper action. After filtering the features of the specific channels are recognizable enough for automatic analysis. The files thus far are Spike2 data files, which cannot be processed by Matlab directly. The export function in Spike is used to produce three comma separated values (CSV) text files from any single Spike file. Each file represents a channel. Due to the fact that CSV files have headers of different style, the data sections cannot be separated easily from the headers and the footers by the Matlab software. It was decided upon that removal by hand is easier than writing sophisticated data section recognition. With the headers and footers in the text file Matlab sometimes even denies importing. The text files are extremely large and can reach many hundred Megabytes in size. A simple text editing tool is not appropriate for removal of the headers. Instead a freeware hex editor XVI32 by Christian Moos is used. It loads large files quickly and it performs block modifications immediately.

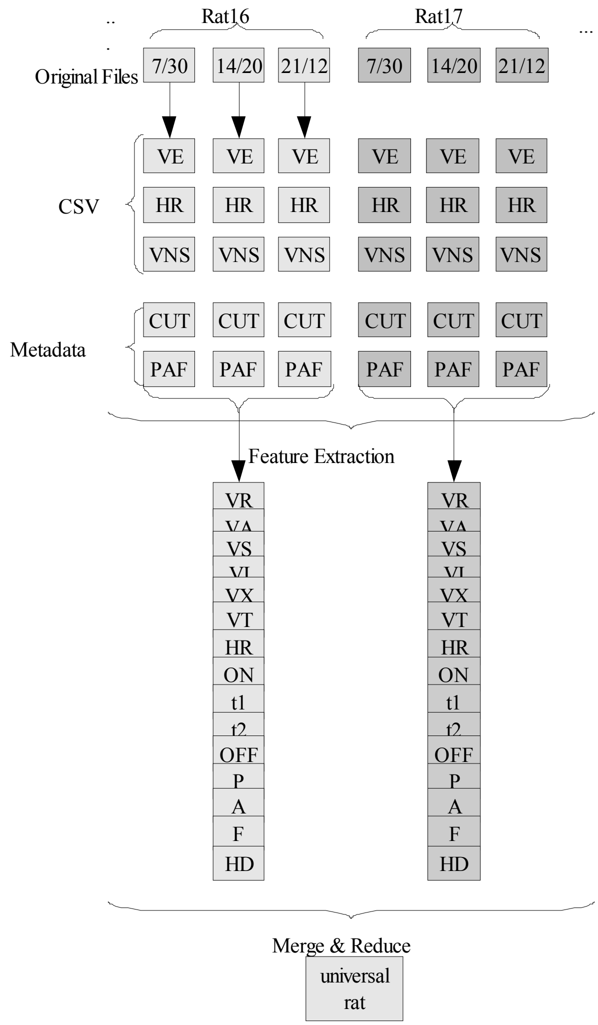

Image 4. Data extraction, transformation and merging scheme

After manipulation the files must be saved in a directory specially created for each rat. The data requires some additional information which is best described as metadata. This metadata contains the following information:

- *Sleep state and garbage separation times.* The data channels are reviewed manually in order to recognize a wake state or the opening of the barometric box (PG). This step requires the knowledge of how the PG signal is modified when the box is opened and requires a careful read of the keyboard channel in which sleep and wake states are held on record. Sometimes it is needed to mark other parts of the data for deletion, because no filtering can help to make a good signal out of the record. The files describing the parts for deletion are referred to as the CUT-files.

- *Manual description of when which parameter vectors were used.* This information is typed into Spike2 during record. The files' keyboard channel has to be reviewed manually in order to extract the typed information about the parameter vector. The files resulting from this process are referred to as the PAF-files.

2.4 Extraction Process

In this process the three channels representing ventilation, heart and stimulator operation are transformed into eight channels 'ventilation rate' (VR), 'ventilation amplitude' (VA), 'ventilation slope' (VS), 'inhilaiton time' (VI), 'exhalation time' (VX), 'minute ventilation' (VT), 'heart rate' (HR), 'heart deviation' (HD). The HD is connected to HR and represents deviations from average in percent.

