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Developing solutions for present and future neurotherapy

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Abstract: This White Paper has been prepared as a result of a symposium and of existing Philips research activities in the diverse and complex area of neurotherapy. For the symposium, key note speakers specializing in the main neurotherapy areas of brain stimulation, pain management and neuro-rehabilitation were invited to speak and provide insight on their subjects. Their talks and workshops would subsequently highlight areas of treatment and diagnoses that could be identified as potential research subjects in the area of neurotherapy.

Conclusions:
Developing solutions for present and future neurotherapy

Summary of symposium held 13th – 14th June 2006 in Eindhoven

Overview

This White Paper has been prepared as a result of a symposium and of existing Philips research activities in the diverse and complex area of neurotherapy. For the symposium, key note speakers specializing in the main neurotherapy areas of brain stimulation, pain management and neuro-rehabilitation were invited to speak and provide insight on their subjects. Their talks and workshops would subsequently highlight areas of treatment and diagnoses that could be identified as potential research subjects in the area of neurotherapy.

Among all open questions that science has set out to unravel, three are considered by most as the outstanding challenges of our world: how did our universe appear, how did life appear, and how does our brain work? In its quest to answer the last of those three questions, the scientific community will also find better cures and therapies of the brain. This will improve and even save the lives of millions of patients, help relatives and caregivers, and reduce healthcare costs of disorders of the brain that claim about one third of the global burden of disease in developed countries.1

From its current position in medical diagnostics, monitoring and treatment equipment, it is therefore only natural that Philips wants to contribute to the advancement of “brain health” and neurotherapy. Furthermore, thanks to its wide experience in other technology fields such as personal care, electronics miniaturization and integration, and user-media interaction, Philips is ideally positioned to innovate and improve the way patients and caregivers, including doctors, will provide and experience healthcare in the future.

The areas chosen for treatment in this White Paper - brain stimulation, pain management and neuro-rehabilitation (see boxes) – address major categories of brain and nervous system conditions, from chronic pain and headache, to stroke, neurodegenerative diseases (Parkinson’s, Alzheimer’s), and even possibly chronic depression. During the symposium and subsequent workshops, the participants have identified clear ways in which Philips can contribute to the improvement of neurotherapies.

Chronic pain, neuro-rehabilitation and chronic/degenerative brain conditions all require daily, if not permanent, attention from patients and caregivers. Ways of providing simple, intuitive yet efficient devices are thus much awaited by patients and doctors. New technologies will improve patient autonomy and his/her ability to manage treatment or training at home or in light, outpatient medical environments. The integration of treatment systems with entertainment and coaching methods, coupled to ease of use, will improve treatment compliance and provide rewarding experiences for conditions that

In its drive towards increasing its presence as a healthcare and wellness company, and in line with leveraging its current range of diagnostic products and building synergy with its strong electronics and miniaturization proficiencies, Philips invited keynote neurotherapy speakers to a symposium at its Eindhoven High Tech Campus on June 13th 2006. The speakers addressed Philips' R&D staff with inspiring 45 minute talks about future developments in the exciting field of neurotechnologies for clinical and rehabilitation neurology. The objective of the meeting was to identify possible research areas for Philips that complement the company's future positioning, R&D capabilities and that have a promising future market.

The presentations were in the following areas:

- Deep Brain Stimulation by Professor Benabid, Head of “Preclinical Neurobiology”, Research Unit, INSERM; Head of Neurosurgery, Grenoble University Hospital; Professor of Biophysics, U. Joseph Fourier, Grenoble

- Transcranial Magnetic Stimulation by Ziad Nahas, MD; MSCR, Associate Professor; Director, Mood Disorders Program; Medical Director, Brain Stimulation Lab; Medical University of South Carolina, Charleston, SC

- Transcutaneous Electric Nerve Stimulation (TENS) by Dr. Marc Johnson, Professor of Pain and Analgesia, Leeds Metropolitan University, UK

- Emerging Technologies and Clinical Assessment in Neurorehabilitation by Professor Maarten J Ijzerman from the University of Twente, Biomedical Technological Institute, Enschede, The Netherlands.
Symposium kicks off
The symposium kicked-off with an extensive talk by Prof. Benabid, pioneer and co-inventor of Deep Brain Stimulation for Parkinson’s disease on his theory of Deep Brain Stimulation, and concluded with an open panel session. More about his and the other talks is covered in later sections in this paper.

