Utrecht Neural Prosthesis (UNP)
A pilot study on controllability of brain signals and application in locked-in patients

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The main goal is to achieve a means of communication solely based on brain signals for severely paralyzed patients. Success will constitute a significant advance in the field of BCI and of severe paralysis because it will be the first system that...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56387

Source
ToetsingOnline

Brief title
UNP

Condition

- Other condition

Synonym
Locked-in syndrome

Health condition

Zeer ernstige verlamming door trauma of ziekte (Locked in syndroom)

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,NWO-STW;NWO,NIDCD(NIH)

Intervention

Keyword: brain, brain-computer interface, implant, locked-in

Outcome measures

Primary outcome

Primary endpoint is proficiency of use of the BCI system. For this we recognize three levels of proficiency: First, the level of proficiency described as the primary objective, being unsupervised BCI performance (with system switched on/off by caregiver), with the criterion that the system correctly detects a switch brain signal within 10 sec in a real life, cognitively engaging context, such as operating a spelling device. A formal test has been designed, in which the patient has to copy a 30 character sentence within 30 minutes, with a margin of 20 faulty characters (see Section 8.3.7, Level 2 proficiency). For this test, scanning software is employed. Second, we define lower level of proficiency , which represents a level equivalent to that of the communication channel that the patient had before participation, being supervised BCI performance, where the patient is able to generate switch commands with at least 80 % correct, with the help of a BCI researcher and/or caregiver (using a formal test, see Section 8.3.7, Level 1 proficiency). A third level of control is defined as independent BCI performance, where the patient is capable of switching the BCI system on and off by himself. This requires the highest level

of control achievable. Thus, the three levels, in order of proficiency are:

1) Supervised use, dependent on continuous assistance for communication

2) Unsupervised use, ability to communicate without assistance for limited periods

3) Independent use, ability to communicate without assistance at any time of day or night.

Note that level 2 is the primary objective of the study, and that only levels 1 and 2 will be tested using formal tests. Success of the study is defined as: At least 50% of participants (3/5) reach level 2 proficiency and can thus communicate effectively as assessed with a formal test.

Secondary outcome

Secondary study parameters are patient satisfaction (subjective ratings, hours use of BCI system per week, quality of life), and definition of a set of metrics for evaluation of efficacy of the BCI system for a larger clinical trial.

Study description

Background summary

In this pilot study we will provide locked-in people with a new means of communication which has not been possible up to now. For the first time, we will test whether we can record and decode neural signals obtained directly from the brain, for control over a computer. The target population is severely paralyzed, due to trauma, brainstem stroke, neuromotor disease or another cause, and has no means of communication other than for instance eye blinks.

For these patients there is no technique available to allow them to communicate unaided. We have developed a system that can read activity directly from the brain, and can convert the activity to a digital yes/no switch. The system, called the Utrecht Neural Prosthesis (UNP), consists of an implantable amplifier for electrical brain signals, a set of electrodes positioned on the surface of the brain and a wireless receiver (constituting the *Medtronic System*). This was recently developed by Medtronic, a company specialized in medical implantable devices such as Deep Brain Stimulators and pacemakers among others, and has been tested for the current application by our group at the UMC. A dedicated computer will convert the signals to electrical pulses for standard Assistive Technology (AT) devices (UMC Brain Interpreter, developed at the UMC with the Medical Technology Dept). The amplifier and electrodes are fully implanted and signal is transmitted wirelessly through the skin. Crucial elements of the UNP are exact positioning of electrodes on the cortex (after accurate localization of two brain functions and associated regions), and the specific features extracted from the complex brain signals. The UNP can in principle enable the patient to engage in any activity that is offered by commercial Assistive Technology companies that can be performed with yes/no signals, for instance operating home apparatus such as lights, tv, curtains etcetera, or writing text for emailing. However, since we do not yet know how proficient participants can operate the BCI system, the ability to switch home devices on or off may not be safe. Therefore for the current pilot study we will limit use of the BCI system to selecting a yes/no indicator on a computer screen, and to writing text. Most importantly, we aim to achieve unsupervised function of the BCI, meaning that the patient will be able to use it at home without the aid of researchers or other experts (but with minimal caregiver assistance). The device, consisting of amplifier, electrodes and the wires connecting them to each other, will be implanted in 5 patients over a period of 5 years. Research will be conducted for 12 months after implant and may be extended each year for 12 months.