First, the features must be extracted. For each channel a Matlab program is applied that generates related information. After feature extraction, some channels must be generated from metadata. Finally the sections marked for deletion are removed. This happens quite late because the discarded parts of the data cannot be deleted right away. If they were then tracks generated later on would have complicated shifts against original data. The easiest way avoiding this is to operate on full data (including discarded sections) until all data tracks are generated and later to perform delete operations on all tracks simultaneously.

At that point a raw binary file was created including all of the rats' data. A statistical component is run over that file in order to display the final product. This includes graphs for averages of any occurring parameter vector and graphs with the data base of that average. Excel files are generated with the data shown in the graphs with the averages. From this Excel data custom diagrams can be made

2.5 Merging to source

In the final step as shown in image 8 the many single files are merged into one single binary file with the name "universal.double". The file is a raw binary file with a sequence of records formed of 15 double values per record. Each such record represents a sample for all of the 15 values. The file is loaded by invoking the LoadUniversal() function.

2.6 Network design by genetic algorithms

Each of the seven dimensions VR, VA, VS, VI, VX, VT and HR depends on a set of input parameters, namely ON, OFF, t1, t2, P, A, F which are referred to as the parameter vector. There are many ways to design a network that has seven inputs and an output. There is even the possibility to design a single network that generates all seven outputs, but the quality of such networks is low, because strongly non linear separations must occur in the last layer. In this project it is assumed, that there are strongly non linear relationships between input and output and that there are little or no similarities between the outputs. Seven single ended feed forward networks are the logical consequence. Feed backed networks are excluded from the consideration because data cannot be provided in continuous streams.

The following features of a network can be varied in order to make it optimal suitable for a specific purpose:

- No. of layers
- Size of the layers
- Neuron's activation function
- Learning rate
- Other parameters depending on the training algorithm.
- Kind of feedback
- Training algorithm

The purpose of the artificial neural network is to serve as a carrier for a transfer function between the seven inputs and each of the outputs. Data is known to contain contradictious states. Hence the artificial neural network is to be seen as a kind of smart statistical tool. As contradictions are trained some kind of average is expected to emerge describing the situations observed during the data acquisition process in real rats. The average is not necessarily an arithmetic mean but it is rather an intelligently weighted average.

As the result of the genetic (evolutionary) design process a familiar architecture is expected that can be trained with available tools. It is not the aim to produce new kinds of architectures along with the often required specific training algorithm.

2.7 Network Analysis

After an artificial network has been trained it contains a description of the dependencies between the input and the output neurons. At some vector and time it can be precisely said what relationships the inputs have in respect to the output. In order to learn from the network it is important to extract and to visualize this information. This is done during the network analysis phase. During this analysis each feature is investigated. For each of the features all combinations of the input parameters are tested. This is a two from five combinatory problem.

Because it is not feasible to produce half a million diagrams a method for reduction was chosen that works in such a way that it...

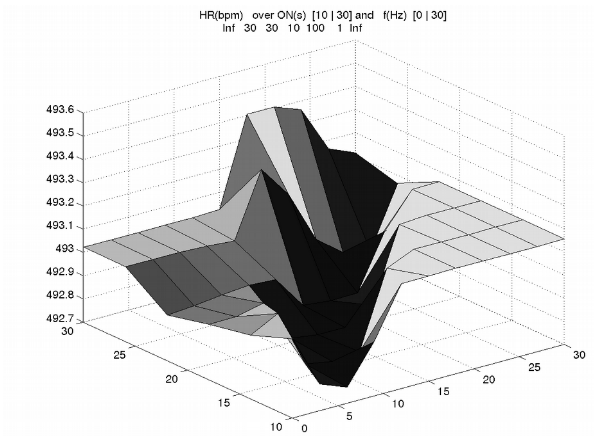

Image 5. Strongest effect diagram

- ...generates a diagram only when it had a greater height span effect than the previously generated diagram for the same pair of tested dimensions.