The symposium was followed the next day by a restricted Philips internal workshop, which drew the lessons learned from the symposium and elaborated on them. The workshop was also a platform to share knowledge from the participants about neurotherapy-related research projects, and to create a draft towards a common research strategy in neurotherapy Participation to the workshop was by invitation only, and the workshop participants comprised members of research projects in neurology and psychiatry, plus specialists from Philips’ product divisions, incubators, and management.

For the first half of the second day workshop, time was spent identifying possible research areas for Philips in the area of neurotherapy. The results were then classified into the three applications of Pain Management, Brain Stimulation and Rehabilitation. Common questions were raised for each of the applications:

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Conclusions from the three brainstorm sessions
- In the area of rehabilitation, there is huge potential in using remote patient solutions to encourage regular and consistent therapy in the home, with the goal of increasing the patient’s motivation for carrying out rehabilitation therapy in the home. Furthermore, with greater and more consistent documentation of results from therapy, caregivers will have better information for decision making. Decision Support tools will benefit from increased and better data resulting from regular patient feedback.

- In the area of brain stimulation, “4D” brain mapping will offer first, short term improvements by gathering individual brain maps from patients and merging the data to produce a “4D” map that surgeons can use to accurately pinpoint optimal implantation targets. Further, longer-term improvements will come from the integration of disease detection, treatment planning, implantation and patient follow-up in comprehensive “clinical decision support systems”. Eventually, brain stimulation therapies will combine drug, cell, and physical techniques in active microsystems that will respond to neural activity and empower curative treatments.

- In the area of pain management, one of the key areas highlighted during the discussion, was that there was a need to develop non-invasive, drug-free pain management techniques such as TENS, for use in the home. By improving and creating pain management techniques for the home, this reduces the number of patients in hospitals thereby lowering health service costs and offering patients more control on - and involvement with - their treatment.

The sessions by application
1. The rehabilitation session
Neurological impairments, for example, following a stroke, put a severe strain on the patient, the caregiver and ultimately the healthcare system. The emerging field of neuro-rehabilitation can be divided into the following three categories:

1. The training of the impaired limb
2. Replacement of functions
3. Assisting in execution of specific tasks.
From these three categories, one can build a roadmap for rehabilitation.

The rehabilitation workshop intended to identify the areas that offer an attractive opportunity for Philips’ research and business development and to sketch out a strategy about how the relevant fields can be addressed by research projects.

- Rehabilitation: a wide field of activities and challenging economics
Rehabilitation encompasses a wide range of medical activities, but also brings about the biggest economical challenges and opportunities for the future. Stroke patients alone provide a huge burden to state economies. For example, in Germany alone, the overall cost per first-year survivor of first-ever ischemic stroke was estimated to be 18 517 Euros. Rehabilitation accounted for 37% of this cost, whereas in subsequent years, outpatient care was the major cost driver. Discounted lifetime cost per case was 43 129 Euros overall and was higher in men (45 549 EUR) than in women (41 304 EUR). National projections for the period 2006 to 2015 showed 1.5 million and 1.9 million new cases of ischemic stroke in men and women respectively, thereby representing a present value of 51.5 and 57.5 billion Euros respectively (2).

The resulting conclusion is that stroke prevention and reduction of stroke-related disability should be made priorities in health planning policies. Consequently, it is easy to imagine the pressure to develop more effective rehabilitation methods and tools for this area.

- What is stroke rehabilitation?
Rehabilitation helps stroke survivors relearn skills that are lost when part of the brain is damaged. For example, these skills can include coordinating leg movements in order to walk or carrying out the steps involved in any complex activity. Rehabilitation also teaches survivors new ways of performing tasks to circumvent or compensate for any residual disabilities. Patients may need to learn how to bathe and dress using only one hand, or how to communicate effectively when their ability to use language has been compromised. There is a strong consensus among rehabilitation experts that the most important element in any rehabilitation program is carefully directed, well-focused, repetitive practice - the same kind of practice used by all people when they learn a new skill, such as playing the piano or pitching a baseball.

