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Ethical Issues in the Development of a Vestibular Prosthesis

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Abstract—**During the development of a neural prosthesis, various ethical aspects have to be considered. These range from the basic design of the prosthesis and manufacturing of the various components and the system using biocompatible materials to extensive *in vitro* and *in vivo* testing and investigations in the animal model, before taking the final step and going to human trials. As medical systems, neural prostheses have to be proven absolutely safe before considering any clinical study. In this work, the various steps accompanying the development are described taking the example of a vestibular prosthesis currently developed within the European project CLONS.**

I. Introduction

Neuroprostheses have a broad field of application in medicine. They are used for modulation, bridging and substitution of disturbed or lost structures and functions in the human nervous system. Neuroprostheses use electrical stimuli to stimulate muscular and neural tissue, and use recorded bioelectric signals to control biological and technical functions.

The most prominent example of a neuroprosthesis is the cardiac pacemaker. In the period of 1990 to 2002, more than 2 million cardiac pacemakers were implanted in the United States [1]. Another success story is the cochlear implant providing auditory sensation to deaf and hardly hearing people. The first system for auditory nerve stimulation was implanted in 1957 by Djourno and Eyriès [2], and today around 200,000 cochlear implants have been implanted worldwide [3]. Moreover, the first Brindley stimulators for bladder management of paraplegic patients were already implanted at the sacral nerves of the spinal cord in the 1970s [4], and today more than 2,500 bladder management systems have been implanted to patients all over the world [5]. Other recent developments in the field of neuroprosthetics have focused on functional electrical stimulation of the extremities [6], restoration of visual sensation by retina stimulation [7], deep brain stimulation used e.g. for the treatment of Parkinson's disease [8], or pain management using neuromodulation [9]. In the last years, also the control of extremity prostheses by signals recorded with implantable systems has gained considerable interest [10, 11]. Finally, brain-computer interfaces have been developed which enable for instance patients suffering from the so-called "locked-in syndrome" to communicate with their environment [12, 13].

A relatively new and emerging field of application for neuroprostheses is the management of vestibular disorders [14, 15]. The number of qualifying patients is difficult to estimate, but in the US alone there are at least 300,000 patients suffering from symptoms related to vestibular dysfunction [16]. Many of these would be implant candidates.

Currently, within the European Project CLONS, a closed loop prosthetic system for the treatment of vestibular disorders is being developed [17]. This system will be able to restore vestibular information by recording signals provided by inertial sensors embedded in a device attached to the head, and stimulating the semicircular canals of the vestibular system.

As medical devices, the design and development of neural prostheses is associated with a variety of ethical issues to be considered, including manufacturing, animal experiments, human trials, scope of use as well as individual and societal concerns [18]. In the following, the various development steps to cope with these issues and to ensure sensible and responsible development and use of neural prostheses are described on the example of the development of a vestibular prosthesis.

II. Design and Manufacturing of Neural Prostheses

Already at the very first stage of prosthesis design, ethical and medical issues come into play. For instance, during the basic design of the system, the implications of applying the prosthesis on the patient have to be considered and weighed up against the potential benefits. In this context, also questions of patient acceptance are of importance. For instance, patients suffering from vestibular disorders have to experience chronic disequilibrium, motion perception deficits and loss of vestibulo-ocular reflexes. By supplying them with a vestibular prosthesis, a significant increase of quality of life can be expected. For this reason, the development of such a prosthesis can be considered as an adequate measure to treat such patients.

The vestibular prosthesis developed within the CLONS

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project consists of two main components. On the one hand, sensors are likely to be implanted in a final implantation but may be external in initial implementations. On the other hand, there is external power supply and an implantable part that includes stimulation circuitry and electrodes to stimulate the vestibular neurons. Such a two-component concept is similar to the systems used for instance in cochlear implants or visual prostheses.

As a first step, the external part might include inertial sensors, but for future development, implanting the sensors will probably be beneficial. This is also important for patient acceptance, as people suffering from vestibular disorders will not be willing to wear a large external component all the time and would prefer wearing a system as invisible as possible. Moreover, safety and functionality of the sensor part have to be considered in further development.

The second part of the prosthesis is implanted in the body. This implies considerable stress to the patient, as a surgery is required to place the implant in the vestibular system. In the development of the implant, biocompatibility and biostability are of utmost importance, to avoid any potential harm to the patient. As a consequence, before going to animal tests and finally human trials, extensive testing of the devices is required. This includes both the raw materials and the complete system.