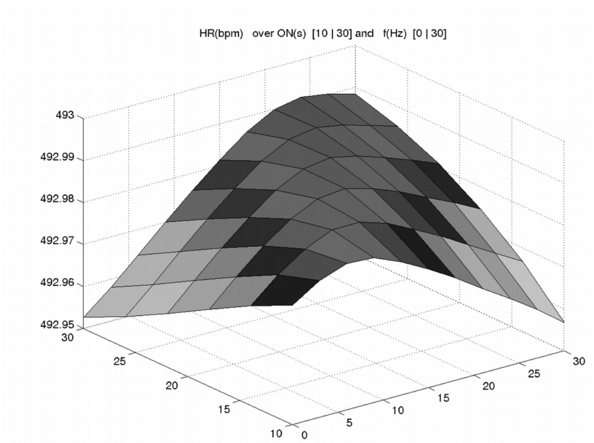

Image 6. Average relationship across two dimensions

- ...forms an arithmetic average over all of the generated data in order to produce a generic diagram for a specified pair of parameters in a manner that's independent of the other five parameters. These diagrams stand out through rather smooth surfaces. The lower example has a net change of roughly 0.04 BPM.

As it can be clearly seen, strong differences between the single working point diagram and the overall average occur. In the case of the heart rate across ON-time and the frequency the diagrams seem to have inverse relationships. This is not a conflict but shows that it cannot be safely concluded that individual setups always look like the average in their effect. Nevertheless the tendency diagram shows that along the hilly back in image 42 rather an increase than a decrease should be expected. Additionally it can be read from the diagram that heart rate depends on both, the frequency and how long the VNS was applied.

2.8 Interrogation module

In order to evaluate the many diagrams a special interrogation module was developed. The idea behind it was the ability to express one's own assumptions about a good therapy closely to the human language. The machine then segments all the diagrams according to the fulfilment of the request. These are partial results that take into account only the two dimensions in the diagram and ignore the other five. After segmentation the many 2D data arrays form quality maps that must be retrofitted into the original 7 dimensional results space. In such a space each coordinate vector is the parameter vector and the value in that 7D grid is the fitness of the parameter vector. The higher the value the better it suits the initially stated requirements.

Often it is not important to see the many thousands of parameter vectors all sorted by the final score but it is only needed to obtain the best few that can be tested on rats. Before segmentation and before inference it is possible to specify the fraction of the maximal score that will appear in the final list.

3. Results

The original assumption which led to the investigation of the data was that changes to ventilation rate and minimal changes to heart rate offer the best therapy due to some possible neuroprotective mechanisms. The TherapyFinder module was set to look for the right parameter vectors. The following table shows the result. The first entries in the table represent the parameters that seem to match the required biological response of a statistical rat population the best.

Only a small elite fraction of the obtained parameter vectors are shown:

ON(s)	OFF(s)	P(us)	A(mA)	F(Hz)	Score(Points)
14	22	200	1	30	**40**
14	22	200	0,1	30	**39**
14	22	200	0,4	30	**39**
14	22	200	0,7	30	**39**
14	22	200	1	24	**39**
14	22	200	1	27	**39**
14	22	200	1	27	**38**
14	22	200	1	30	**38**
14	18	200	1	30	**38**
14	22	200	0,1	24	**38**
14	22	200	0,4	24	**38**

ON(s)	OFF(s)	P(us)	A(mA)	F(Hz)	Score(Points)
14	22	200	0,7	24	**38**
14	22	200	1	21	**38**
14	26	200	1	21	**38**
14	26	200	1	24	**38**
14	26	200	1	27	**38**
14	26	200	1	30	**38**
14	22	200	1	30	**38**
10	22	200	0,1	24	**37**
10	22	200	0,1	30	**37**
10	22	200	0,4	24	**37**

The planes generated during the final analysis show interesting results on the meaning of the input parameters. The most striking finding is that the current strength measured in mA has almost no relevance for the outcome of the stimulation. If current strength surpasses some very low level required for penetrating of the Vagus Nerve any further increase in current does not benefit a statistical increase or decrease of the observed effects in the rat population.

