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Organ Neuroprosthetics: Connecting Transplanted and Artificial Organs with the Nervous System

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Implantable neural interfaces with the central and peripheral nervous systems are currently used to restore sensory, motor, and cognitive functions in disabled people with very promising results. They have also been used to modulate autonomic activities to treat diseases such as diabetes or hypertension. Here, this study proposes to extend the use of these technologies to (re-)establish the connection between new (transplanted or artificial) organs and the nervous system in order to increase the long-term efficacy and the effective biointegration of these solutions. In this perspective paper, some clinically relevant applications of this approach are briefly described. Then, the choices that neural engineers must implement about the type, implantation location, and closed-loop control algorithms to successfully realize this approach are highlighted. It is believed that these new "organ neuroprostheses" are going to become more and more valuable and very effective solutions in the years to come.

1. Introduction

Neural engineering is a discipline aiming at developing and exploiting engineering knowledge, systems, and methods including micro and nanotechnology, electrical and mechanical technologies, and computer science to tackle important problems of neuroscience, neurology, and neurorehabilitation such as increasing our basic knowledge of how the nervous system works, and developing systems able to restore neural function in people affected by different types of disease and disability.

In the past years, neural engineers in different fields have reached several breakthroughs. Neuroprostheses have been developed and tested to restore functions in people with diverse neurological disorders.[1–3] Electrodes have been implanted into the peripheral and central nervous systems to restore grasping, locomotion, vision, speech, and touch with very encouraging clinical results. Preliminary experimental evidence has shown that neuromodulation can be also used to help people with cognitive disorders such as memory deficit or depression.

Similarly, several groups have started working on a new area of neural engineering called "electroceuticals" (or bioelectronic medicine, BM), which is a nonpharmacological approach which could treat diseases preventing dysfunctions using electronic devices to modulate the activity of the human autonomic nervous system.[4–6] This new approach holds great potentials, and several groups are now working on this field with important funding from US, EU, and Asian public agencies and private investments.[4]

The key innovation of electroceutical is instead to act indirectly on a dysfunctional tissue by modulating the activity of the neural circuits that innervate it. Therefore, it is particularly suited for systemic diseases even involving two or more internal organs. FDA-approved clinical studies have shown the potential of BM to

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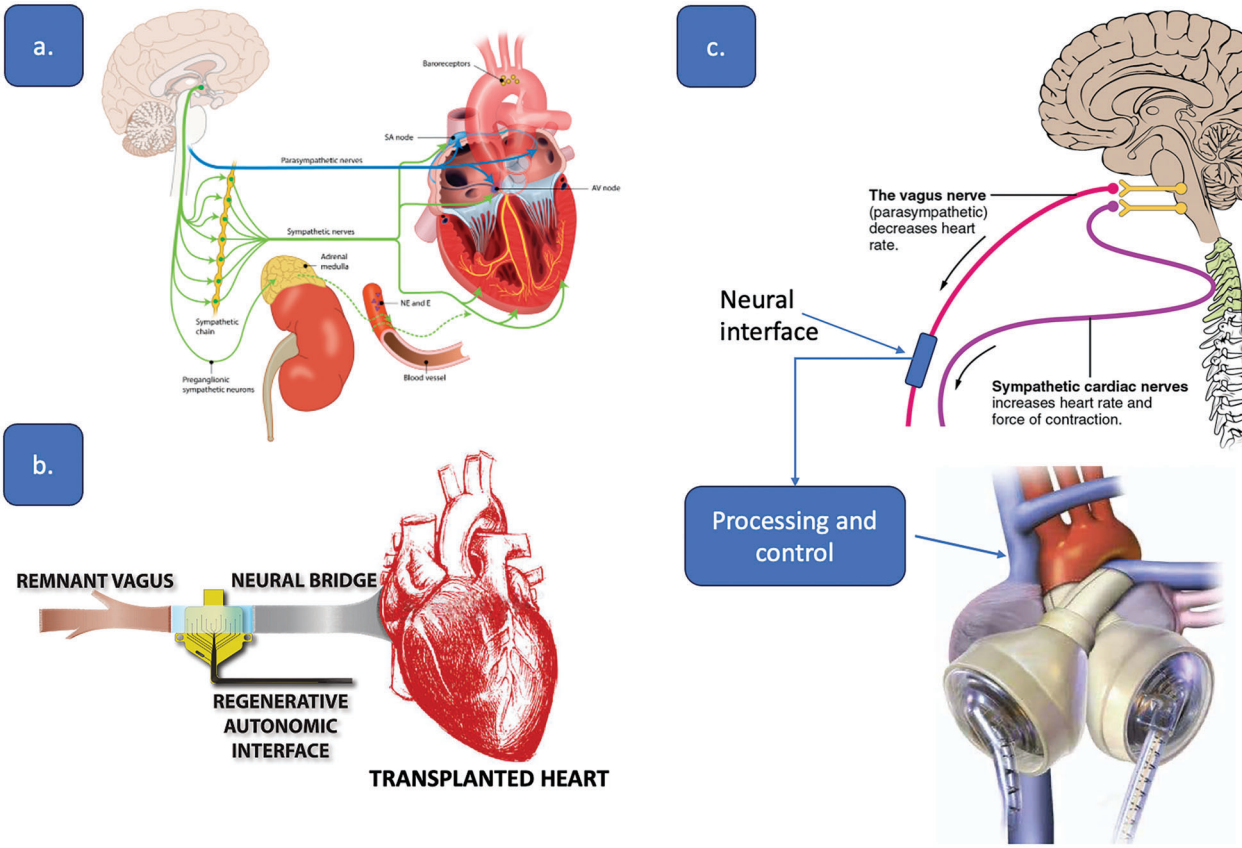

