



ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

## **Restoring natural motor and sensory function after spinal cord injury**

**GROUP 6**

JADE THERRAS, GAËLLE VERDON, IRIS TOYE, IAN ENDERLI, JULES ORSAT, JOSH  
CERVANTES PEREZ, MATTHIAS KOCKISCH

# Contents

<b>1</b>	<b>Introduction</b>	<b>1</b>
<b>2</b>	<b>Biological background</b>	<b>2</b>
2.1	Spinal Cord Injuries . . . . .	2
2.2	Motor impairment and anatomy . . . . .	2
2.3	Sensory impairment and anatomy . . . . .	3
<b>3</b>	<b>State of the art</b>	<b>4</b>
3.1	Using a BSI to restore motor control . . . . .	4
3.2	Current solutions and propositions to restore sensory feedback . . . . .	5
3.2.1	Vibrotactile stimulation . . . . .	5
3.2.2	Stimulation of spinal cord above lesion . . . . .	5
3.2.3	Intracortical stimulation . . . . .	6
3.2.4	Subdural extracortical stimulation . . . . .	6
<b>4</b>	<b>Product</b>	<b>7</b>
4.1	Overview . . . . .	7
4.2	Sensors and computing unit . . . . .	8
4.3	Electrode choice and implementation . . . . .	8
4.3.1	Stimulation pattern . . . . .	10
4.3.2	Surgical procedure . . . . .	10
4.4	Implantable pulse generator . . . . .	10
4.5	Studies and clinical trials . . . . .	10
4.5.1	Approvals . . . . .	10
4.5.2	Bio-compatibility and long-term safety . . . . .	11
4.5.3	Proprioception . . . . .	12
4.5.4	Expected issues and tests to overcome them . . . . .	12
4.6	Daily use . . . . .	12
<b>5</b>	<b>Conclusion and limitations</b>	<b>14</b>
5.1	Limitations . . . . .	14
5.1.1	Sensors and computing unit . . . . .	14
5.1.2	Electrode choice and implementation . . . . .	14
5.1.3	Studies and clinical trials . . . . .	14
5.2	Conclusion . . . . .	15
<b>5</b>	<b>Bibliography</b>	<b>I</b>

---

# Introduction

Spinal cord injuries (SCI) occur when the spinal cord is damaged, interrupting the communication between the brain and the sites under the lesion, and thus impairing motor and sensory functions. It is a life-altering event that can have devastating consequences, affecting individuals' physical abilities and overall well-being. Every year, an estimated 250,000 to 500,000 new cases of spinal cord injuries are reported worldwide, underscoring the magnitude of this health issue. SCI can have various causes such as traumatic accidents, falls, sports injuries, diseases or degeneration (i.e. cancer). Symptoms and consequences depend on the severity and the location of the injury, but SCI is often associated with confinement to a wheelchair which significantly affects mobility, independence and overall quality of life.

To improve the lives of individuals with SCI, it is vital to prioritise their needs and aspirations. Studies have indeed shown that patients' priorities include several areas. For instance, paraplegic patients commonly highlight the importance of general health and physical functions, as well as their relationships with friends and family and social activities. In terms of physical health, specific functions such as bladder and bowel control, sexual functions, and walking or lower limb function have been mentioned to play a significant role in their overall well-being [1].

Based on the priorities of these patients, studies have been carried out to restore lower limb function, in particular motor function. Muscles and nerves stimulation has been used to artificially connect the brain and the region below the lesion site, allowing the restoration of some functions after an SCI; this nevertheless requires individual controllers for separate target muscles or nerves and can lead to muscle fatigue, limiting their applications[2]. Epidural electrical stimulation (EES) is a promising technique which overcomes these limitations. Even if it is an invasive one, the electrode implantation is made under the lesion site, and therefore involves less risk than if it was made above, as communication with the brain is already interrupted. Moreover, EES has already been approved for pain control in human and tested to restore voluntary limb movements, in particular, it allowed to restore walking and standing in people with paralysis[3]. Integrating this technology is possible by developing a brain-spine interface (BSI), an innovative and promising alternative for treating an SCI. In a study by Henri Lorach, prof. Courtine's laboratory implanted such a device in one SCI patient allowing him to walk naturally by decoding cortical signals [4].

In addition to restoring motor function, the restoration of sensory feedback is a critical aspect of improving the lives of individuals with SCI. Sensory impairments resulting from SCI can lead to a loss of sensation and proprioception, greatly impacting daily activities and overall quality of life. Studies have shown that the restoration of sensory feedback can significantly enhance motor control and promote better body awareness [5]. EES has shown partial restoration of sensations [4, 6], but the effect is still abroad. Our research aims to investigate different solutions, more or less invasive, to improve sensory restoration and particularly proprioception.

While significant progress has been made in the restoration of sensory feedback for individuals with SCI, it is important to note that most studies have focused on the upper limb stimulation area. For example, intracortical stimulation allowed to evoke sensations of pressure, touch, and warmth in the upper limbs of quadriplegic SCI patients [7]7. Depending on the intensity of the stimulation, the SCI patient reported a sensation of arm movement [8]8. Restoration of sensory feedback for lower limbs remains an area that requires further investigation and development. The goal of our project is to elaborate a system restoring proprioception of the lower limbs and integrate it into a state-of-the-art brain spine interface handling motor control.

# Biological background

## 2.1 SPINAL CORD INJURIES

There are different types of SCI and we must understand them and their differences to target the correct population for our device. First, an SCI is classified by its position on the spinal cord (figure 2.1). For example, a T8 SCI corresponds to a lesion at the eighth thoracic vertebra, meaning that the neuronal communication going through that level of the spinal cord may be altered or interrupted, while the paths leaving above this level aren't. The second classification is complete or incomplete (figure 2.2): a complete SCI means that every neuronal communication going through that level is blocked, and transferring information between the brain and the region below the injury is thus impossible. On the contrary, an incomplete SCI means that some neuronal connections at the level of the injury and below remain functional, either fully or partially. Furthermore, there are different types of incomplete SCI for the same level depending on the impaired region of the spinal cord. Incomplete SCI account for approximately 65% of all SCI in the United States. 9[9].

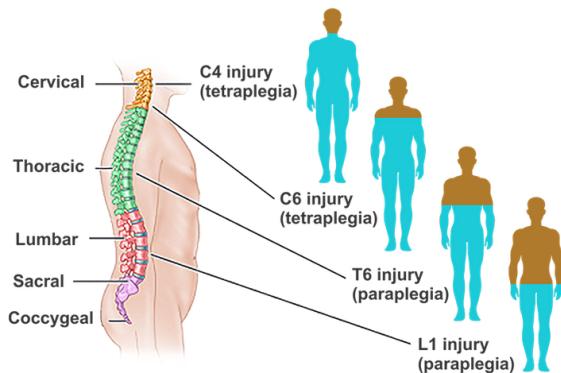


FIGURE 2.1 – Level of SCI

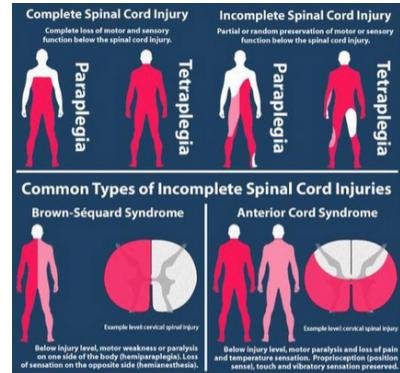


FIGURE 2.2 – Incomplete and complete SCI paralysis

## 2.2 MOTOR IMPAIRMENT AND ANATOMY

Having a background of the motor path is crucial to implement our device properly, as it completes another device that uses this path. With an SCI, communication with the brain is interrupted, but both the brain and the spinal cord below the injury are still functional. In humans, the motor control of the body is initiated essentially in the brain, in the primary motor cortex (M1). M1 is located in the central gyrus, right in front of the somatosensory cortex (figure 2.5). Each part of the primary motor cortex is dedicated to the motion of a specific region of the body. The region of interest for this project are the lower limbs, which are mapped to the top and the medial part of M1. The total path consists of a chain of two neurons: the first perceives the signal from the brain through its dendrites and transmits the motor information to the second neuron in the spinal cord. Then, the second neuron receives the signal and transmits it to the specific muscle or group of muscles to initiate its contraction, and therefore motion of the limb (figure 2.3).

In the spinal cord, walking is initiated by proprioceptive circuits and their reflex responses. Supra-spinal modulation controls the activation of gamma neurons that control the length of the muscle. This part of motor control allows for creating movement. On the neuron scale, excitatory lumbar spinal cord neurons expressing VSx2 have been proven to have a major role in the restoration of walking 10[10].