In the case of CLONS, the implantable electrodes are made of flexible polyimide, with platinum electrode contacts and tracks integrated in a thin-film structure [19]. For these materials and the corresponding process technology, biological *in vitro* and *in vivo* tests were already done in the past to prove biocompatibility. However, as the vestibular prosthesis is based on both a new design and a variation of the process technology (enabling of double-sided electrodes) [20], further biocompatibility tests will be performed in order to guarantee safety for this particular type of electrode.

Regarding the implanted electronic components used for generation of the stimulation pulses, adequate encapsulation is required, in order to protect the implant from adverse reaction of the immune system of the body, and to generate an appropriate host response. Such encapsulation layers have to remain stable over the complete lifetime of the implant. Two different approaches can be used to encapsulate implantable electronic components: either the complete system is hermetically sealed using e.g. titanium or ceramic housings, or hermetically sealed individual components are joined together and are encapsulated non-hermetically using e.g. polymer materials such as silicone or Parylene C [5].

All steps in the design development of a neural prosthesis have to be accompanied by an adequate risk management process, in order to identify all potential risks associated with the system and to initiate measures and modifications to counteract those [21]. In Europe, risk management is done according to the standard ISO 14971.

III. Animal Experiments

After extensive *in vitro* testing of a neuroprosthesis, the next step in the development phase is to test the system in a living organism. As human trials are not justifiable especially in earlier development phases, suitable animal models are selected, meeting the demands related to anatomic and physiological properties. Whenever possible, animals of lower taxonomical classification should be used [18].

During testing, scientists and physicians have to ensure that all experimental protocols are implemented in observance to the national or European regulations. As a guideline for adequate use of animal models, Russell and Burch introduced the concept of the Three R's (Reduce, Refine, Replace) [22]. The idea is to 1) reduce the need for in-vivo experiments and thus the number of animals used as much as possible, 2) refine the experimental procedures to minimize pain and suffer to the animals, and 3) replace animal models with non-animal alternatives (e.g. *in vitro* tests or mathematical simulations) wherever scientifically possible.

The guidelines are considered and strictly followed in the development of the vestibular prosthesis within the CLONS project. For the animal experiments, guinea pigs, squirrel monkeys and rhesus monkeys are used. The guinea pigs are instrumented to develop and to test new procedures for the insertion of the newly developed shaft-like electrodes [19], and to test the efficacy of these electrodes. These tests are justified as the CLONS project includes a completely new type of electrode, and thus practical experience of implantation is absolutely necessary to refine electrode development, e.g. related to the required mechanical properties. During the tests, special care is taken to avoid any stress and pain to the animals by carefully watching them. Stimulation amplitudes are slowly increased from a low level, in order to guarantee safe stimulation levels.

In order to achieve the goals of the CLONS project, animal testing with a limited number of non-human primates (squirrel monkeys and rhesus monkeys) is absolutely necessary. Rhesus monkeys are required because their complex cortical organization, their capacity to manipulate objects, and their reflexive eye responses are similar to those found in humans. All animals are provided by high quality breeding centers.

In order to perform different behavioral tests after electrode implantation, the rhesus monkeys are trained using standard positive reinforcement techniques on three tasks: 1) to maintain a stable upright quadrupedal posture while standing on a balance platform, 2) to estimate the earth vertical by performing a visual task, and 3) to make eye and head movements to visual targets. Water or juice is provided to the animals as reward.

For the CLONS consortium, it is of utmost importance that minimum harm is caused to the animals to achieve the scientific objectives. Thus, the used protocols are the result of several years of iterative efforts in cooperation with the animal care committee including a veterinarian.

IV. Human Trials

After successful completion of animal trials, the final step in the development of a neural prosthesis before going to the market is to perform clinical trials on a limited number of patients, in order to prove the non-hazardous functionality and efficacy of the system [18]. As mentioned above, several neural prostheses such as the cochlear implant have already been used for decades with positive long-term results. Nevertheless, each neuroprosthesis is unique with respect to its design, the materials used and the site of application.

Before testing a new development in a clinical trial, patients have to give their informed consent. This requires the investigators to carefully clarify all possible consequences of the test to the patients, in order to minimize confusion and concerns [18]. Patients also have to be aware that clinical trials are rather performed on an experimental base than as a real treatment option. For instance, even though they may benefit from implantation of a neural prosthesis, they have to be aware that ethical guidelines might require removal of the prosthesis after the trial.