Figure 1. a) The normal innervation of the heart; b) neural reconnection using a regenerative interface for heart transplantation; and c) connection with an intact branch of the nerve in case of an artificial organ.

treat some drug-resistant chronic diseases such as inflammation-mediated autoimmune diseases.[7–8]

We propose to further extend this concept by designing neurotechnologies able to achieve the closed-loop control of "new" (for the patients) internal organs such as transplanted or implanted artificial organs. Indeed, natural internal organs strongly rely on complex neural mechanisms used to make them function in an effective way in different experimental conditions. This aspect is currently not considered, but this lack of neural connection dramatically reduces the efficacy and long-term usability of artificial and transplanted organs (as already clinically known, see next sections). This issue can compromise their performance especially over the long term.

Closed-loop regulation is indispensable for the intricate functioning of vital organs like the heart, lungs, and pancreas. It allows for continuous monitoring and adjustment to maintain homeostasis of physiological parameters such as heart rate (HR), blood pressure, blood gases levels, depth and rate of breathing, and glucose metabolism in response to internal and external stimuli. This dynamic control mechanism ensures that these organs operate within optimal ranges, facilitating efficient circulation, gas exchange, and metabolic regulation to sustain the body's overall health and functionality in response to changing conditions.

On the contrary, unfortunately, implanted bionic organs or organ components helping to restore compromised functionalities or missing organs (e.g., cardiac contractility, bladder function, and hormone release) are controlled artificially without any connection with the natural nervous system and therefore with limited performance and long-term usability.

The "organ neuroprosthetics" concept could be exploited in two conceptually different cases: 1) when a transplanted organ needs to be neurally connected to the receiver; 2) when an artificial device is implanted in a subject with the need to achieve an effective neurointegration of the device. In the next sections, we are going to provide more information about the challenges for neurotechnologies to achieve these goals and some examples of potentially interesting applications.

In **Figure 1**, an example of the overall concept is provided. The heart activity is controlled by the neuromodulation of different nerves (Figure 1a, see also next section). When a donor heart is implanted in a patient, it could be useful to restore the connection using an interface promoting the connection between the donor and the receiver remnant nerves (neural regeneration, Figure 1b, see also later). In case of an artificial heart, it is necessary to interface the desired nerve (which is in this case intact) to mimic the normal neural activity controlling the heart (Figure 1c, see also later).

2. Examples of Relevant Applications

As previously pointed out, in this specific case, the organs to be (re-)connected with the nervous system could be internal organs transplanted from donors or artificial organs based on

mechatronic solutions. In this section, we provide some examples of possible applications.

2.1. Heart Transplantation

Heart transplantation is an interesting example of the potential of "organ neuroprosthetics." Heart transplantation is often the final treatment option for a growing number of patients suffering from end-stage heart failure (HF).[9–10] While heart transplantation significantly extends the life span of HF patients, enhancing their long-term outcome, exercise capacity, and quality of life related to health remains a challenge.[11] This is largely due to an increased occurrence of late-stage complications. Such complications are primarily associated with an inability to adequately control heart rate due to cardiac denervation and a lack of effective parasympathetic reinnervation.[12,13]

Orthotopic heart transplantation (HTx) using bicaval technique stands as the predominant method for heart transplants. This procedure necessitates the full removal of the patient's original heart, resulting in unavoidable surgical denervation. Consequently, the interplay between the heart rate, load and contractile function in the transplanted heart is considerably changed after surgery. The loss of efferent and afferent sympathetic cardiac fibers leaves the endogenous electromechanical cardiac coupling under the slow control of circulating catecholamine until the establishment of complete myocardial reinnervation.[14] Conversely, the parasympathetic control of heart rate (HR)-dependent cardiac activity by the vagus nerve (VN), a mixed cranial parasympathetic nerve, is totally lost.[15] The right VN predominantly innervates the atria and the seno-atrial (SA) node. Conversely, the left VN predominantly innervates the atrio-ventricular (AV) node and the ventricular myocardium. The recruitment of vagal nerve (VN) fibers targeting the heart results in a reduction of heart rate by diminishing excitability within the sinoatrial (SA) and atrioventricular (AV) nodes. This also leads to a decreased strength of contraction in the atria and ventricles, a slower AV conduction rate, and a reduction of ventricular arrhythmia.[16]

The absence of vagal signals to the postganglionic neurons is characterized by an increased intrinsic HR and a diminished HR response to physiological and environmental changes, including physical activity or alterations in body position. Thus, resting HR in recipients ranges from 90 to 110 beats per minute (bpm). Although intrinsic cardiac impulse formation and conduction are intact, the donor-denervated heart is critically preload dependent and higher LV filling pressures are needed, particularly during exercise. As shown in animal and human studies,[17–19] the heart is an asymmetric organ under nonphysiological conditions, and it may be therapeutically relevant to consider the cardiac laterality of the VN. Indeed, restoring the regional vagal connection and developing a closed-loop organic neuroprosthetic system would improve the overall long-term success of HTx.