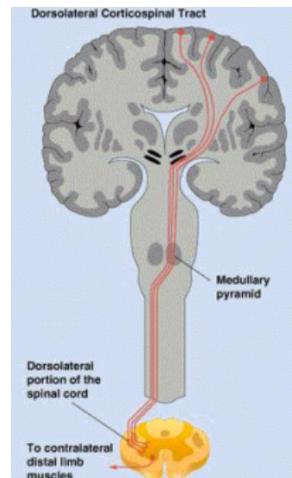


FIGURE 2.3 – Motor neuronal path

## 2.3 SENSORY IMPAIRMENT AND ANATOMY

The damage to the spine from an SCI also impedes the afferent signals, coming from the limbs and to be perceived by the CNS. For our purposes, we see two main types of sensory signals: haptic information from the pressure on the skin, and proprioceptive information about the position and movements of the limbs. Touch signals are detected by multiple types of mechanoreceptive cells and corpuscles in different layers of the skin, each specialised for contacts of certain widths and frequencies. Proprioceptive signals are mainly read as the muscle tension by the Golgi tendon organs, and the muscle length by the muscle spindles. Similarly to motor signals, the somatosensory information normally travels from the sensor cells through first, second and third-order neurons up to the post-central gyrus in the primary somatosensory cortex (S1) (figure 2.5), and the first-order neurons are assumed to be nonfunctional.

In S1, haptic sensations are mainly processed in the Brodmann areas 1 and 3b. Each part of the body is represented proportionally to the number of receptors they have, which allowed experimental construction of a so-called sensory homunculus (figure 2.4). The homunculus shows the predominance of haptic signals from the hands, due to their importance and precision in primates, as well as the ease of access of their areas on the flanks of the brain. Touch sensations from the hands have been thoroughly mapped and used for prosthesis control in the past [11]. On the other hand, leg haptics are processed in a much smaller area near and inside the central sulcus, and are thus much harder to access by current high-precision micro-electrode arrays. Both the sensory and spatial limitations render the study of this brain region virtually nonexistent in neuroscientific papers.

Unlike the haptics, the proprioceptive information flow from the legs is much more important compared to the one from the upper limbs. This is due to the strong integration of proprioception in gait and balance reflexes, which are essential parts of human bipedal locomotion and executed in both the spine and the cortex. Also, the upper limbs can usually retrieve similar information from the visual cortex. Conscious proprioceptive sensations are processed mainly by the Brodmann areas 2 and 3a, which lie parallel to the ones responsible for haptic signals; the homunculus therefore still approximately applies for this type of signals. Additionally, haptic and proprioceptive areas exhibit sub-cortical connections that can lead to mixed sensation types generated by strong stimulation of either area [8]. The proprioception areas have not yet revealed a structure as clear as that of the haptic or motor cortices, and neurons can be seen reacting to a mix of limb position, velocity and acceleration. They still exhibit behaviour similar to those in the M1 cortex, as close-by neurons show ties to the same muscles as well as preferred movement directions [12]. Unfortunately, the small space inside the central sulcus makes also the study of proprioception from the legs very limited in current neuroscience.

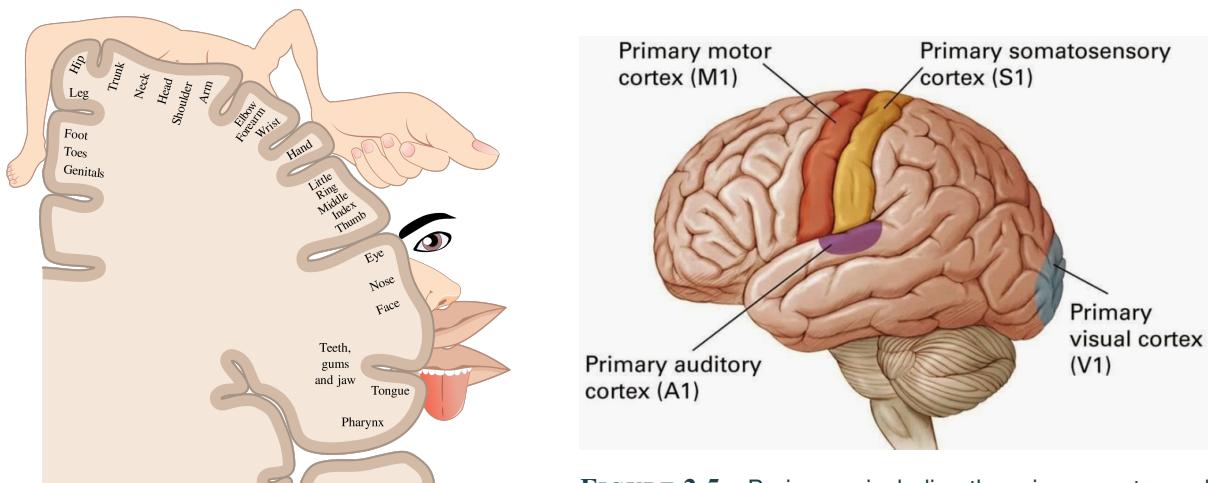


FIGURE 2.4 – Sensory homunculus [13]

FIGURE 2.5 – Brain map including the primary motor and sensory cortex

# State of the art

## 3.1 USING A BSI TO RESTORE MOTOR CONTROL

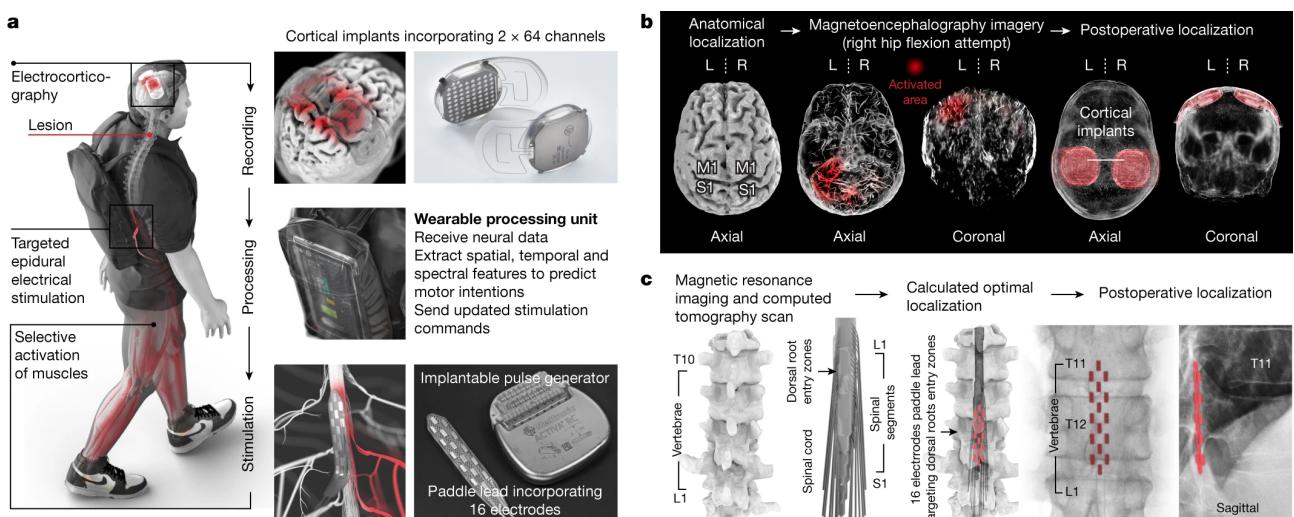
We aim to restore sensory feedback in patients already implanted with a brain-spine interface (BSI) for motor control. A BSI is a system aiming to create a digital bridge between the brain and the spinal cord to restore information flow after a spinal cord injury. Observing the most recent achievements [4], we identify three main parts in a motor BSI:

- **The brain implant (ECoG)** records activity from the motor cortex and sends it to the computing unit;
- **The computing unit** selects features related to walking and modulates specific synergies of lower limb muscles;
- **Epidural electrical stimulation (EES)** activates neural circuits below the injury site and restores some of the lost motor function, by mobilising the hip, ankle and joints.

The implementation and function of the BSI system is as follows:

- First, the ECoG electrodes are implanted at the surface of the M1 region of the brain, replacing a part of the skull. These electrodes can record brain activity and transmit them wirelessly to a helmet. The helmet is equipped with induction technology to recharge the electrodes.
- After the signal is recorded, it is sent to the computer unit, which processes and decodes the signal to select spatial and temporal relevant features related to movement intention. This mapping is then translated into stimulation programs that are to be delivered by the implantable pulse generator.
- The stimulation program is sent to the paddle lead of 16 electrodes with different configurations of anodes and cathodes to stimulate the motor pools. They can regulate extension and flexion of the hip, knee and ankle joints by mobilising antagonist muscles [4].
- The optimisation of the recording and the stimulation patterns is achieved during the training phase. First, the brain signal decoder is developed using a digital avatar that the patient controls. Subsequently, the spinal cord stimulation is tuned to target the specific hotspot for each movement we want to perform. The pattern generation algorithm links a certain decoding of the intended movement to a correlating stimulation of the spinal cord.

The BSI aims to recreate the link between the brain and lower limbs that are impaired due to SCI. Section 2.2 developed on the role of two types of neurons transmitting motor signals: one between the brain and the spine, the other between the spine and the targeted limb. We can see the BSI as a replacement of the first of the two neurons, as it decodes the motor intention from the brain and stimulates the spinal cord according of the detected intention.