The human experiments within the CLONS project are in accordance with any kind of national and international regulation, e.g. the Charter of Fundamental Rights of the EU, or the Convention of the Council of Europe on Human Rights and Biomedicine, regarding free consensus of healthy and disabled people for human experiments. Human experiments are only performed if they are strictly necessary to achieve the scientific goals of the project.

Surgical approach for the implantation of the CLONS electrodes in the vicinity of the vestibular apparatus was chosen based on the following criteria: 1) surgery should allow to position the electrodes so that each vestibular end organ or nerve branch can be stimulated independently, 2) surgery has to be minimally invasive to avoid risks linked to long-term procedures, 3) surgery has to be feasible for local anesthesia to be able to test the responses to electrical stimulation during surgery and therefore position the electrodes at the most appropriate sites, 4) opening the inner ear has to be avoided to reduce the risks of labyrinthitis and irreversible hearing impairment.

Acute electrical stimulation of the human posterior ampullary nerve has already been performed at the institution prior to the CLONS project [23]. In contrast to cochlear implant surgery, insertion of vestibular electrodes requires a completely different surgical approach, as the electrodes have to be placed near the ampulla of the semicircular canals without destroying the peripheral dendrite between the end organ and the first order neuron. The outcome of these acute stimulation experiments were very important to the project, as they could strongly influence the further development of the prosthesis, considering that if no vestibular response could be elicited, the concept of the prosthesis might have had to be significantly modified.

For these experiments, patients were selected undergoing surgery for cochlear implant insertion or labyrinthectomy. Standard middle ear surgery techniques were used to access the posterior ampullary nerve via the external auditory canal [24]. The surgery was no added risk to the patient, as the external auditory canal is always approached for cochlear implant insertion and labyrinthectomy at the institution.

Prior to the acute stimulation experiments, all patients received an oral and written explanation of the experiment, and signed a consent agreement. The institution covered the fee for an eventual damage.

To verify the feasibility of the concept, also chronic stimulation experiments are necessary. It is known from animal trials that the "on and off" stimulation causes vertigo to the animals diminishing over the repetition of phases [25]. Although it is reasonable to estimate that a similar adaptation occurs in humans, experimental confirmation is necessary. Moreover, it has to be demonstrated that such adaptation can be achieved without causing unbearable vertigo.

Patients are recruited among candidates for cochlear implantation. As for the acute experiments, surgery for chronic implantation does not add any further risk to the patients. The only structure which could be damaged when approaching the posterior ampullary nerve is the round window membrane. As this could cause deafness in normal hearing patients, deaf ears are always chosen for the experiments.

Moreover, during the surgical approach of the branch innervating the lateral semicircular canal, the facial nerve is at risk [26]. From an ethical point of view, it was thus important to evaluate the potential benefit of the future vestibular implant versus the potential drama of a facial nerve paralysis. We could demonstrate that it is possible to reach and stimulate the lateral ampullary nerve without damaging the facial nerve [27].

A unique aspect in the development and application of a vestibular prosthesis is the fact that after implantation, patients will have a very hard time at the beginning, before they can draw some benefit from the prosthesis. They may suffer from vertigo until they become adapted to the restoration of a baseline neural activity in the vestibular system. This is a very critical issue, as the expected pain has to be weighed up against the potential benefit. Moreover, as no animal could describe this initial period of discomfort, patients giving their agreement to the experiments do not know in advance what they have to expect. Fortunately, we demonstrated that baseline activity can be restored without causing too much discomfort [28].

V. Conclusion and Outlook

During the development of a neural prosthesis, such as a system for restoration of vestibular sensation as it is developed in the CLONS project, various ethical aspects have to be considered during the whole concept and development phase. Already at the very first stage, the concept has to be scrutinized critically to avoid later

unexpected critical problems related to safe and ethical testing and application of the system.

For technological development, a very important issue is the creation of a safe, long-term stable and absolutely biocompatible system, in particular for the implantable parts of a neural prosthesis. From a medical point of view, all experiments on animals and humans have to be carefully accompanied by an ethical review, and the number of necessary experiments has to be chosen as low as possible to achieve the desired scientific goals.

For future development, especially with respect to clinical certification and commercialization of the prosthesis, further refinements of the system are necessary. This concerns not only the implantable part, but also the external components. For instance, suitable placement and fixation of the inertial sensors has to be determined. If the sensors are attached to glasses worn by the patient, movement of the glasses on the face would cause inappropriate vestibular stimulation. Thus, in the future, it will probably be appropriate to implant the inertial sensors as well.

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