Study objective

The main goal is to achieve a means of communication solely based on brain signals for severely paralyzed patients. Success will constitute a significant advance in the field of BCI and of severe paralysis because it will be the first system that allows for unsupervised operation. For this, we need to investigate feasibility in the current pilot study. Several objectives are defined, all representing performance of the BCI system in real life. The primary objective is to achieve communication via our BCI system in locked in patients, as measured in terms of writing a sentence on a computer without help from a member of the BCI research team (unsupervised use). Two secondary objectives are defined being a) Improve Quality of Life and user satisfaction with the BCI system, and b) Assess experimental parameters for a larger clinical study.

Study design

This study is an interventional study, lasting 5 years. It is a pilot study preparing the ground for a larger clinical trial, and has an adaptive trial design, where we allow for modifications to be made concurrently (e.g. in/exclusion criteria) or prospectively (e.g. discontinuation following interim evaluation, modification of end-of-study date), in communication with DSMB and METC committee (Thabane et al., 2010).

Intervention

A device will be implanted, to detect and analyze brain signals. After the surgical implant procedure, feedback is given of brain activity via a visual display. Successful control over the brain signal will improve a patient*s wellbeing since it offers a means of communicating. Failure to control the signal will induce disappointment. No detrimental effects on physical or mental health are to be expected.

Study burden and risks

General
The research is fully directed at the patient population participating in the study. The participating patients are likely to experience benefit from participation in terms of acquiring a new means of communication for the duration of the study. If the study succeeds in its objectives, it can provide patients with the means to engage in interaction with others and with their environment without the help of others, and at any time. This degree of autonomy is not available in any other way for these patients.
However, the research is high risk, in spite of the significant amount of proof-of-principle research leading up to this study, because there are no data from chronic implants yet that would allow us to estimate performance of the BCI system in real life. The current medical device is the first to be implanted for the purpose of BCI worldwide so there are no data to further strengthen the proof of principle research. There is a risk that the system fails due to unforeseen phenomena. Nevertheless, the prior research results strongly suggest that the experiment should work well in at least 50 % of the participants, and reasonably well in the other 50%, provided that electrodes are in the proper position (Vansteensel et al., 2010).
The participants will spend time in the UMC for the procedure, which involves two surgeries: one to position sets of electrodes and their leads, and one three days later to place the device and connect the leads. During their stay they undergo testing for determining the optimal electrode pairs for use, and start practising BCI with the signals. In case a participant already has ECoG electrodes and Activa PC+S implanted, one of the surgeries and the inter-surgery testing will not take place and its associated risks and burden do not apply. After recovery the patients go home and training continues until

they can operate an AT device (Touchy). They continue to participate in research sessions aimed at obtaining performance measures, measures of use and satisfaction, and at improving the decoding technique to further improve performance (less error, faster switching). Hence the burden will be medical (surgical procedure), and devoting time and energy to the experiment. If the correct decoding of brain signals fails, and a patient is not able to gain accurate control over the BCI, this patient has no benefit of contributing to the study. If, however, correct decoding is successful, the benefit is possibly large, since he or she will have a new means of communicating with others and control of home environment.
After implantation, MRIs and the use of diathermia are no longer possible. If, during the study, an MRI is required for urgent medical reasons, the implanted parts need to be surgically removed before the scan.
Risks include those related to the fMRI scan, surgery, technical aspects of the device and emotional wellbeing. These risks are discussed below.

fMRI*
fMRI scanning is considered a safe procedure, and potential risks will be minimized by excluding patients who do not meet the inclusion/exclusion standards. Special care is taken to ensure that the patient has no metal objects present in the body. Of particular concern are metal fragments in brain tissue or eyes, surgical clips and non-removable electronic devices, such as pacemakers. Potential risks associated with the transport of a patient on artificial ventilation from the ICU to the MRI suite, and switching to the MRI compatible respiratory aid equipment in the MRI suite, are minimized by following the Standard Operation Procedure (see Section 8.3.3 and 15.1). The patient*s vital signs such as heart rate, respiratory rate and oxygen saturation will be monitored continuously by the anesthesiology team. Furthermore, a member of the research team will be monitoring the available communication channel with the patient for the total duration of the fMRI scan. In the case of unreliable communication, this monitoring will not be possible possible and the vital signs of the patient will be informative about the patient*s wellbeing. In consultation with the caretaker, one or more interruptions of the scan session may be scheduled for extra checkups and care if needed.
* Because electrodes are already in place, imaging, electrode placement surgery and strip selection procedures are not relevant for new participants with existing implant