**FIGURE 3.1 – Walking naturally after spinal cord injury using a brain–spine interface [4].**

## 3.2 CURRENT SOLUTIONS AND PROPOSITIONS TO RESTORE SENSORY FEEDBACK

Patients implanted with a motor BSI can already report a partial restoration of sensation, since the EES can also stimulate the dorsal part of the spinal cord that contains the sensory nerves. If the injury is incomplete, this stimulation can reactivate these nerves and provide some afferent signals to the brain. Motor training can further enhance this effect [4, 6], but the restoration remains partial and highly depends on the injury's gravity. In the same way and with more limitations, patients report partial restoration of sensation from external spinal cord stimulation.

We explored several stimulation methods to restore sensations from the lower limbs. The main concepts are shown in figure 3.2. To have an idea of the afferent information for these solutions, we assumed the use of smart shoes containing pressure sensors and accelerometers [14] to record information about leg movement; more details about these sensors are provided in section 4.2. This information will be converted into stimulation patterns to give back proprioception to the patient; the exact encoding is explored in section 4.5.3. Our main stimulation solutions are the following:

### 3.2.1 VIBROTACTILE STIMULATION

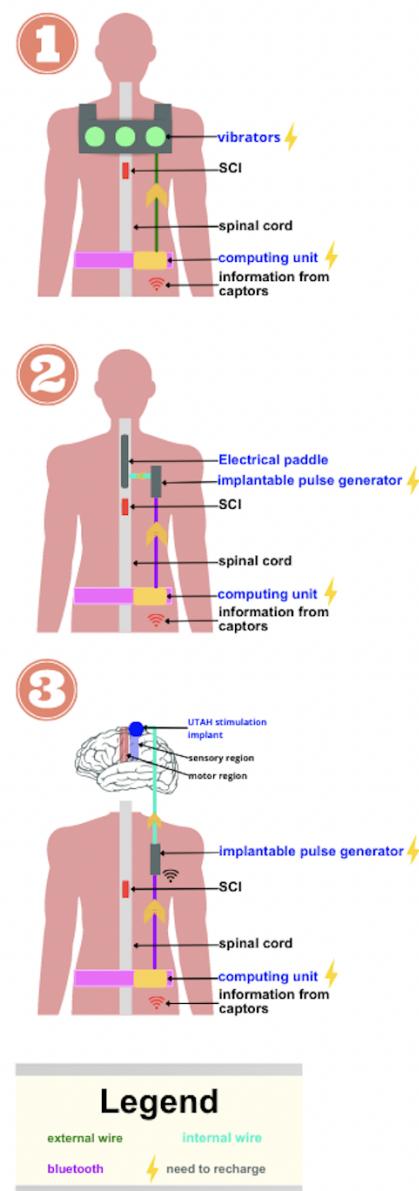
Sensory substitution can be performed by remapping the recorded information on another part of the body using vibrotactile stimulation. With stimulation on the torso, the intensity and the direction can be modulated depending on the position in the gait cycle and the acceleration of the foot. After training, the patient will perceive the vibration as a proprioception signal from the legs [15].

This solution has the advantage of being non-invasive, cheap and easy to implement. The patient's training could be done autonomously at home. However, the amount of information that can be transmitted is limited and the feeling will not be natural as it doesn't use the proprioception path but another one as substitution. Furthermore learning to equip and use the devices coupled to the BSI will need a lot of effort for the patient.

### 3.2.2 STIMULATION OF SPINAL CORD ABOVE LESION

Since the device targets a patient with a SCI below T5, the upper part of the spinal cord is still functional and transmits information about the upper part of the body. The sensory pathway from the legs still exists; we can therefore use stimulation of the spinal cord above the lesion. Another electrical paddle on the upper part of the spinal cord would be implanted, connected to an Implantable Pulse Generator (IPG) and another computing unit. This solution already yielded good results in studies [16]. The setup is similar to the spinal cord stimulation of the BSI, but the device will target sensory pathways for the lower body.

This solution uses an already existing implant and avoids surgery on the brain. It also ensures no interference with the BSI. However, the device is still invasive and it could be complicated to transmit a natural signal to the patient since no study on targeting proprioception directly on the spinal cord was found. Using this stimulation site, it is possible to restore a natural sensitive feedback as it targets the innate sensory path. The main drawback is that this part of the spinal cord is still functional, implying that an optimal stimulation for proprioception feedback is likely to stimulate other paths due to their small size and concentration in the spinal cord. Also, a problem during the operation could lead to worsened paralysis for the patient or even death. The risk for the quality of life is higher than operating below the injury site, where motricity is already lost anyway.



**FIGURE 3.2 – Sensory restoring device propositions**

---

### **3.2.3 INTRACORTICAL STIMULATION**

Another solution will be to target directly the brain via intracortical stimulation. An intracortical implant such as a UTAH array could target the leg's region in the primary sensory cortex (S1). This stimulation location is ideal as it targets the end of the sensory path. This site has the advantage to contain neurons specified in sensation of the lower limbs, which wouldn't impact another path. Also, the exploitable region is larger than in the spinal cord, allowing wider stimulation location and combination, leading to a more precise sensory feedback. After a training relying on brain plasticity, the patient can perceive the synthetic signal as proprioceptive sensations [12].

UTAH arrays are very selective and have already been implemented on animals. However, the surgery is risky and it is impossible to remove the implant without removing a part of the brain, possibly causing important damage. In addition, the leg area is large, and multiple UTAH arrays would be needed to cover it. Moreover, the legs region is inside the longitudinal fissure of the brain, where it is currently impossible to implant a UTAH array since it requires a perpendicular pneumatic insertion. Even if the UTAH array could otherwise be a good candidate, implementation in humans will not be possible.

### **3.2.4 SUBDURAL EXTRACORTICAL STIMULATION**

Starting from the last proposition, brain stimulation could be the best way to restore proprioception. It targets the end of the proprioceptive sensory path with precision, should not impair other neuronal path and is reasonably safe to implant. Subdural extracortical stimulation using electrocorticography (ECoG) was chosen. Past studies already used ECoG stimulation to restore touch sensation in upper limbs [17] and the goal is to follow a similar path for lower body sensation. These electrodes are less selective but can be implanted in the targeted region and cover it. They can also be easily and safely removed, and are overall less invasive than intracortical implants.

# Product

## 4.1 OVERVIEW

Our device aims to target patients with complete and incomplete SCI at thoracic and lower levels, as well as patients with incomplete cervical SCI. This choice is motivated by some main considerations: first, our implementation completes a device that already exists and so far has been implemented on a patient with incomplete cervical SCI, for which the patient needs to be able to use a computer to configure the stimulation, and some residual force in the arms is therefore necessary to help stand and use the device. Patients with a total cervical SCI will also lose other functions, like their upper limbs (brachial plexus emerges from C5 to T1 intervertebral nerves), thus the function of their lower limbs will certainly no longer be a priority [1].

Our device concept contains different parts: spinal cord stimulation by an electrode paddle, allowing motor movements and controlled by an ECoG recording of motor intentions, is indicated in red in figure 4.1 and is similar to the pre-existing device [4]. In blue are depicted the sensing and stimulating electronics: these are composed of pressure captors and accelerometers situated in shoes, an IPG implanted in the subclavicular space and a thin flexible ECoG placed in the central sulcus of the brain. The device is made to have no apparent wires. When using the device, a helmet is placed on the head of the patient, allowing induction charging of the ECoGs as in the motor BSI design, and transmitting recordings wirelessly to the computing unit situated on a belt, allowing Bluetooth communication with the motor IPG. Bluetooth communication is also used to send the information collected by the foot captors to the computing unit and the stimulation instructions to the motor IPG. The wires connecting the IPGs to the sensory ECoG and electrode paddle on the spinal cord are fully implanted, and could potentially be replaced by wireless equipment.