Rehabilitative therapy begins in the acute-care hospital after the patient’s medical condition has been stabilized, often within 24 to 48 hours after the stroke. The first steps involve promoting independent movement because many patients are paralyzed or seriously weakened. Patients are prompted to change positions frequently while lying in bed and to engage in passive or active range-of-motion exercises to strengthen their stroke-impaired limbs. (“Passive” range-of-motion exercises are those in which the therapist actively helps the patient move a limb repeatedly, whereas “active” exercises are performed by the patient with no physical assistance from the therapist.) Patients progress from sitting up and transferring between the bed and a chair to standing, bearing their own weight, and walking with or without assistance. Rehabilitation nurses and therapists help patients perform progressively more complex and demanding tasks, such as bathing, dressing, and using a toilet, and they encourage patients to begin using their stroke-impaired limbs while engaging in those tasks. Beginning to reacquire the ability to carry out these basic activities of daily living represents the first stage in a stroke survivor’s return to functional independence.

(2) Taken from “Lifetime Cost of Ischemic Stroke in Germany: Results and National Projections from a Population-Based Stroke Registry”, The Erlangen Stroke Project, by Peter L. Kolominsky-Rabas, MD, PhD, et al. 2006.
What is TENS?

Transcutaneous electrical nerve stimulation (TENS) is the application of electrical stimulation at the surface of the skin (transcutaneous), primarily for pain relief. TENS is applied via external surface electrodes with some sort of electrical waveform characterised by frequency, pulse duration and amplitude. The technique of applying electricity is as old as the discovery of electricity but gained substantial scientific interest after the Melzack & Wall publication on the gate control theory in 1965 providing a scientific base on the mechanism of pain reduction. TENS is drug-free, non-invasive, non-addictive and has hardly any contraindications. Currently there are many manufacturers of TENS devices either for the professional clinical market or the home use market providing TENS devices range from $100 to $1000.

Challenges and opportunities of current rehabilitation techniques

An interesting point from Ijzerman’s lecture was that patients were far more interested in having non-invasive user-friendly rehabilitation techniques than in the functional outcomes of the techniques themselves. However, as already noted, the data source evidence for what techniques are more effective was inadequate. Astoundingly, Ijzerman also mentioned that it is more important to keep up the frequency of rehabilitation rather than improve the quality of the rehabilitation activities. The conclusion of this statement is that compliance and willingness of the patient is a leading objective in the development of new devices. To keep up motivation by developing user friendly and motivating applications was one of Ijzerman’s key demands.

Following these points, it was discussed how the compliance of patients could be improved. This topic related well to the issue of patient-centered solutions. For example, by using telemonitoring solutions, patients would be able to receive immediate and interactive feedback on their rehabilitation techniques remotely. By being in charge of their own rehabilitation technique from the comfort and safety of their homes, and by getting regular feedback and encouragement, patients will be far more motivated to comply with their rehabilitation requirements.

Decision Support Systems and Outpatient solutions

Besides the area of neuroprothesis and motor improvement, the symposium discussed intensively the topic of decision support solutions. A main objective for all activities in rehabilitation is to put the life of the patient back into his/her own hands, thereby giving him/her more freedom and independence. How impaired patients at home can be guided through their everyday life challenges was a hot topic for discussion, with ideas ranging from homecare robots to distance support. Interestingly, all the ideas that were discussed pointed in one direction: that all devices and solutions needed to be centered on patient demand, ergo – patient-centered solutions.

The workshop was instrumental in defining research directions in pain management that would expand the current Philips portfolio of both professional and homecare pain relief products such as InfraCare and InfraPhil.

Challenges and opportunities in pain treatments

Johnson emphasised in his lecture the strong connectivity between the cause of the pain and the perception, summarised as the interaction between brain and pain. The platitude “no brain, no pain” might sound like a joke, however the causal link is there. What is not clear is the border between cause of pain and its perception. Pain is sensory – it has both an emotional and a thought dimension. Therefore a lot of the senses of pain are based on cognition, psychosomatic states and physiological dysfunction of the brain. These are not easily measurable physical states. Johnson drew a comparison between the brain and a computer: there are a lot of areas where the software and the hardware of the brain are indistinguishable. However, if indeed it was possible to find and define a universal measurement for pain, this would open up a world of possibilities for the development of alternative treatments for pain.