Surgery
The experiments involve a surgical procedure with implantation of electrodes underneath the skull, lead wires under the skin from the head to the chest, and/or positioning of a medical device under the skin on the chest. This procedure is the same as for deep-brain stimulators, but with a less invasive electrode positioning as they do not penetrate brain tissue (deep-brain stimulators travel through much of the brain white matter to reach their goal

in the thalamus). Medtronic has already delivered 85.000 DBS stimulators for implantation in Parkinson patients alone, indicating that implantation of the device is by now a standard procedure.
The surgical implantation procedures (implantation of the electrodes and implantation of the Activa PC+S device) carry the same risks associated with any other brain surgery. In the worst case, risks of brain surgery may include serious complications such as coma, bleeding inside the brain, seizures and infection. Some of these may be fatal. However, the chance that complications occur is very low, among others since electrodes do not penetrate the cortex. The risk of subdural or epidural hemorrhage ranges from none to 2%. This literature is mostly based on devices penetrating the cortex (Bronstein et al., 2011; Franzini et al., 2011). Once implanted, the system may become infected. The risk of intracranial infection after implantation surgery is around 5% in the literature. The risk of infection at the scalp where the cables are externalized is likely smaller. Depending on the severity and the location of the infection, parts of the system may have to be explanted. After implantation, parts may wear through the skin, and the lead or lead/extension connector may move. Any of these situations may require additional surgery. Notably, having two brain surgeries close together in time is standard clinical practice in the treatment of severe intractable epilepsy and other conditions, and does in itself not add any additional risks.
Risks related to the explantation scenarios (see Section 8.3.12) include infection (~3%) and, in the case of explantation of all implanted parts (including the electrodes), subdural or epidural hemorrhage (0-2%).

Technical aspects of the device
In case the UNP does not work (properly), or stops working after a period of good performance, the source of the problem has to be identified. There are a number of technical aspects or causes that need to be considered:
- The brain signal may show unexpected characteristics, making it an unreliable source of signals for UNP control. Based on our prior research with epilepsy patients we expect that the chance that this happens is very small, especially in the first period after surgery. The longterm effects of the use of a certain brain area for controlling the UNP on the characteristics of the measured signal is, however, presently unknown and one of the parameters investigated in the current study. Evidence from a recent study looking at action potentials indicates that five years after implant signals are still usable for BCI purposes (Hochberg et al. 2012). If the characteristics of the primary control signal (see Section 8.3.7) prove to be too unreliable for correct UNP performance, we will switch to the secondary control signal and attempt to achieve UNP control using that.
- One of the external parts (outside the body) of the UNP is defective. In this case, the broken part may be repaired or replaced.
- One of th

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Age 18 - 75
2) Locked-in status (i.e. severely paralyzed with communication problems)
- in case of trauma or stroke: at least 1 year after the event
- in case of a neuromuscular disease: slow progression allowed
3) Mentally and physically capable of giving informed consent
. If at the time of the informed consent procedure (details in 11.2.2) the patient is not capable to unequivocally communicate consent, earlier expressions of the wish to participate after the patient was given information on the study will suffice.
4) Lives in or close to the Netherlands
5) MR compatible*
- able to lie flat in the scanner

- no metal objects in or attached to the body
- no claustrophobia
6) Visus (largely) intact
7) Cognition intact (IQ>80)
- In the case of unreliable communication at the time of inclusion, tests of cognitive functioning will not be conducted and results of fMRI analysis will inform the neuropsychologist about the patient*s cognitive ability to understand and follow instructions.
8) Compatible with implantation procedure
- good respiratory function or stable respiratory situation using ventilation assistance

* Because electrodes are already in place, imaging, electrode placement surgery and strip selection procedures are not relevant for new participants with existing implant.

Exclusion criteria

1) Strong and frequent spasms
2) Vital indication for blood thinners
3) Current brain tumor or history of tumor resection
4) Quick medical or neurological deterioration
5) Patients who are considered legally incapable (and who therefore will not be able to give
informed consent), unless there is evidence of earlier expressions of the will to participate after information about the study was given to the patient (eg legal document)
6) Current or recent psychiatric disorder
7) Catabolic state
8) Allergy to the materials of the implant

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-09-2015
Enrollment:	5
Type:	Actual

Medical products/devices used

Generic name:	Neural Prosthesis
Registration:	No

Ethics review

Approved WMO Date:	21-11-2013
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-12-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-04-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-07-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-02-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2015

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-09-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-11-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-05-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-02-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-11-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-07-2024

Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL40539.041.12