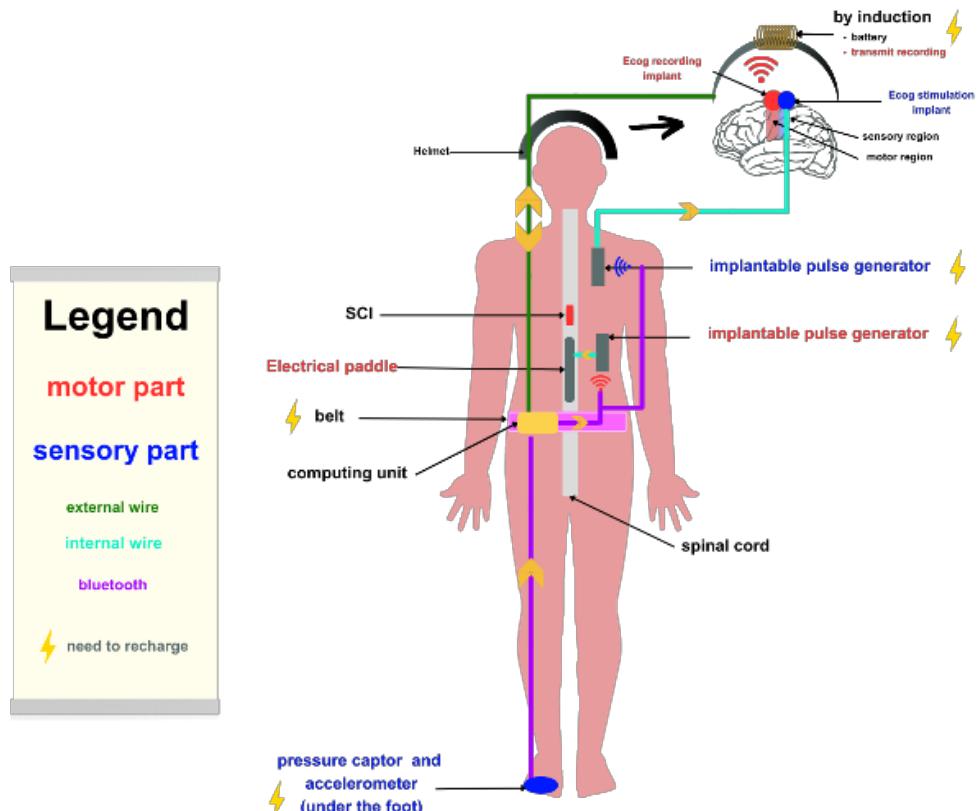
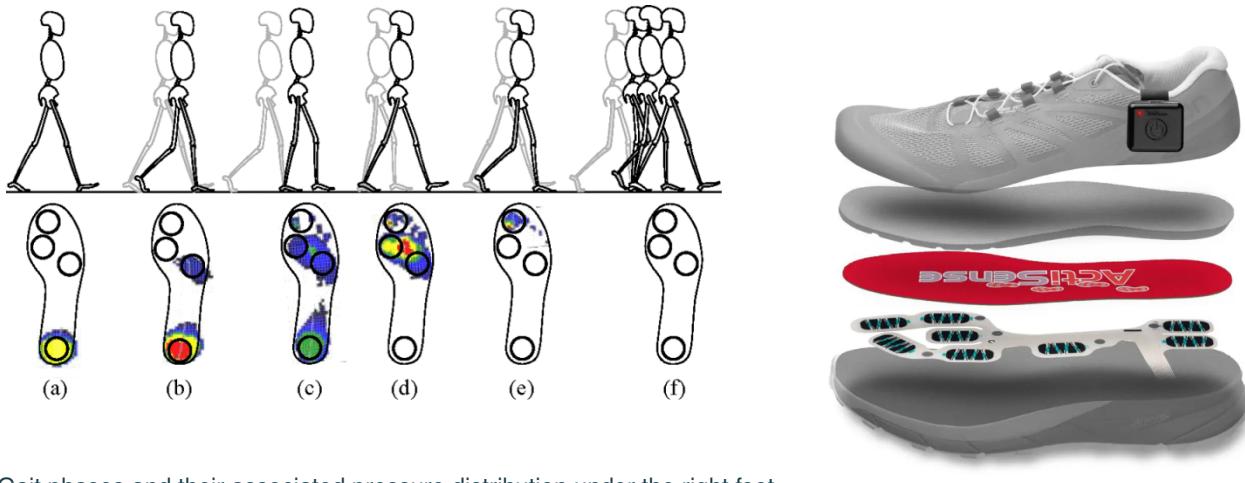


FIGURE 4.1 – Overview of the device

## 4.2 SENSORS AND COMPUTING UNIT

Sensors are used to extract the relevant information from leg movements and transmit them to the computing unit. The latter processes them and transmits a stimulation program to the ECoG used for stimulating S1.

The captors must meet several requirements to ensure optimal functionality and daily usability. Firstly, they should be unobtrusive and comfortable, allowing the patient to wear them for extended periods. Secondly, they should be easily usable by the paraplegic patient, enabling straightforward operations and adjustments. Additionally, computational capacity and efficiency are essential, as the electronics should allow real-time data processing without noticeable heat or weight disadvantages. Finally, affordability is a consideration to take into account for a widespread use of the product.



(A) Gait phases and their associated pressure distribution under the right foot

(a) Initial contact, (b) Loading Response, (c) Mid Stance, (d) Terminal stance, (e) Pre-swing, (f) Swing[18]

(B) Smart-shoe containing pressure sensors and an accelerometer[14]

**FIGURE 4.2 – Captors and gait phases**

The goal is to restore proprioception and the pressure under the foot since knowing the position of the legs without visual feedback is essential for natural and intuitive walking. To do so, the smart shoes developed by IEE Smart Sensing Solutions [14] were chosen, which compactly integrate 8 notch pressure sensors and an inertial measurement unit into a slim sole. The information recorded by the captors can be sent via Bluetooth to a processing device thanks to a small external antenna box, which could forward it to the computing unit. These captors allow the identification of gait phases: capturing data and timings of foot movement and pressure distribution, allows one to accurately determine the current gait phase of the individual (Figure 4.2a). This discrimination ability is an essential part of proprioception.

The computing unit should convert the foot movement and pressure information to a comprehensible stimulation pattern. Since studies are still required to determine the optimal patterns to send to the cortex, the most general translation algorithm would be a simple neural network. The inputs will be the accelerometer signal with speed and position derivatives, as well as the individual or averaged pressure signals, depending on the results of the studies presented in section 4.5.3. The outputs could be amplitudes and frequencies per electrode for a simple signal, coefficients for template biomimetic signals or a model such as TouchSim [19] for more advanced stimulation. Such a neural algorithm allows for easy training once ground truths are established during studies. An FPU-equipped microcontroller should be enough to run such a relatively small algorithm at an acceptable frequency.

The approach of the biomimetic encoding strategy described by Valle et Al. [20], adapted for brain stimulation and SCI patient could be tested too. The process would be to first identify which active site of the electrode elicits sensations, with stimulation amplitude proportional to skin stretching or foot pressure, and a range of signal frequencies. The results can then be used for the construction of a model that predicts which fibres are activated by a certain stimulation pattern. An additional complication here would be to back-trace this nerve activity to the brain since this communication is altered for the patient. The frequency and amplitude of the stimulation will be modulated and optimised in function of the input, according to this protocol. The data will be recorded by auto-feedback from the patient, to minimise the number of professionals that will be in charge of recording data.

## 4.3 ELECTRODE CHOICE AND IMPLEMENTATION

The choice of the electrode has been made in consideration of its feasibility, which was the main criterion. Aiming for a home use of the device, non-invasive stimulation was less considered for this study. Indeed, this kind of stimulation often required bulky equipment or visible devices that would not be ideal for installation the injured patient, or for leading a normal life with natural sensations.

Even with these observations, non-invasive vibrotactile stimulation was found to be technologically simple and less experimental, and thus studied in the first place. However, it seemed to be hard to handle for the patient, with numerous stimulators to place every day on the skin. Moreover, the sensations restored would be unnatural and require a lot of effort to learn. Even if they could potentially facilitate walking, a solution that would have a chance to give back natural feelings to the patients was preferred.

To be able to assess this feasibility, different alternatives were discussed with experts. One of them being a neurosurgeon, she was aware of the feasibility of the surgery. Considering the implantation method of Utah arrays, being pneumatically inserted, it is impossible to place it in the longitudinal fissure, where the sensory area for the legs is situated. Moreover, multiple arrays should have been inserted to cover the whole region, which would be unfeasible in terms of numbers, the diameter of cables and compatibility with IPGs on the number of channels. Additionally, in case of a problem, those devices are hard to remove, as parts of the brain would adhere to them. Finally, the current needed for those tiny electrodes (considering their impedance) would be bigger than the capacity of the IPG. This is why despite a better resolution that would be allowed by it, intracortical stimulation was not chosen.

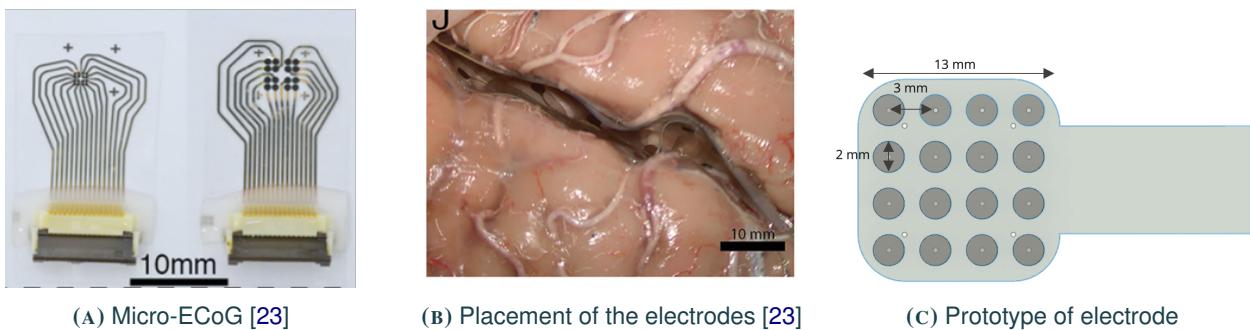
The spinal cord stimulation above the injury solution was also examined, as it seems to be a less invasive alternative, with a procedure well handled by Professor Bloch. However, it seemed dangerous for the patient, who already lost a large part of their mobility, as a healthy zone would be targeted. Moreover, it would be very difficult to stimulate selectively the sensory afferent fibres, and other fibres would be stimulated, which could have unwanted effects (like unexpected movements in the upper body).