The pain management session

The fact that one in five Europeans suffers from chronic pain was a primary initiative for the theme of this workshop on drug-free, non-invasive pain management therapies. Chronic pain treatment in the UK alone, for example, costs 3.8 billion GBP annually. This factor plus the increasing population of aged people in society are creating greater demand for more sustainable and cost effective solutions for pain management.

Drug-free, non-invasive pain reduction therapies using externally applied transcutaneous electrical nerve stimulation (TENS) was discussed at length. Despite some shortcomings of current electrical stimulation therapies, the technology has the potential to be changed from a medical therapy prescribed by clinical professionals into an easy-to-use consumer treatment that patients could administer themselves.

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Cultural considerations for pain management

An interesting but important factor in pain treatment is culture. Alternative medicines, such as homeopathy and acupuncture are obvious examples of how cultures accept alternative treatments as effective in the treatment of pain. Therefore, in the development of new Western pain management devices, a move towards understanding other cultural methods and thus change management is obligatory.

A further useful conclusion from Johnson’s symposium was: Whether something is of therapeutic use or not can only be judged by the person who is in pain. The symptoms for one patient might be healed successfully, while this is not true for another patient. Pain is so far not scalable or objectively measurable. Consequently, an opportunity would be to create techniques or technology to somehow measure pain and store the information in pain diaries. Note that with patient-centered solutions, collating information in pain diaries is indeed an achievable objective.

Another major issue with current pain management is based on the effects of standard therapies: Pharmaceuticals are easy to handle. The patient simply swallows a pill and following a small time lag the pain should disappear. There are two negative aspects of using pharmaceuticals to treat chronic pain. First, the time lag for some pains is too painful. Second, every pharmaceutical component has a side effect, which can affect the results of the pain measurement.

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When a patient receives too many treatments
If a patient receives too many treatments for his/her pain, there is the danger that the pain could become psychological. Specifically, the acute pain could rapidly become chronic pain. This process has to be stopped. Pain has a cognitive element that is difficult to treat.

Patients have limited control over the treatment that they receive. To date, the treatment of pain in clinical environments has been controlled by clinicians, primarily through doses of pharmaceutical pain relievers. What eventually would be helpful would be devices and methods that would put the control of the pain more in the patient’s hands, hence the move towards more patient-centered solutions. Indeed, non-invasive therapies such as TENS have this potential. However, both clinicians and patients must first increase their awareness and acceptance of such therapies.

What is Deep Brain Stimulation?
Deep brain stimulation (DBS) is one of a group of treatments involving surgical implantation of a medical device called a “brain pacemaker,” which sends electrical impulses to specific parts of the brain. This surgical procedure is used to treat severe essential tremor, rigidity and bradykinesia (slow movement) associated with Parkinson, as well as primary dystonia and other conditions. Brain pacemakers were approved by the (FDA) in 1997 as a treatment for Parkinson’s disease as well as essential tremor, and in April 2003 as a treatment for primary dystonia. In March 2005, the results of a Canadian study performed by doctors from the University of Toronto were published indicating that DBS may also alleviate symptoms in patients suffering from clinical resistance depression.

What is TMS?
Transcranial magnetic stimulation (TMS) is the use of powerful rapidly changing magnetic fields to induce electric fields in the brain by electromagnetic induction without the need for surgery or external electrodes. Repetitive transcranial magnetic stimulation is known as rTMS. TMS is a powerful tool in research for mapping out how the brain functions, and has shown promise for noninvasive treatment of a host of disorders, including depression and auditory hallucinations.

Making pain management methods easy to use
In educating both patients and health care professionals about unconventional pain management devices, a major consideration is how simple it would be for the patient to use the device him/herself. Therefore, in planning research for such products, a critical factor governing the research should be ease of use, bearing in mind that the end user of the device could be the patient. Additionally, to link these devices to established technologies would represent an exciting and great opportunity in the market.

Considerations for developing pain management devices
In short, when developing solutions for patient-centered pain management devices, the following should be considered:
1. Can the device be controlled by the patient?
2. How quick is the response rate on the device?
3. What are the safety features?
4. Does the device have telemonitoring capabilities?
5. Is the device user-friendly and easy to use?