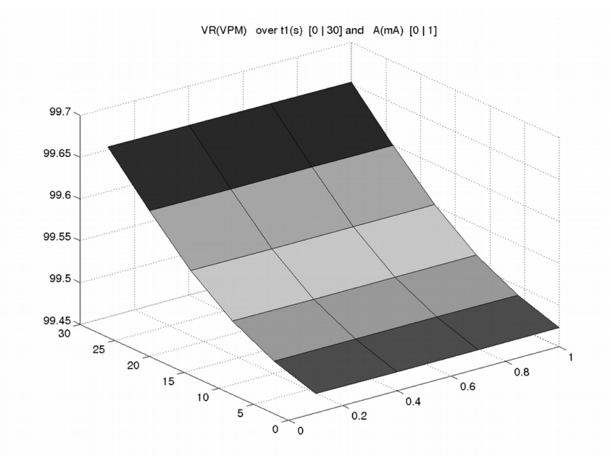

Abbildung 2: The many tendency diagrams suggest that there is no statistical evidence for the importance of current strength for any of the investigated response effects.

4. Discussion

The parameter vector decides how a VN-Stimulator produces its electrical pulses. A small rat population was used to record its physical response to some 81 typically used parameter vectors. From this data numerous features were extracted: ventilation rate, ventilation amplitude, ventilation slope, inhalation time, exhalation time, minute ventilation and heart rate. For each of the features a separate artificial network was designed by means of a genetic algorithm. After training the networks some statistical representation of the relationships between the inputs and the outputs was obtained. These relationships are not human readable. Therefore this knowledge had to be obtained with the help of a program that extracts working point dependent transfer functions. Each of the transfer function depends on 7 input dimensions. Many thousands of such transfer functions result from this transformation. In the next step they are compacted into many less functions by averaging the effects over five dimensions. In the end of this process there are numerous planes, one for each pair wise combination of the 7 input dimensions that show how a specific feature depends on the values in the dimensions of the plane. After specifying the looked for features like i.e. 'constant heart rate' or 'increased ventilation slope' etc. the planes are segmented accordingly. Finally, the full result space is restored from the segmented planes resulting in a score even for parameter vectors that had not been investigated experimentally. This way it can be explained why the methods predict optimum vectors that lay outside the original protocol.

The fidelity of this method is difficult to estimate. There are some arguments that could go against it.

1. The relationship of the feature strength and the values between each dimension is truly statistical and can be very different for specific choice of the working point among the other five dimensions. That means that even though the vector was identified to be good or bad there must be a step where the pattern is actually generated and checked for validity. The validity criteria are not yet available.

2. The planes are generated by forming mean averages over the other dimensions. The method could be improved if the grading would be depending on some kind of weighted variance.

3. Currently, dimensions of time t1 and t2 handled just like any other dimension which is not quite correct, because any stimulation cycle contains many relations to t1 and t2. A new module with GUI could be designed to specify timely behaviour as an envelope that would be taken into account during segmentation. This would save the additional check as suggested under point 1.

4. The classification of probable decreases and increases is built on the assumption that they correspondent to low or high values in the plane. This assumption hasn't been proven, yet. Therefore it is strongly recommends to add methods as described under point 1 and 3.

5. The data is based upon 11 relatively uniform rats. Eventually the database could be improved by adding up more rats and rats of other races.

6. Ventilation rate and amplitude seem to be depending on each other due to the principle of plethysmography. This suggests that direct amplitude measurement is not sufficient. An improvement would be if VA was expressed as ventilation amplitude to ventilation rate ratio.

7. The exact specification of what features are to be expected in order to obtain the best therapy is not known. Therefore the results table must be enjoyed with caution. Depending on what input is done in the interrogation module different tables will be generated.

Because of the upper regressions the results table is to be regarded as a mediate result of a work in progress.

The generated optimum vectors are valid for an average rat that does not exist. In the discourse of the project a smaller recording protocol along a calibration method will be designed in order to make it usable on unique individuals.

5. References

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