Finally, extra-cortical subdural stimulation was studied. Indeed, those implants can be made very flexible and compliant with the brain, and the surgeon said to be able to implant them (and remove them if needed) safely. They can be tuned in size and can cover the whole region. Less current would be needed from the IPG compared to the Utah arrays, and thanks to the compliance of the array, stimulation of the zone should be possible. This, combined with the efficiency of restoring fingertips sensation [21], led to choose ECoGs to stimulate the sensory cortex.

There are still challenges: during the stimulation, electrodes corrode, therefore it will be important to choose well the thickness of the electrode, and to encapsulate the array. This encapsulation can be done with Atomic Layer Deposition, allowing resistance to humidity while keeping the softness of the array [22] and in vitro tests will be made to ensure safety.

To cover the region, an array of 13x13 mm will be chosen, with 2mm diameter round electrodes, spaced by 3 mm (4.3c). 16 channels will be used at first, to be able to use it with an IPG. All those parameters will be subject to modifications, depending on in-vivo tests. Here, they have been chosen following a study [21], in which researchers were able to restore touch sensation in the fingertips of primates with ECoGs. As the hand region for the sensory cortex is bigger than the leg's, but the monkey's brain is smaller than the human's, it seemed to be a good starting point, that will be further optimised. During the design of the electrodes, it will be important to simulate the electrodes and to compute the Volume of Tissue Activated, which will allow us to be sure of the selectivity of the device, and that it does not stimulate unwanted parts of the brain.

The electrode itself will be inspired by Falleger et Al. [23], who were able to make flexible electrodes, with tunable size and MRI compatibility. Their impedance is stable when folded, and they were able to place the electrode in a sulcus, so the implantation would be possible (4.3b). These electrodes will be fabricated with silicon technologies and microfabrication. They also were used to stimulate, and not only to record.



**FIGURE 4.3 – Images of the electrode**

The choice to use a brain implant comes with a risk: it is possible that other brain functions could be impaired, if the stimulation parameters are not properly tuned, or if the simulation is not selective enough. For example, the implant will be located close to the primary motor cortex. It could interfere with arms movements, and cause damages to the patient. This is why the selectivity will be a very important test, while developing the device. Even if this solution is less invasive than an intracortical one, there could also be damages to the brain. The softness of the implant should prevent that issue.

### 4.3.1 STIMULATION PATTERN

The patterns of stimulation will be firstly inspired by Chandrasekaran et Al. [24], who was able to give back fingertips sensations with ECoGs. The stimulation will be current-regulated, with symmetric biphasic square-wave pulses, 0.2 ms width per phase and 20 to 50 Hz stimulation. The amplitude will start at 0.5 mA (lowest possible), to increase if needed to 6 mA depending on the patient's sensations, while remaining in a safe and non painful range. Additional studies will be done to link the input signal to output stimulation. They will depend on a series of tests done to determine how proprioception is best encoded for the brain (described in section 4.5.3).

### 4.3.2 SURGICAL PROCEDURE

To know where to implant the ECoG, non-invasive stimulation, using for example Trans-cutaneous magnetic stimulation, will be carried out. It will allow us to verify that the patient is responsive to stimulation to the sensory cortex. fMRI can also be used to find the correct region. This procedure allows to map brain region active during a task. Here, the task would be to imaging sensation on the legs, or imaging moving the legs, if we assume the patient imagine the sensations when thinking about the movement. This mapping should be done before implantation of the IPG, considering the magnetic field of the MRI and the risk it would present for the patient. It will also be important to image the brain of the patient and simulate stimulation of the brain according to the placement of the ECoG. It will also allow us to verify that other functions won't be impaired. Then, a craniotomy will be operated and the ECoG will be placed. This operation could be done at the same time as the placement of motor-intention recording ECoGs.

## 4.4 IMPLANTABLE PULSE GENERATOR

The IPG is a key component of neurostimulation. These battery-powered microelectronic devices are surgically implanted in the body to deliver electrical stimulation to the nervous system. These devices have been used to block or stimulate nervous signals depending on the condition that it has been treated, and usually represent a convenient alternative, allowing patients to manage their condition without the need for constant medication, for example in deep brain stimulation [25].

For the current device, the IPG would deliver mild electrical currents to targeted areas of the brain through implanted electrodes connected to a device placed under the skin near the collarbone. The characteristics of the electrode chosen are directly linked with the specifications of the implantable pulse generator. In this iteration, the IPG chosen is the Boston Scientific Versice Genus R32. There are 2 main reasons for using an IPG: the battery is rechargeable and there are several ports. [26].



Features	Specifications
Contacts	32
Contacts/Port	8
Case Material	Titanium
Dimensions	55 mm x 46 mm x 11 mm
Battery	Rechargeable
Freq. Range (Hz)	2 - 255
Pulse Width ( $\mu$ s)	20 - 450
Weight	27 g

▪ BS Versice Genus R32

FIGURE 4.4 – IPG BS Versice Genus R32 features and specifications

The Versice Genus R32 has four ports with 8 contacts each, which fits the need for our two electrodes placed on the sensory cortex with 16 electrodes each. Additionally, the rechargeable battery increases significantly the life span of the IPG, which is a crucial aspect to consider when designing our device [27].

It is good to note that the IPG will have to be real-time controlled, depending on the input from the sensors. Such IPG is not commercialised yet but is feasible considering that it is already used [4].

## 4.5 STUDIES AND CLINICAL TRIALS

### 4.5.1 APPROVALS

To translate the concept to humans, tests and approvals are necessary. The tests will start with the development of the device and fine-tuning of the electrodes. The tests are composed of mechanical and electrical characterisation, charge injection tests, modelisation of the electrode's electric field, in vitro cytotoxicity, accelerated ageing tests and hermeticity tests. Multiple challenges should emerge from those tests, and after re-adaptation, the electrode will be able to be used for

stimulation pattern tests in-vivo, long-term in-vivo tests and tests in humans. To perform in-vivo studies in humans and to put the device on the market, approvals are necessary.

The clinical trials will be composed of, firstly, a clinical evaluation, in vivo and animals. Then, the clinical investigation will be performed, in humans. It will follow the GCP standard ISO 14 155. It will first be implanted in one patient, as a proof of concept. If the results are positive, three patients will be implanted for in-vivo clinical trials. Patients will be patients already implanted with the BSI [3], and who did not get sensory feedback restoration from the BSI alone. The performance of sensory feedback will be assessed by patient's feedback on their sensations, and on diverse metrics to measure gait improvements with sensory feedback: EMG will be measured, and an observational gait analysis form will be filled by a physiotherapist, assessing criteria from the questionnaires G.A.I.T., SCI-FAI and Tinetti Test [4].

To be able to do those trials, it will be necessary to have the protocols approved by an ethics committee, like CER-VD. Then, the competent authority in Switzerland, Swissmedic will be involved, and a notified body at the European Union level. The approvals required will be the Medical Device Regulation in the European Union (with the need to prove safety and performance). For the development of the device in the USA, the FDA (Food and Drug Administration) will have to approve the device. After the commercialisation of the device, an evaluation report will be made every year. The entire approval process is estimated to last at least five years.

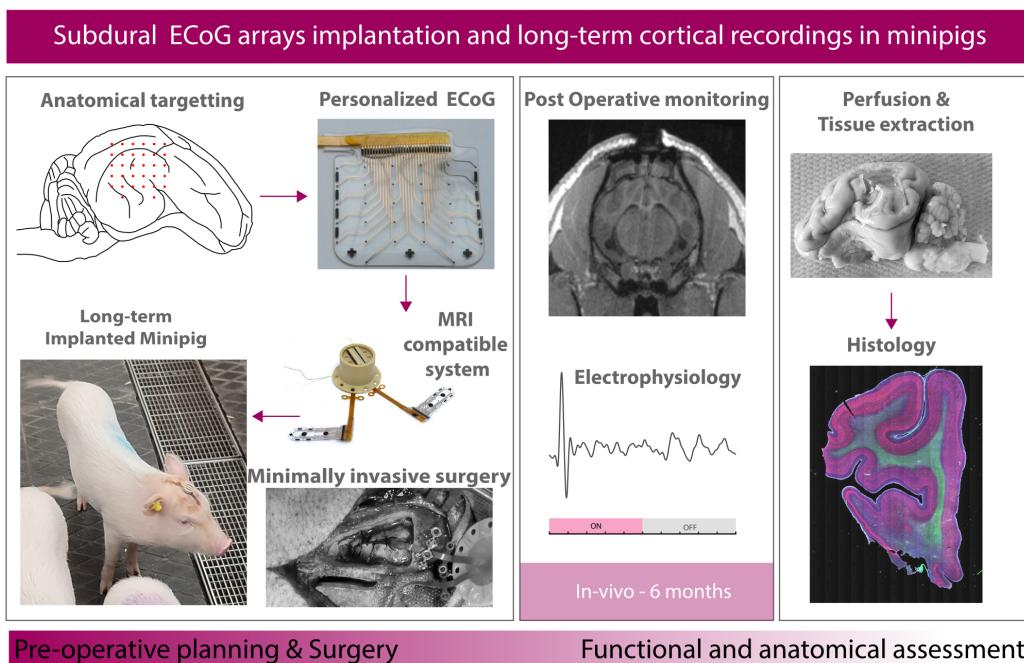
#### 4.5.2 BIO-COMPATIBILITY AND LONG-TERM SAFETY

Assessment of the long-term safety of our device, and in particular of the use of subdural electrodes can be divided into two parts. On one hand, it is important to ensure that the long-term implantation of a subdural electrode in the somatosensory cortex does not cause damage to the surrounding tissues. On the other hand, it is also needed to study the effect of the electrical stimulation that would be applied for years and show that it does not damage the brain either. Stimulation should also be efficient during its whole implantation, even though it is likely to be increasingly encapsulated by fibrotic tissue.