3. The brain stimulation session
Brain stimulation techniques such as Deep Brain Stimulation (DBS), Cortical Stimulation, Transcranial Magnetic Stimulation (TMS) and Vagus Nerve Stimulation (VNS) are all techniques that attempt to reduce neurological symptoms by sending electrical impulses to the brain, for example, through surgical implantation of a “brain pacemaker” (Deep Brain Stimulation), or the use of powerful rapidly changing magnetic fields to induce electric fields in the brain by electromagnetic induction without the need for surgery or external electrodes (Transcranial Magnetic Stimulation). DBS and VNS are FDA approved treatments for Parkinson’s disease and epilepsy, respectively, and clinical research is constantly investigating new indications, e.g. depression.

Hot areas for development
Imaging and monitoring of treatments are currently high up on the brain stimulation agenda. During the symposium, Prof. Benabid – keynote speaker on deep brain stimulation – identified that the greatest opportunities for improvements in brain stimulation lie in the areas of localization, bio-sensing, and correct positioning of electrodes in the brain for stimulation and treatment. Nowadays, optimal electrode position equals optimal patient improvement, meaning that a closer merging of target identification by imaging with implantation trajectory planning and intraoperative placement control will warrant better treatment. Benabid also mentioned the availability of multi-positionable electrodes as a desirable development to more accurately adapt the spatial distribution of stimulation to the specific functional somatotopy of each patient.

The workshop sessions clearly identified planning, tracking and guiding of interventions in the neurosurgery theater (neuro-lab) as a leading opportunity. MRI compatible devices, increased spatial resolution for implant placement and merged modalities supported by adequate software will be needed to offer a comprehensive solution for neuro-intervention, an important development in the future. Non-invasive TMS would also greatly benefit from targeting improvement and new methods to access deeper brain structures.
Challenges and opportunities in brain stimulation

From the long list of expected innovations in brain stimulation therapies, device miniaturization, novel electrode designs and first efforts towards defining better targeted, less intrusive techniques are most readily achievable.

To a large extent, the accuracy of stimulation targeting for each individual patient depends on our understanding of the exact functional structure of their brain. Therefore, imaging suppliers must begin to collaborate more closely with researchers working on brain-mapping and functional networks to create a “4D” brain mapping solution that can be used interactively in the operating environment. In the longer run, functional and diffusion-tensor MR, SPECT and PET technologies will be combined and will benefit from novel molecular imaging advances in the brain. While the first step is in principle already technically possible, it remains a challenging task in view of the necessary requirement of producing standard software that will seamlessly blend the functions of brain imaging, mapping, and modeling to provide the specific patient brain analysis necessary for functional neurosurgery.

Another trend is the expectation that Clinical Decision Support Systems (CDSS) will become available in the next 5 – 10 years for neurostimulation therapies, as targeting, implantation surgery and stimulation parameter settings become more accurate, better documented, universal and standardized, i.e. enter evidence-based medicine practices. The benefits will be in improving average patient outcome, making the treatment more widely available, reducing the time required for decision making, and eventually bringing down the costs of the treatment.

A very exciting promise lies in the prospect of a technology that will stimulate the brain only when and if it is needed. Although most of the research in this field is geared at offering neuroprostheses for patients suffering e.g. from post-stroke neurological impairments, traumatic brain injury, or spinal cord injury; other neurological indications such as epilepsy will benefit from so-called “closed-loop” brain stimulation. Progress in this field critically depends on insights gained into the inner workings of neural in vivo circuits, and will therefore expectedly reach fruition in the far future while first, simpler implementations of this concept are being investigated by various research groups and neurotech companies.

A vision for the future

In the long term, a wider definition of brain stimulation could play a role for novel, curative therapies. As we progressively get to know more about neurons and how to influence their function, a more “organic” approach to brain stimulation techniques will be available, as opposed to the current electrical or systemic drug solutions. We will be able to detect and control neuronal dysfunctions by probing, influencing or controlling the relevant cells in the brain at the protein level.

The science of brain stimulation will therefore become more proactive than the current passive, “switch-off” approaches. It will at the same time be miniaturized and more integrated, with microsystems delivering specific therapies at their specific targets, making best combined use of drug, genetic, proteinaceous or physical (e.g. electro-magnetic) approaches, thereby claiming its legitimate place in the neurotherapeutic arsenal of the future.