The use of a closed-loop system based on continuous simultaneous recording of ventricular stiffness and VN activity of the donor heart reconnected to the VN (at least to the right VN) will be helpful to trigger vagal stimulation in order to prevent the alteration of the delicate balance between sympathetic and parasympathetic influences which increase the risk of cardiovascular disorders. Indeed, increased ventricular stiffness, which refers to the resistance of the heart muscle to stretching during contraction, can have a significant impact on vagal feedback. Normally, the VN signals the heart to slow down and relax, contributing to efficient energy expenditure and cardiovascular stability. However, when ventricular stiffness increases, the heart must work harder to pump blood effectively. This increased workload triggers baroreceptor reflexes, sensory mechanisms that detect changes in blood pressure and transmit signals to the central nervous system. In response to baroreceptor activation, the central nervous system sends signals to the VN, instructing it to further dampen sympathetic activity and enhance parasympathetic tone. This coordinated response helps to protect the heart from the detrimental effects of excessive workload and potential damage. However, prolonged or severe ventricular stiffness can overwhelm the compensatory mechanisms of vagal feedback, leading to a maladaptive state characterized by sympathetic dominance and impaired vagal tone. The sympatho-vagal imbalance balance can contribute to various cardiac complications, including heart failure, arrhythmias, and endothelial dysfunction.[20]

2.2. Pancreas Transplantation

In the last decades, pancreas transplantation has become a great opportunity to restore glucose metabolism in patients with insulin-dependent type 1 diabetes, with the potential to cure the disease and prevent cardiovascular complications.[21] This procedure can be performed alone or in parallel or subsequently of a kidney transplantation. The transplanted pancreas is completely denervated. This is challenging because, in addition to fluctuations in blood glucose levels, signals from the autonomic nervous system play a vital role in the physiological release of pancreatic hormones and the maintenance of metabolic equilibrium.[22,23] Pancreas autonomic innervation is remarkably complex and comprises sympathetic efferent fibers and both afferent and efferent parasympathetic fibers,[23] see **Figure 2**.

In addition, nerve fibers originating from the walls of the gastrointestinal tract extend to the pancreas, establishing a network of innervation between the intestine and pancreas. Studies in vertebrates have demonstrated that parasympathetic axons directly influence islet function and beta-cell proliferation, leading to higher insulin release lowering plasma levels of glucose.[24] Efferent, largely cholinergic parasympathetic fibers originate from the dorsal motor nucleus of the vagus nerve directed to intrapancreatic ganglia, which are interconnected and dispersed throughout the pancreas eventually projecting to the islets.[23] Nerve fibers emanating from ganglia within the pancreas extend to the islets and additional ganglionic structures, creating an intricate network within the pancreas.[25] The efferent parasympathetic nerves, communicating through muscarinic receptors, are engaged both in the anticipatory cephalic phase of insulin release and after eating. The fact that vagal system controls the release of insulin and other hormones, such as pancreatic polypeptide (PP), before the increase in plasma glucose in response to sensory (i.e., gustatory, olfactory, and visual signals) feedbacks integrated in the hypothalamus, is fundamental in glucose tolerance. Vagotomy as well as atropine blockade of the muscarinic receptors markedly reduce glucose tolerance, in the presence of normal pancreatic tissue.