In theory, the flexible electrodes that will be used are already bio-compatible and safe to implant in human patients. [28] Furthermore, the use of flexible materials enables moderation of the brain's Foreign-body-response [29] and the problem of increasing impedance that could block stimulation of the targeted tissue. It has also been shown that stimulation does not cause damage to the brain, and the main risk of such technology is electrode implantation [30]. However, this technology lacks long-term studies to assess the safety and longevity of these electrodes.

In this context, a long-term study will be implemented, using a framework inspired by previous pre-clinical trials in mini-pigs [29] (also for subdural ECoG, see Fig. 4.5). Following this framework, a minimally invasive surgery will firstly be developed, to be able to safely implant the electrodes in a deep region of the somatosensory system. Then, in-vivo the electrophysiological properties of the electrodes will be monitored to ensure that stimulation is stable and efficient throughout the whole implantation. Finally, post-mortem histological analysis will be conducted to assess if the implantation and/or stimulation caused damage to the brain tissues.

If results conform to the expectations and show that electrodes are safe to implant, translate this study would be translated into monkey models, which are brain models even closer to human patients. Provided that conclusions from this last pre-clinical trial are the same as the ones in mini-pigs, we would then apply for approval of a clinical trial in human patients.



**FIGURE 4.5 – Framework for pre-clinical trials of implantation safety of soft subdural ECoG [29]**

### **4.5.3 PROPRIOCEPTION**

A key practical issue is the format of the information transmitted through the implant to the sensory cortex. The sensors allow extraction of the leg state, mixing the position and its derivatives or simply gathering the raw data, and the goal is to identify the optimal information for the patient, as well as optimal stimulation patterns.

Studies have shown that both bio-mimetic signals on humans [8] and simple, unnatural pulses on monkeys [31] can accurately elicit the expected reactions by the subjects; the main difference is the adapting object, which is the stimulation algorithm or the subject's brain respectively. For the former solution, more brain recordings from the patient imagining different leg movements would be used to carry out machine learning; for the latter, the patient will have to be subjected to extended training sessions, using for example a mix of electrode and visual signals to correlate between expectations and stimuli, as was done in the cited paper.

Both solutions rely on basic identification of the preferred directions of the cortex neurons, as was explained in section 2.3 so that the direction of the sensation can be encoded by certain stimulations of neuronal regions with different preferred directions. The spatial length of the perceived movement is naively encoded via pulse trains of linearly decreasing frequency for the simple variant, while the paper with a focus on bio-mimetism used more advanced frequency gradients, different current amplitudes and a separate stimulation study for antagonist muscles at different limb loads.

Both methods should be tested for accuracy, precision and repeatability between the stimulus' expectation and the patient's reaction. Additionally, although we can expect a good adaptation of the methods from monkeys to humans, the naturalness and comfort of the stimulation are not well known from current studies on monkeys and will be an important testing criterion for humans. In the scope of more widespread adoption of the product, training speed also is an interesting factor.

### **4.5.4 EXPECTED ISSUES AND TESTS TO OVERCOME THEM**

#### **CROSS-TALK**

One expected issue will be the cross-talk between the recording of motor intentions and the stimulation of the sensory cortex, because those two regions are very close, and the same range of frequencies will be emitted and recorded (20-50 Hz for stimulation, 1-300 Hz for recording [4]). Different solutions will be tested to prevent this issue: first, alternating recording and stimulation and an attempt to integrate stimulation parameters into the machine learning algorithm that is used to decode motor intentions will be tested. Then, it can be tested to filter the stimulation frequencies using a band-pass filter and verify that motor intention decoding is still possible. However, this method can degrade the signal. If they don't work, an auxiliary stimulating dipole will be implanted and will allow weak stimulation between the stimulator and recorder. Location and amplitude will be found with constrained optimization algorithm [32].

Diminution of cross-talk could also be inspired by other techniques developed for closed-loop deep brain stimulation. For example, Stanslaski et al.[33] separated the detected information and the stimulation through a support vector machine classification algorithm by processing the spectral fluctuations. Another example is Zbrzeski et al, [34] who introduced an integrated neural amplifier to reduce artefacts for the recording.

#### **DELAY**

To give back natural feedback, the delay between the sensory perception by the captors and the stimulation will have to be comparable to the biological one. The biological delay is approximately 100 ms. The technical one was approximated to be around 100-150 ms [4]. If this delay is too high, different tests will be made to optimize the machine learning algorithm to make the processing faster, or to find another communication technology. Tests will be made to determine if possible unrealistic sensations may be due to the delay.

#### **SELECTIVITY**

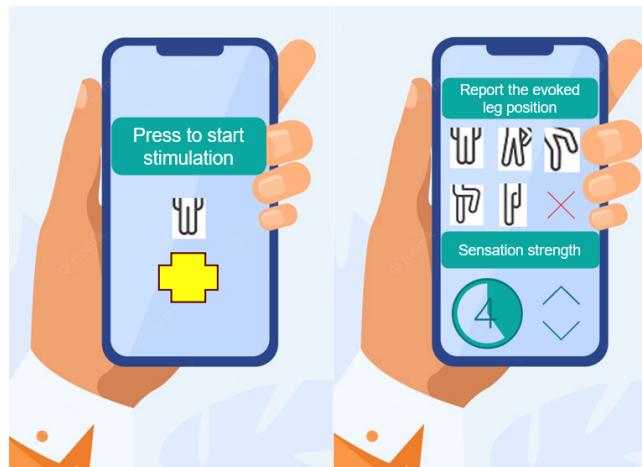
For now, research is insufficient to know if the electrodes allow stimulation that would be selective enough to restore proprioception. It will be rapidly visible during the tests. If selectivity is not good enough, the electrodes should be optimised, for example by reducing their size and augmenting their number. A new IPG will be then needed: its power should be sufficient to produce the current needed in smaller electrodes since impedance increases with smaller areas, and the number of contact should be bigger than what exists for commercial IPGs yet (limited to 32 for now). A multiplexer could be also used, to allow a bigger number of electrodes. Studies to verify selectivity could be done by 2-points discrimination sensation for example, or may already be visible during the simulation.

## **4.6 DAILY USE**

Once the patient has been implanted with the whole device (BSI and subdural ECoG for proprioception), we still need to determine how it could be used in daily life, as the goal of the product is for the patient to gain autonomy and be able to use the device on his own. Concerning the epidural stimulation and BSI, the training and daily life use would most likely resemble its current execution, that is training sessions in the lab supervised by health professionals for EES, in

parallel with the fast calibration of the BSI. Then, for proprioception restoration, a program that could be used at home by the patient was developed. The patient would be able to realise training sessions alone at home, with the aid of a phone app. An example of such an app is shown in Fig. 4.6. These training sessions are designed to enable optimisation of the implanted soft ECoG, that is to precisely map the somatosensory cortex of each patient and find regions responsible for the different proprioceptive sensations. Using a machine learning algorithm, areas would be stimulated. It could start by random stimulation, or stimulation of zones pre-discovered with non-invasive stimulation. Then, the stimulation will be further optimised to obtain a precise map of the somatosensory cortex regions responsible for lower limbs, adapted to each patient. This optimisation will be made following a machine learning algorithm with the labels being the patient's feedback. This automated configuration could for example use reinforcement learning, with a reward system.

Following these training sessions, the patients would be able to use the device for daily life similar to the current BSI implementation, with the additional proprioceptive feedback provided by the subdural ECoG. The main drawback might be the considerable amount of parts from the device that would need charging, although all batteries are capable of lasting a whole day and could be charged at night.



**FIGURE 4.6** – Example of a phone app used for the home training sessions and optimisation of electrode array

For daily life use, it is important to know what would happen in unexpected cases. If the patient falls for example, it should be detected (by the captors, for example, or an accelerometer on the belt), and the sensory stimulation should stop, in order to avoid confusion for the patient. A message could be sent directly to the hospital if the patient does not stand in a few minutes, in case of unconsciousness. Moreover, during prolonged standing or sitting, it will be important to optimise the stimulation, so that it does not feel unnatural. During sleep, and as long as the helmet is not in place on the skull, stimulation will be stopped: stimulation will be on only when the patient wants it and needs it. It will allow to preserve the battery, and to let the control to the patient.

# Conclusion and limitations

## 5.1 LIMITATIONS

### 5.1.1 SENSORS AND COMPUTING UNIT

The patient with an SCI would be using these sensors daily, which makes the compliance of the device compulsory. The sensors capturing the leg movements should be unobtrusive, comfortable, user-friendly, computationally efficient, and affordable. The smart shoes developed by IEE Smart Sensing Solutions, integrating pressure sensors and an accelerometer, fulfil these requirements. These sensors enable the identification of gait phases, which is crucial for restoring proprioception and natural walking.

Nevertheless, there is still some research to develop in the area. For starters, the sensors could cause skin irritation or pressure sores caused by prolonged device usage, so finding better biocompatible materials as well as different designs for the captors could improve the comfort of the patient. Improving the design would also overcome other issues that come with the scalability of the sensor, since there are different foot sizes as well as pressure distributions regarding the gait phases for different patients. Optimisation of the hotspots of pressure would ensure the reliability of the device for any patient with an SCI.

The computing unit would optimise the pressure spots of the sensor data and translate them into a stimulation pattern for the ECoG in the sensory cortex. A neural network algorithm is proposed, with inputs including the accelerometer signal, speed, position derivatives, and pressure signals. The computing unit should be equipped with a microcontroller capable of running the algorithm in real-time, which could be a complicated task to manage since there are multiple artefacts to handle in signal processing. Developing the neural network algorithm is part of the challenges.

### 5.1.2 ELECTRODE CHOICE AND IMPLEMENTATION

The choice of the ECoG electrode for sensory stimulation is based on feasibility and the potential to restore natural sensations. Intracortical stimulation was not chosen due to its limited implantation location, invasiveness, and stimulation selectivity challenges. Spinal cord stimulation above the injury was also considered but deemed risky and less selective. Extra-cortical subdural stimulation with ECoGs was chosen due to the flexibility and safe option that can cover the sensory cortex.

However, the electrodes that are planned to be used in the system are still in early research which leads to putting resources in the development of these electrodes. The life span of these devices needs to be increased to make it feasible for a daily system, issues such as corrosion during stimulation and encapsulation still need to be improved. The optimisation of the design of the electrodes would improve the sensory feedback since targeting the right spots on the sensory cortex would enhance the stimulation of the sensory cortex.

Additionally, the IPG specifications depend on the electrode characteristics. Not to mention, the wires that interconnect the IPG with the electrode still can be improved to minimise the invasiveness within the patient. The miniaturisation of the IPG would also allow room for improvement to change the interconnects into some kind of thin film interconnect, which tends to be less invasive. The IPG should still provide the required current and be compatible with the electrode's impedance and stimulation parameters.

### 5.1.3 STUDIES AND CLINICAL TRIALS

For the translation of the device concept to humans, various tests and approvals are necessary. These include mechanical and electrical characterisation, in vitro cytotoxicity tests, accelerated ageing tests, hermeticity tests, in vivo tests, long-term in vivo tests, and ultimately, clinical trials. The process is estimated to take at least five years, however, considering all the requirements and challenges to translate the technology, the system could face multiple delays before being a widely available solution for SCI.

A key practical issue is the format of the information transmitted through the implant to the sensory cortex. Our sensors allow extraction of the leg state, mixing the position and its derivatives or simply gathering the raw data, and the goal is to identify the optimal information for the patient, as well as optimal stimulation patterns. Even though studies in animals

---

have shown promising results, adapting the models from animals to humans can be challenging in terms of translating the accuracy and precision of the patient. Not to mention, there is still a concern in the cross-talk between the recording of motor intentions and stimulation of the sensory cortex, since both targeted regions are closed, and the operation relies on similar frequencies.

## 5.2 CONCLUSION

SCIs end up in sensorimotor paralysis of the patients, the number of patients suffering from SCI reported each year highlights the magnitude of this health issue. SCI blocks the communication between the brain and the sites below the injury, leading to an impairment of the sensor and motor function. Improving the lives of patients that suffer from SCI has become an important research field by restoring motor function.

The state-of-the-art for restoring motor function has been developed as a digital bridge between the brain and spine known as BSI. The BSI system consists of a brain implant (ECoG) that records activity from the sensorimotor cortex, a computing unit that processes and decodes the recorded signals, and epidural electrical stimulation (EES) that activates neural circuits below the injury site to restore motor function. Although the system itself allows the patient with SCI to walk naturally, to improve it we proposed adding sensory feedback to the system.

The proposed device aims to restore sensory feedback in individuals with SCI. The device consists of various components: the BSI components, pressure captors, accelerometers in shoes, an implantable pulse generator (IPG), and a thin flexible ECoG placed in the brain. The device in charge of the sensory feedback operates by capturing leg movements and pressure distribution data using sensors, processing the information in a computing unit, and transmitting stimulation instructions to the IPG connected to the ECoG.

In conclusion, the proposed device aims to restore sensory feedback for individuals with spinal cord injuries (SCI) using a combination of spinal cord stimulation and sensory cortex stimulation. Although there are still challenges to overcome, this system sets an improvement to the previous BSI by adding sensory feedback. In the next years hopefully, there would be the possibility to implement electrodes that record and stimulate to overcome some of the previously mentioned issues, also, the miniaturisation of most of the components could lead to facilitate the implementation in the patient for daily usage.

# Bibliography

- [1] Lisa A. Simpson et al. ‘The health and life priorities of individuals with spinal cord injury: a systematic review’. eng. In: *Journal of Neurotrauma* 29.8 (May 2012), pp. 1548–1555. ISSN: 1557-9042. DOI: [10.1089/neu.2011.2226](https://doi.org/10.1089/neu.2011.2226).
- [2] Soshi Samejima et al. ‘Brain-Computer-Spinal Interface Restores Upper Limb Function After Spinal Cord Injury’. eng. In: *IEEE transactions on neural systems and rehabilitation engineering: a publication of the IEEE Engineering in Medicine and Biology Society* 29 (2021), pp. 1233–1242. ISSN: 1558-0210. DOI: [10.1109/TNSRE.2021.3090269](https://doi.org/10.1109/TNSRE.2021.3090269).
- [3] Andreas Rowald et al. ‘Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis’. en. In: *Nature Medicine* 28.2 (Feb. 2022). Number: 2 Publisher: Nature Publishing Group, pp. 260–271. ISSN: 1546-170X. DOI: [10.1038/s41591-021-01663-5](https://doi.org/10.1038/s41591-021-01663-5). URL: <https://www.nature.com/articles/s41591-021-01663-5> (visited on 23rd June 2023).
- [4] Henri Lorach et al. ‘Walking naturally after spinal cord injury using a brain-spine interface’. en. In: *Nature* 618.7963 (June 2023). Number: 7963 Publisher: Nature Publishing Group, pp. 126–133. ISSN: 1476-4687. DOI: [10.1038/s41586-023-06094-5](https://doi.org/10.1038/s41586-023-06094-5). URL: <https://www.nature.com/articles/s41586-023-06094-5> (visited on 10th June 2023).
- [5] Francesco Maria Petrini et al. ‘Sensory feedback restoration in leg amputees improves walking speed, metabolic cost and phantom pain’. en. In: *Nature Medicine* 25.9 (Sept. 2019). Number: 9 Publisher: Nature Publishing Group, pp. 1356–1363. ISSN: 1546-170X. DOI: [10.1038/s41591-019-0567-3](https://doi.org/10.1038/s41591-019-0567-3). URL: <https://www.nature.com/articles/s41591-019-0567-3> (visited on 23rd June 2023).
- [6] Fabien B. Wagner et al. ‘Targeted neurotechnology restores walking in humans with spinal cord injury’. en. In: *Nature* 563.7729 (Nov. 2018). Number: 7729 Publisher: Nature Publishing Group, pp. 65–71. ISSN: 1476-4687. DOI: [10.1038/s41586-018-0649-2](https://doi.org/10.1038/s41586-018-0649-2). URL: <https://www.nature.com/articles/s41586-018-0649-2> (visited on 21st Mar. 2023).
- [7] Jennifer L. Collinger, Robert A. Gaunt and Andrew B. Schwartz. ‘Progress towards restoring upper limb movement and sensation through intracortical brain-computer interfaces’. en. In: *Current Opinion in Biomedical Engineering*. Neural Engineering/ Novel Biomedical Technologies: Neuromodulation 8 (Dec. 2018), pp. 84–92. ISSN: 2468-4511. DOI: [10.1016/j.cobme.2018.11.005](https://doi.org/10.1016/j.cobme.2018.11.005). URL: <https://www.sciencedirect.com/science/article/pii/S2468451118300369> (visited on 23rd June 2023).
- [8] Michelle Armenta Salas et al. ‘Proprioceptive and cutaneous sensations in humans elicited by intracortical microstimulation’. eng. In: *eLife* 7 (Apr. 2018), e32904. ISSN: 2050-084X. DOI: [10.7554/eLife.32904](https://doi.org/10.7554/eLife.32904).
- [9] *Traumatic Spinal Cord Injury Facts and Figures at a Glance*. Statistical Report THE 2021 ANNUAL STATISTICAL REPORT. National Spinal Cord Injury Statistical Center, 2023. URL: <https://www.nscisc.uab.edu/> (visited on 3rd July 2023).
- [10] Claudia Kathe et al. ‘The neurons that restore walking after paralysis’. en. In: *Nature* 611.7936 (Nov. 2022). Number: 7936 Publisher: Nature Publishing Group, pp. 540–547. ISSN: 1476-4687. DOI: [10.1038/s41586-022-05385-7](https://doi.org/10.1038/s41586-022-05385-7). URL: <https://www.nature.com/articles/s41586-022-05385-7> (visited on 3rd July 2023).
- [11] Daniel Janko et al. ‘Somatotopic Mapping of the Fingers in the Somatosensory Cortex Using Functional Magnetic Resonance Imaging: A Review of Literature’. In: *Frontiers in Neuroanatomy* 16 (June 2022), p. 866848. ISSN: 1662-5129. DOI: [10.3389/fnana.2022.866848](https://doi.org/10.3389/fnana.2022.866848). URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9277538/> (visited on 27th June 2023).
- [12] Tucker Tomlinson and Lee E. Miller. ‘Toward a Proprioceptive Neural Interface That Mimics Natural Cortical Activity’. In: *Advances in experimental medicine and biology* 957 (2016), pp. 367–388. ISSN: 0065-2598. DOI: [10.1007/978-3-319-47313-0\\_20](https://doi.org/10.1007/978-3-319-47313-0_20). URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5452683/> (visited on 27th June 2023).
- [13] *Wikiwand - Cortical homunculus*. URL: [https://wikiwand.com/en/Cortical\\_homunculus](https://wikiwand.com/en/Cortical_homunculus) (visited on 27th June 2023).
- [14] *Smart Footwear - IEE Smart Sensing Solutions*. URL: <https://iee-sensing.com/health-tech/medical/smart-footwear-sensing-solutions/> (visited on 24th June 2023).