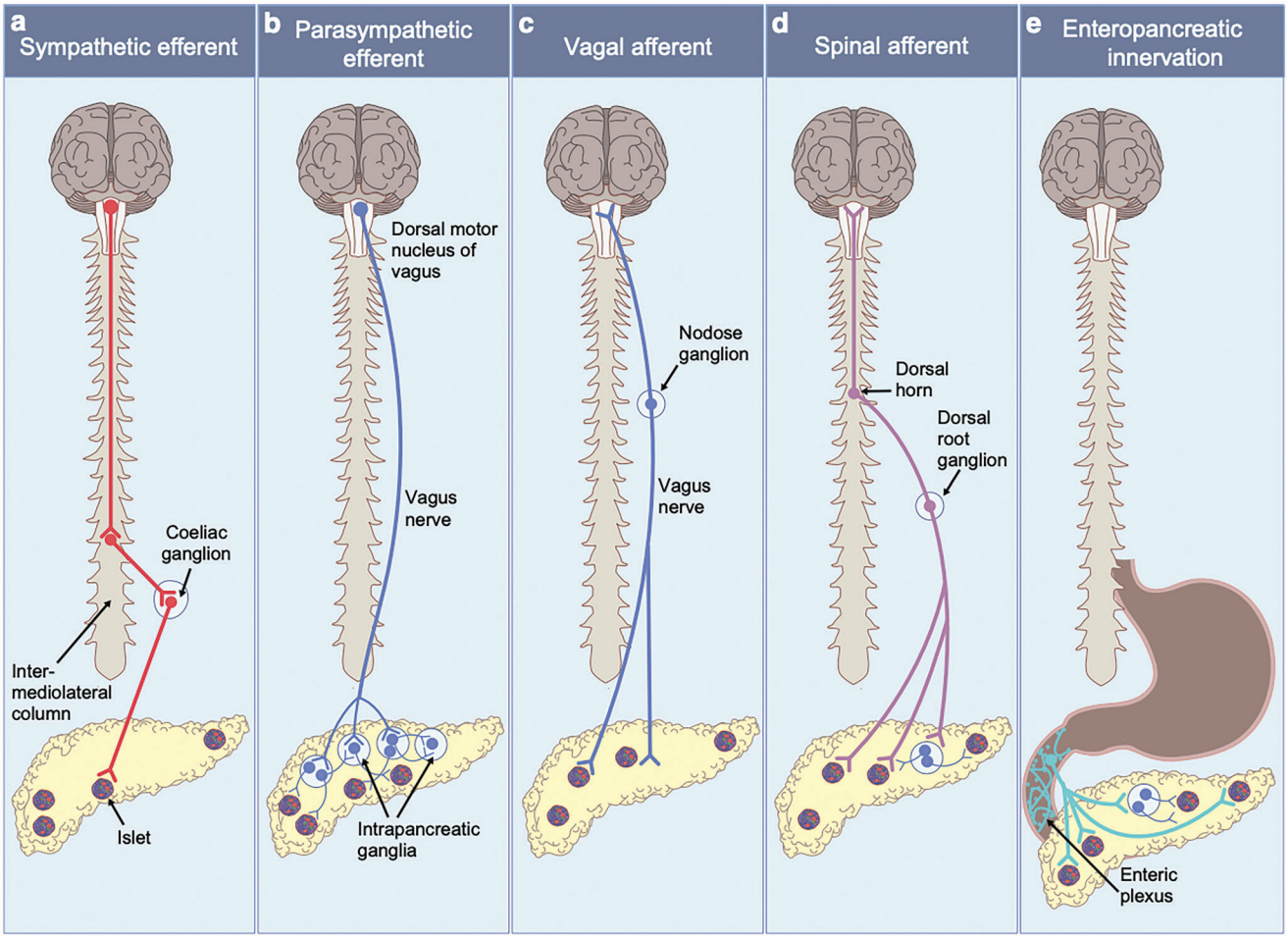

Figure 2. Schematic of the different types of pancreatic innervations.[23] Reproduced from CC-BY open access publications (Creative Commons Attribution 4.0 international license).

Thus, it is conceivable that restoring vagus nerve continuity outside the transplanted pancreas, proximally with respect to pancreas-projecting ramification directed to intrapancreatic ganglia (i.e., hepatic and anterior gastric branches of the vagus), could potentially preserve this autonomic function.[26] Beside insulin, the secretion of other pancreatic hormones such as glucagone could be improved, maintaining a controinsular activity useful in the control of energy metabolism.

2.3. Artificial Organs for Bladder Substitution

When neural reintegration has to be performed onto artificial organs, rather than on transplanted organs or natural organs which have lost neural control, the reinnervation solution detailed in the sections above has to be adapted. With the shortage of donors, significant efforts have been dedicated to replace natural organs with artificial counterparts. Relevant advances have been reached in the recent past to develop "bionic" artificial organs with remarkable improvements in powering, sensing, and actuation technologies, microfabrication techniques, and communication protocols.[27] In this case, artificial organs must incorporate artificial sensors to detect the organ status and to control the organ operation after a proper elaboration of the collected signals. The control can be either not-voluntary (as in the heart) or voluntary, as in the bladder. Among the different artificial organs, the case of the bladder is attracting a lot of interest, in consideration of the many bladder removals for oncological reasons. One of the first examples of artificial control of modified (yet natural) bladder was demonstrated by Mickle et al.[28] In contrast to devices that provide continuous electrical stimulation to nerves for disease treatment, which may lead to unintended side effects and discomfort, Mickle demonstrates a device that employs light to regulate the function of genetically altered nerve cells in the bladder. This approach is used in cases where the bladder is natural but afflicted with neural control disorders. Pushing further the bionic concept, neurostimulation can be necessary not only for genetically modified bladders, but for fully artificial devices. In case of native bladder resection, it could be interesting to address the limits of urinary restoration solutions, such as ureterocutaneostomy or adoption of an orthotopic neobladders, by developing totally artificial bladders (ABs).[29] Many ABs have been put forward and experimented with, but regrettably, they demonstrate less-than-ideal functionality over the medium to long haul.

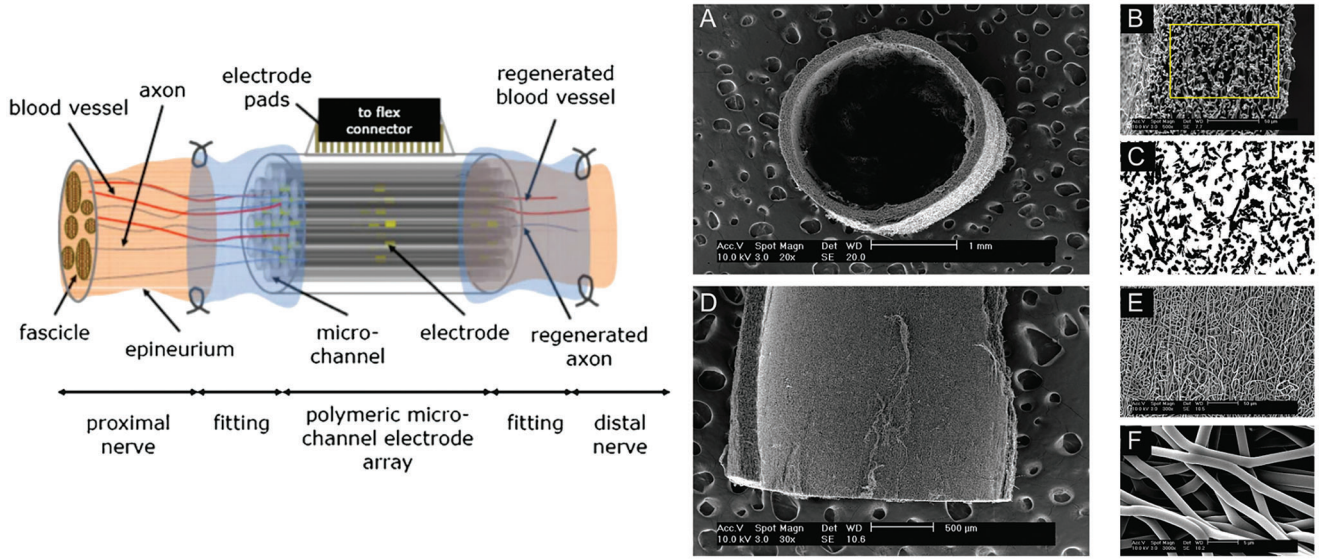

Figure 3. Schematic of regenerative interface usable to connect two parts of a peripheral nerve, and (right) a guidance channel based on poly(ethylene oxide terephthalate) and poly(butylene terephthalate) (PEOT/PBT) copolymer.[31] Adapted with permission.[31] Copyright 2017, Wiley.

This is attributed to their less robust design, limited durability against mineral buildup from urine, and issues with establishing reliable connections to the ureters. In addition to these issues mainly related to the artificial materials and the interaction with the native tissues, one of the main problems is the lack of bidirectional control by the nervous system which significantly reduces the overall usability of the ABs by the users. Also in this case, organ neuroprosthetics combined with artificial sensors integrated into the bionic bladder could significantly improve the overall situation by allowing the users to feel the filling of the bladder and voluntarily control its opening. A preliminary work in this direction is described in Section 3.3.

3. Challenges for Neurotechnologies

The underlying idea of "organ neuroprosthetics" is to restore the closed-loop regulation naturally implemented by the nervous system with the new (transplanted or artificial) organs. As previously mentioned, this concept is a natural extension of existing approaches currently pursued in neuroprosthetics. However, its implementation requires quite specific choices since each regulation system can be quite different as previously shown.

3.1. Effectiveness of the Neural Reconnection

First, it is important to point out that transplanted and artificial organs may require conceptually different peripheral neural interfaces (PNIs). In fact, in case of transplanted organs, it is necessary to use PNIs exploiting the property of the peripheral nervous system (PNS) to regenerate when cut[30] (**Figure 3**, left) since the stumps of the receiver's and donor's nerves but be reconnected. Different approaches have been pursued in the past years to improve PNS regeneration and interface quality (in terms of recording and stimulation). In particular, two main issues must be addressed: i) achieve an effective neural regeneration; and ii) develop selective yet not intrusive approaches to interface the regenerated nerves for stimulation and recording.

For the first goal, new materials can be used to increase the usability and efficacy of the guidance channel (i.e., a tubular structure connecting the two parts of the stumps)[31–33] or drug delivery systems can be exploited to facilitate regeneration[34]). For example, in Figure 3 (right) a new guidance channel exploiting poly(ethylene oxide terephthalate) and poly(butylene terephthalate) (PEOT/ PBT) is shown. This type of materials exhibits appropriate mechanical characteristics, significant porosity, and longitudinally aligned fibers, which are advantageous for their intended purpose.

In all these cases, regeneration seems possible but limited, and this could also limit the efficacy of the organ closed-loop control. Other approaches could mimic what has been recently achieved on the use of regenerative interfaces for the control of artificial limbs.[35,36] The successful regeneration of neural connections is paramount for achieving not only effective but also quasi-natural reconnection of neural pathways. This process is instrumental in restoring the intricate closed-loop control mechanisms crucial for the optimal performance of artificial organs. However, if regeneration is constrained or incomplete, it may significantly compromise the ability of these artificial organs to function seamlessly within the body, potentially leading to suboptimal outcomes and diminished overall efficacy in restoring physiological function. Thus, ensuring robust and comprehensive neural regeneration is imperative for realizing the full potential of artificial organ systems in clinical applications.

Another very important issue in this case is the selection of the proper electrical interface to be inserted in the guidance channel. Long-term experiments have shown that material flexibility is a crucial precondition to achieve an exploitable PNS regeneration.[37] For this reason, stretchable materials[38] or planar structures reducing the overall incumbrance[39] seem to be promising long-term solutions (**Figure 4**).

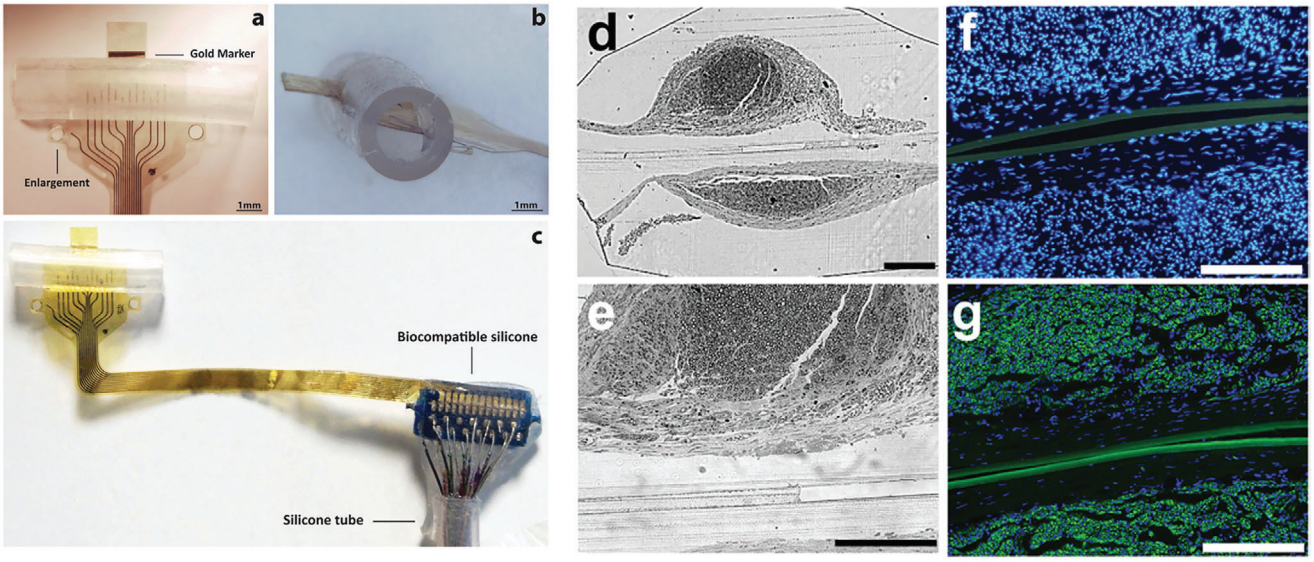

Figure 4. The regenerative interface developed in ref. [39]. The device comprises: a) a detailed view of the double-aisle planar electrode positioned within a silicone conduit, where the employment of a gold marker and magnification ensures accurate placement of the electrode within the conduit; b) a detailed view of the cross-section of the silicone conduit subsequent to the introduction of the polyimide electrode, with a central divider creating two symmetrical channels for nerve regrowth; c) an image capturing the entire assembled interface device. Indicators of successful nerve regeneration include: d) semi-thin cross-sectional views of the regenerating nerve situated midway through the conduit, illustrating two regrown nerve paths flanking the polyimide divider; e) a zoomed-in view showcasing the regenerated nerve enwrapped in a dense perineurial layer; f) cell nuclei stained blue with DAPI, highlighting the regenerated nerve's direct interaction with the polyimide surface; g) myelinated nerve fibers depicted in green, dispersed throughout the nerve cross-section. Adapted with permission.[39] Copyright 2015, IOP.

In case of artificial organs, it is possible to exploit the presence of the intact nerve and PNIs such as cuff or intraneural electrodes can be exploited.[30,40] For example, new cuff electrodes based on advanced printing techniques could allow to have easy-to-integrate and robust solutions[41] (see **Figure 5**). Similarly, intraneural interfaces can be used[42,43] when more selectivity is necessary with an increased implantation invasiveness (even if long-term usability seems possible[44] also in human subjects[45]).

3.2. Selection of Effective Implant Location

In any case, the important decision to take is *where* to implant the PNIs. The location can be chosen to achieve a specific selectivity (i.e., the ability to create a specific connection with the small part of the nerve interesting for the application) but taking into account also possible limits to surgical procedures which can become too complicated in some cases. For an effective design, it is necessary to gather information about the anatomical characteristics of the peripheral nerves along its branching[46] to compare the efficacy of different implantation sites. This type of information can also be used as inputs for advanced biophysical models[47,48] to test in silico different PNIs. Indeed, especially for artificial organs, different types of PNIs can be exploited according to the specific amount of selectivity necessary for the specific goal.[30] For example, epineural (cuff) PNIs could be enough in case of implant around small nerves, while intraneural PNIs could be necessary when large nerves must be interfaces. Indeed, intraneural interfaces provide more invasive solutions that are useful when more selectivity is necessary.

Finally, in the long-term, new "nonelectrical" interfaces (based on optogenetics/electronics, ultrasounds, magnetic stimulation) could be usable (at least in preclinical experiments) to increase the overall selectivity of the bidirectional link nervous system—new organ.[49,50]

3.3. Design of Effective Closed-Loop Control Approaches

Finally, a closed-loop control strategy must be implemented. This requires the extraction of some physiological information related to the specific process controlled by the organ and its use for the closed-loop neuromodulation (as recently done for brain neuroprostheses[51]). In this case, it is crucial to identify the amount of information which can be decoded and how a control approach can be consequentially implemented. In this respect, the recent results on "adaptive" deep brain stimulation[1] can provide useful hints about possible approaches. It could not be possible to fully replicate a natural approach and simplified solutions could also significantly improve the performance of the (transplanted or artificial) organ. The information can be decoded from the processing of neural signals related to some specific events[52,53] (see **Figure 6**) or from artificial sensors embedded in the new (transplanted or artificial) organ.[54]

An example of a possible neurointegration approach for an artificial bladder is provided in **Figure 7**. In this case, the PNIs are used to provide to the subject information about bladder fullness (sensory feedback) according to the status of the artificial organ and to understand when the subject wants to open the artificial bladder (decoding motor commands). It is clear that all the methodologies for decoding and encoding already used for

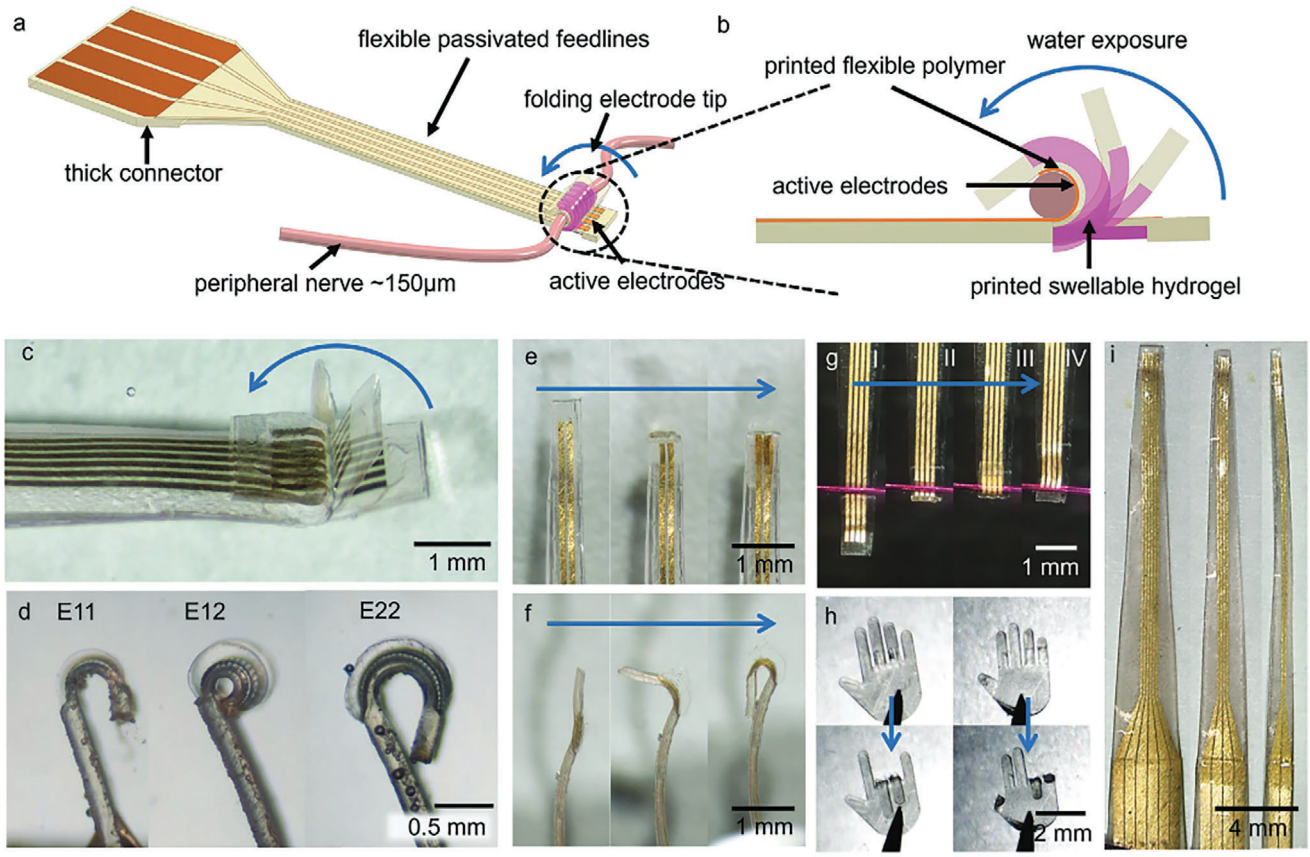

Figure 5. The 4D-printed stretchable self-folding cuff electrodes developed in ref. [41]. Adapted with permission.[41] Reproduced from CC-BY open access publications (Creative Commons Attribution 4.0 international license).

sensory-motor neuroprosthetics can be reused (modified). The information to close the loop can be gathered from artificial sensors or from the neural signals recorded by the PNI.

4. Discussion and Conclusions

The use of implantable neurotechnologies to control physiology and rebalance pathological conditions in vital organs is an exciting biomedical prospect that also opens a new era for developing a deeper understanding of precise molecular and neurophysiological pathophysiological changes. Harnessing the full potential of advanced, highly selective and potentially disruptive next-generation bioelectronic medicine interventions will be useful for the diagnosis, monitoring, and treatment of highly prevalent, high-burden noncommunicable diseases with unmet medical needs to develop a healthier society.

Advancements in surgical procedures and in medical device development are offering new solutions to help people with internal organs failures. However, these new (transplanted or artificial) organs are still not fully and long-term usable by the patients. This is due also to the limited neurointegration of these organs into the receiver's body. In normal conditions, the nervous system is exploiting a sophisticated closed-loop neurocontrol algorithm to achieve an effective use of these organs. We believe that this neuroregulation is also crucial for the control of the new organs which otherwise show long-term problems.

Even if we focused on few specific examples, the paradigm of "organ neuroprosthetics" can also be applied in other cases. For example, precise autonomic nerve innervation, including sympathetic and parasympathetic branches, intricately regulates lung function. Sympathetic fibers dilate airways and increase respiratory rate during fight-or-flight responses, while parasympathetic fibers constrict airways and slow breathing under restful conditions, ensuring the delicate balance needed for efficient gas exchange and pulmonary homeostasis. Similarly, nerve innervation plays a crucial role in regulating liver function by influencing various processes such as metabolism, blood flow, and bile secretion. Sympathetic and parasympathetic nerve fibers modulate hepatic blood flow, impacting nutrient delivery and waste removal. In addition, autonomic nerves regulate hepatic glucose production and storage, lipid metabolism, and detoxification processes, ensuring proper metabolic balance and overall liver function. Dysfunction in nerve innervation can lead to disruptions in these vital processes, contributing to liver diseases and metabolic disorders.

Achieving closed-loop control can also involve directly providing sensory feedback to users ("user in the loop"), as demonstrated in brain–machine interfaces[51] and artificial limbs.[55–57] This alternative approach warrants further exploration. However, in numerous instances of organ control, this might not suffice due to the subjects' limited capacity to effectively and effortlessly control specific functions, such as those of the heart or liver.

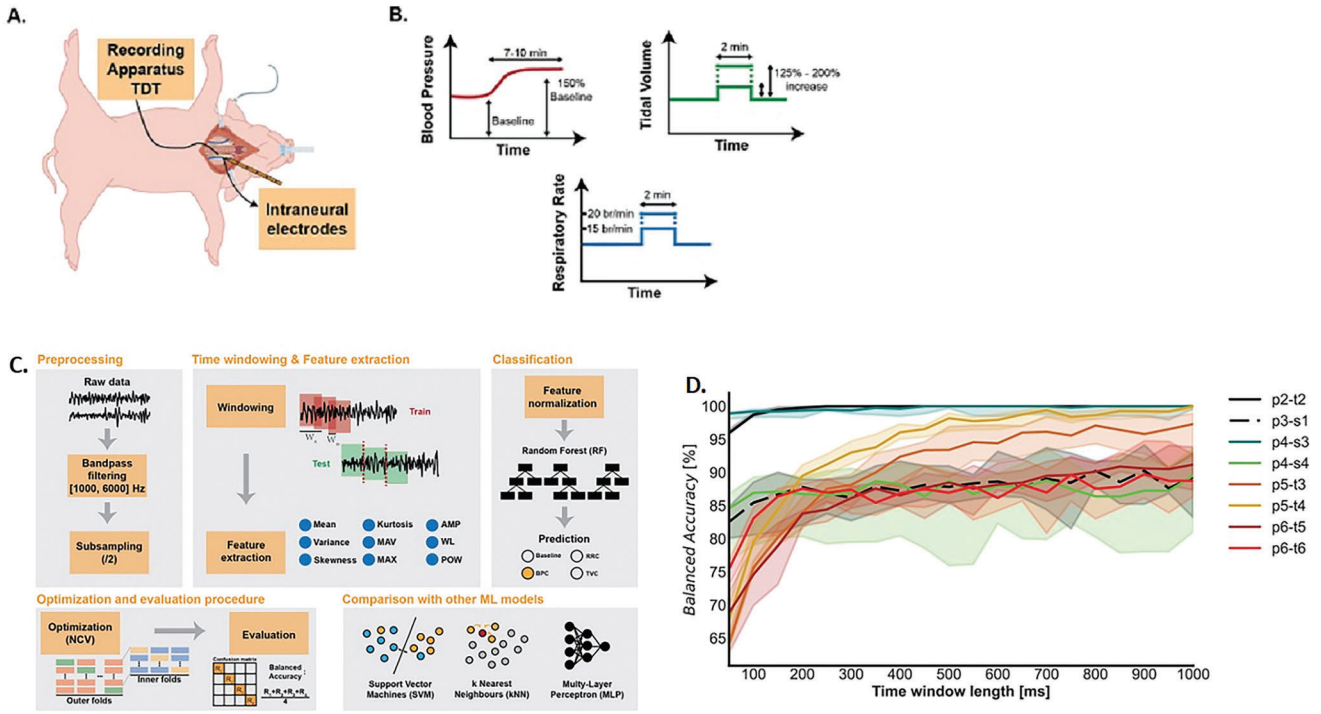

Figure 6. a,b) The experiments described in ref. [52], c) the processing algorithms based on machine learning, and d) the performance achieved. Reproduced from CC-BY open access publications.

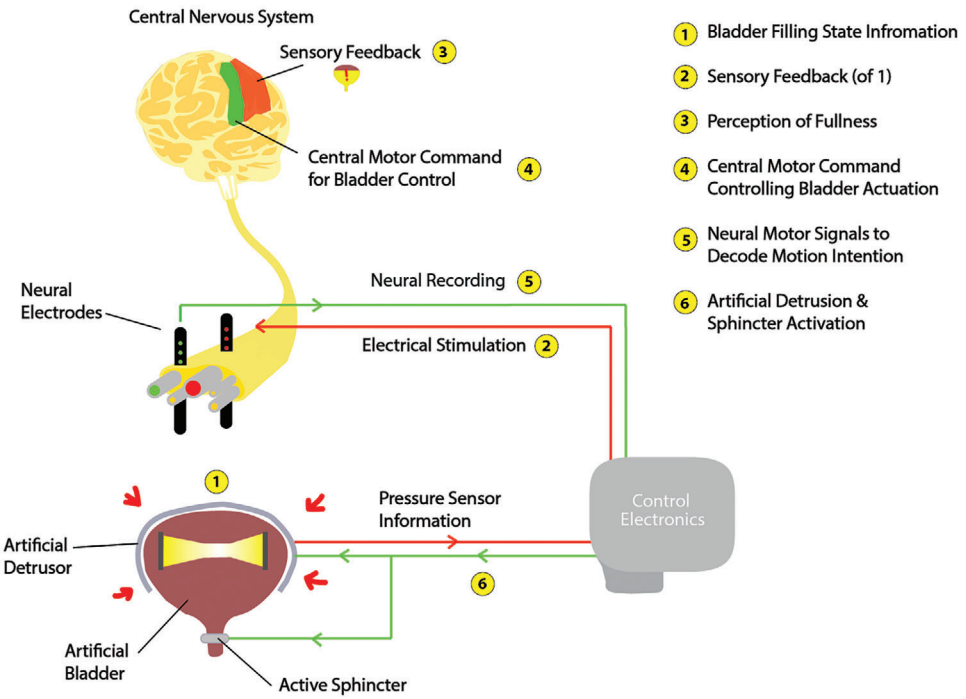

Figure 7. A possible closed-loop approach for the neurointegration of an artificial bladder.

Current neurotechnologies can be used to obtain this closed-loop neurointegration with a proper choice of existing[3] (e.g., specific PNIs or decoding algorithms) and novel (e.g., more specific surgical procedures[36]) solutions. Organ neuroprostheses could have a profound clinical impact in the years to come. In the paper, we have explored potential clinical applications stemming from this approach, providing guidance for the selection of specific neurotechnologies for implantation. By delineating these applications and offering insights into the selection process, we aim to equip clinicians and bioengineers with valuable information to effectively navigate the implementation of neurotechnologies in diverse medical contexts towards the restoration of neural connection with transplanted or artificial organs.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

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