- [15] *Long-Term Training with a Brain-Machine Interface-Based Gait Protocol Induces Partial Neurological Recovery in Paraplegic Patients* | *Scientific Reports*. URL: <https://www.nature.com/articles/srep30383> (visited on 25th June 2023).
- [16] Amol P. Yadav et al. ‘Generating artificial sensations with spinal cord stimulation in primates and rodents’. en. In: *Brain Stimulation* 14.4 (July 2021), pp. 825–836. ISSN: 1935-861X. DOI: [10.1016/j.brs.2021.04.024](https://doi.org/10.1016/j.brs.2021.04.024). URL: <https://www.sciencedirect.com/science/article/pii/S1935861X21000942> (visited on 3rd July 2023).
- [17] Patrick D. Ganzer et al. ‘Restoring the Sense of Touch Using a Sensorimotor Demultiplexing Neural Interface’. English. In: *Cell* 181.4 (May 2020). Publisher: Elsevier, 763–773.e12. ISSN: 0092-8674, 1097-4172. DOI: [10.1016/j.cell.2020.03.054](https://doi.org/10.1016/j.cell.2020.03.054). URL: [https://www.cell.com/cell/abstract/S0092-8674\(20\)30347-0](https://www.cell.com/cell/abstract/S0092-8674(20)30347-0) (visited on 25th June 2023).
- [18] Kyoungchul Kong and Masayoshi Tomizuka. ‘A Gait Monitoring System Based on Air Pressure Sensors Embedded in a Shoe’. In: *IEEE/ASME Transactions on Mechatronics* 14.3 (June 2009). Conference Name: IEEE/ASME Transactions on Mechatronics, pp. 358–370. ISSN: 1941-014X. DOI: [10.1109/TMECH.2008.2008803](https://doi.org/10.1109/TMECH.2008.2008803).
- [19] *Simulating tactile signals from the whole hand with millisecond precision* | *PNAS*. URL: <https://www.pnas.org/doi/10.1073/pnas.1704856114> (visited on 27th June 2023).
- [20] Giacomo Valle et al. ‘Biomimetic Intraneuronal Sensory Feedback Enhances Sensation Naturalness, Tactile Sensitivity, and Manual Dexterity in a Bidirectional Prosthesis’. eng. In: *Neuron* 100.1 (Oct. 2018), 37–45.e7. ISSN: 1097-4199. DOI: [10.1016/j.neuron.2018.08.033](https://doi.org/10.1016/j.neuron.2018.08.033).
- [21] Brian Lee et al. ‘Engineering Artificial Somatosensation Through Cortical Stimulation in Humans’. In: *Frontiers in Systems Neuroscience* 12 (2018). ISSN: 1662-5137. URL: <https://www.frontiersin.org/articles/10.3389/fnsys.2018.00024> (visited on 16th Mar. 2023).
- [22] Richard W. Johnson, Adam Hultqvist and Stacey F. Bent. ‘A brief review of atomic layer deposition: from fundamentals to applications’. en. In: *Materials Today* 17.5 (June 2014), pp. 236–246. ISSN: 1369-7021. DOI: [10.1016/j.mattod.2014.04.026](https://doi.org/10.1016/j.mattod.2014.04.026). URL: <https://www.sciencedirect.com/science/article/pii/S1369702114001436> (visited on 30th June 2023).
- [23] Florian Fallegger et al. ‘MRI-Compatible and Conformal Electrocorticography Grids for Translational Research’. In: *Advanced Science* 8.9 (Mar. 2021), p. 2003761. ISSN: 2198-3844. DOI: [10.1002/advs.202003761](https://doi.org/10.1002/advs.202003761). URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8097365/> (visited on 30th June 2023).
- [24] Santosh Chandrasekaran et al. ‘Evoking highly focal percepts in the fingertips through targeted stimulation of sulcal regions of the brain for sensory restoration’. en. In: *Brain Stimulation* 14.5 (Sept. 2021), pp. 1184–1196. ISSN: 1935-861X. DOI: [10.1016/j.brs.2021.07.009](https://doi.org/10.1016/j.brs.2021.07.009). URL: <https://www.sciencedirect.com/science/article/pii/S1935861X21001479> (visited on 16th Mar. 2023).
- [25] Can Sarica, Christian Iorio Morin and David H. Aguirre-Padilla. ‘Implantable Pulse Generators for Deep Brain Stimulation: Challenges, Complications, and Strategies for Practicality and Longevity’. In: *Frontiers in Human Neuroscience* 15 (Aug. 2021). DOI: [10.3389/fnhum.2021.708481](https://doi.org/10.3389/fnhum.2021.708481).
- [26] Joachim K. Krauss, Nir Lipsman and Tipu Aziz. ‘Technology of deep brain stimulation: current status and future directions’. In: *Nature Reviews* 17 (Feb. 2021). DOI: <https://doi.org/10.1038/s41582-020-00426-z>.
- [27] Boston Scientific. *Versice Deep Brain Stimulation Systems*. Vol. 92495783-02. 2020.
- [28] Stéphanie P. Lacour, Grégoire Courtine and Jochen Guck. ‘Materials and technologies for soft implantable neuroprostheses’. en. In: *Nature Reviews Materials* 1.10 (Sept. 2016). Number: 10 Publisher: Nature Publishing Group, pp. 1–14. ISSN: 2058-8437. DOI: [10.1038/natrevmats.2016.63](https://doi.org/10.1038/natrevmats.2016.63). URL: <https://www.nature.com/articles/natrevmats201663> (visited on 30th June 2023).
- [29] Florian Fallegger, Alix Trouillet and Stéphanie P. Lacour. ‘Subdural Soft Electrocorticography (ECoG) Array Implantation and Long-Term Cortical Recording in Minipigs’. eng. In: *Journal of Visualized Experiments: JoVE* 193 (Mar. 2023). ISSN: 1940-087X. DOI: [10.3791/64997](https://doi.org/10.3791/64997).
- [30] Alexander T. Rajan et al. ‘The effects of chronic intracortical microstimulation on neural tissue and fine motor behavior’. eng. In: *Journal of Neural Engineering* 12.6 (Dec. 2015), p. 066018. ISSN: 1741-2552. DOI: [10.1088/1741-2552/12/6/066018](https://doi.org/10.1088/1741-2552/12/6/066018).
- [31] Maria C. Dadarlat, Joseph E. O’Doherty and Philip N. Sabes. ‘A learning-based approach to artificial sensory feedback leads to optimal integration’. eng. In: *Nature Neuroscience* 18.1 (Jan. 2015), pp. 138–144. ISSN: 1546-1726. DOI: [10.1038/nn.3883](https://doi.org/10.1038/nn.3883).
- [32] Haoran Pu et al. ‘Optimal artifact suppression in simultaneous electrocorticography stimulation and recording for bi-directional brain-computer interface applications’. en. In: *Journal of Neural Engineering* 17.2 (Apr. 2020). Publisher: IOP Publishing, p. 026038. ISSN: 1741-2552. DOI: [10.1088/1741-2552/ab82ac](https://doi.org/10.1088/1741-2552/ab82ac). URL: <https://dx.doi.org/10.1088/1741-2552/ab82ac> (visited on 30th June 2023).
- [33] Scott Stanslaski et al. ‘Design and Validation of a Fully Implantable, Chronic, Closed-Loop Neuromodulation Device With Concurrent Sensing and Stimulation’. In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 20.4 (July 2012). Conference Name: IEEE Transactions on Neural Systems and Rehabilitation Engineering, pp. 410–421. ISSN: 1558-0210. DOI: [10.1109/TNSRE.2012.2183617](https://doi.org/10.1109/TNSRE.2012.2183617).
- [34] Adeline Zbrzeski et al. ‘Low-Gain, Low-Noise Integrated Neuronal Amplifier for Implantable Artifact-Reduction Recording System’. en. In: *Journal of Low Power Electronics and Applications* 3.3 (Sept. 2013). Number: 3 Publisher:

