# Neural interface technologies: medical applications inside the body

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## 1. Introduction and principles

Implantable devices make up a significant portion of the global market for medical devices that is worth over £200+ billion per year. The focus of this chapter is on the current application of these devices in the clinical arena, in the related but distinct fields of brain computer interfaces (BCIs) and therapeutic electrical stimulation. There are some concepts that should be applied when considering any implantable device, which we review below using a current and forward-looking perspective:

### A. Device-related principles

*The purpose of the implant*

The implant, or BCI, can be used in a 'passive' mode to record brain measures for the purposes of 'decoding', a process which attributes meaning to specific parts of the brain signal. This is typically done with neurophysiological signals at the level of the single neuron, detecting spiking activity[1], or with populations of neurons, using local field potentials (LFP)[2], or electrocorticography (ECoG)[3]. The interpreted signals may be used for communication, to control movement prosthetics such as an online speller, or for the treatment of pathological brain activity. Other types of emergent passive recordings include those taken during deep brain stimulation (DBS) surgery. Carbon tip microelectrodes can be used to acquire measures of sub-second, real-time changes in neurotransmitters such as dopamine, using fast-scan cyclic voltommetry[4]. These types of BCI approaches come under the designation of 'open-loop' BCIs because the output is made available to a third party, such as an experimental observer or a treating clinician, rather than the patient participant.

Alternatively, BCIs can be used in an 'active' mode, whereby the recorded brain activity is feedback to the patient to elicit volitional self-control of brain activations, with the purpose of improving the signal, or of increasing or decreasing the signal for a specific purpose such as a reduction of pathological activity, or an increase in a behaviourally or therapeutically relevant signal. This is called 'neurofeedback', and is a defining feature of 'closed-loop' BCIs[5,6].

The most common active mode for a BCI is to deliver an electrical or optical stimulation to a group or a target population of neural cells. Electrical stimulation fits with the majority of therapeutic neuromodulation performed in the UK under the National Health Service (NHS), and comes under the term 'electroceuticals'[7]. Optical stimulation is an emergent technique currently awaiting first-in-human trials, incorporating the field of optogenetics, and the use of targeted biological interventions, termed biologics or 'bioceuticals'[8].

*The implant*

The implant typically takes the form of a collection of electrodes, known as an array, or a single electrode[9]. The former may be microelectrodes of sub millimetre length, while the latter

are usually macroelectrodes measuring 1-1.5mm. The electrode may stimulate along its length, as in the case of the Michigan probe[10], at specific points, such as with Medtronic electrodes for DBS, or only at its tip – as with the Utah electrode array[11]. Electrodes can be pencil-like probes such as the Utah microelectrode array or DBS electrodes, or they may also be cortical implants, which take the form of a flat paddle, as in the case of the Medtronic Nexus D lead, and NeuroPace devices[12]. A variety of other implants are in design or prototyping phases, but, unlike the ones listed above, have not been used in humans. These are taking a variety of forms including injectable nanoparticles[13] such as 'neural dust' and mesh-like constructs[14] such as neural lace.

In terms of its functionality, an implant can be used for recording and/or stimulating brain tissue. The stimulation may be produced in a 'sphere' around the electrode tip, which can then be 'steered' in a particular direction[15] providing increased precision for targeting local anatomical targets. The implant can be used to record or stimulate neural tissue through electrical, optical, and/or chemical means. A prototype carbon-tip 'optrode' has been reported which can perform all of these functions on a millisecond timescale[4].

*Where is the interface?*

The target for BCI interfacing can be muscle, the neuromuscular interface between neural tissue and muscle, or neural tissue itself – with targeting over (extradural), on (extrapial) or in (intraparenchymal) the neural tissue. Neural structures may be targeted in the central nervous system (CNS) or the peripheral nervous system (PNS). The CNS includes the brain, its 12 cranial nerves, including for example the optic nerve and auditory nerve, and the spinal cord. Within the CNS tissue, white matter or grey matter may be targeted.

Further anatomical precision for BCI implants is likely to be possible soon, including cellular populations that have neurotransmitter specificity, or distributed brain areas that subserve a particular function, for example motor or language networks[16].

*What is the implant schematic?*

A standard device template has become prevalent, in part shaped by the success of industry leaders, Medtronic. A stimulating and/or recording electrode (or electrodes) is linked via connector cables to an implantable pulse generator (IPG). A further option may exist for the electrodes to be externalised, using extension cables connected to a recording device, or an external trigger for stimulation. All implantable devices will therefore have: 1/ **an input** (typically the electrode tip) 2/ **a sensor** 3/ **a detection algorithm**, and 4/ **an actuator**. With regards to the described template, the electrode serves as the input point, with the IPG acting as the power source, which may be battery operated or rechargeable. It will additionally contain the sensor and a detection algorithm, that act in concert to identify pathological activity, as well as the actuator.

Several variations on this theme exist, with the direction of travel being towards an all-in-one rechargeable device that can be implanted at the site of stimulation, providing a superior cosmetic result. An existing prototype of this is the sphenopalatine ganglion stimulation device (developed by Autonomic Technologies) for cluster headache[17]. This is an all-in-device which is inserted into the pterygopalatine fossa, providing an 'invisible' housing in the skull.

A further consideration is whether the implant is fully magnetic resonance imaging (MRI)-safe or MRI- conditional. The former indicates that it is fully safe for use within an MR environment, whereas the latter indicates that the device poses no known hazards provided specific conditions of the device and scanner are met. This is operationally important, particularly given the benefits of using structural imaging to assess the location of the implant, and functional imaging to measure brain changes in relation to BCI use.

*Surgical access*

Surgical implantation is an important consideration in the drive towards increasing the versatility of current and emerging BCIs. CNS implants that require deep brain access are more complex to plan, involving increased surgical time and associated hospital stay, as well as potentially being more challenging to replace. Targeting multiple or distributed neural tissue loci requires non-trivial technical considerations such as accessing the skull via a craniotomy flap versus multiple smaller burr-hole or twist-drill entries. The former results in a larger brain tissue exposure which can increases the risk of infection. The latter is less invasive, but effectively requires multiple blind cortical entries. Accuracy of placement of the implants, particularly if several deep brain locations are required, will benefit from well-validated machine learning programs for automated anatomical planning, together with surgical robots to automate placement guidance[18].

*Surgical risks*

These relate to the invasiveness of the operation and neural structures that are either being targeted or are in the surgical path. They include common, non-serious events, such as wound breakdown, localised infection and localised haematoma; less common, medium-severity events: such as cerebrospinal fluid leak for cranial and spinal procedures; and uncommon, serious events: such as neural tissue injury leading to neural dysfunction and functional loss, systemic infection, intra-parenchymal infections/abscesses, vascular injury leading to functional loss (e.g. stroke for cranial procedures), intraparenchymal haematomas, seizures and death.

*Device and stimulation risks*

'Off-target' effects should be considered together with accuracy of placement of the implant. One example would be vagal nerve stimulation (VNS), a treatment for epilepsy and depression, which has more recently been tested for conditions such as migraine[19]. Risks from this form of stimulation include throat pain, cough and shortness of breath. Another is functional electrical stimulation (FES) for muscle stimulation in spinal cord injury (SCI) which can lead to disorderly recruitment of motor units. The cardinal case study for cranial stimulation is DBS for Parkinson's disease, which can lead to off-target effects such as speech disturbance from stimulation of the internal capsule. As well as these possible effects, device-related risks include lead migration, lead fracture and device failure necessitating replacement and repeat surgery.

## B. Approach related principles

Below existing and emerging principles governing BCI approaches as whole are discussed, with specific reference to implantable BCIs:

*Next generation stimulation systems – the holy grail of a 'wireless, rechargeable, adaptive, closed-loop device, capable of multi-site stimulation)*

Virtually all current therapeutic implantable BCI devices can be considered 'electroceuticals', in that an electric current is used as the medium for modulating or recording neural activity. However the link between electrical stimulation, tissue response and behaviour is not linear nor always predictable. As such there is an increasing move towards developing devices that are capable of adaptive or 'responsive' stimulation. The NeuroPace system[20] for refractory (or drug-resistant) epilepsy serves as the prototype for the next generation of stimulation systems. It is fully implanted as a 'head-only' procedure, with components that store several hundreds of hours of data and can be accessed wirelessly. Stimulation is activated at cortical and subcortical locations in response to abnormal ECoG activity identified by a built-in sensor. DBS for Parkinson's disease and tremor is also moving towards this type of device solution, with a number of research patients confirming the therapeutic benefit of responsive or adaptive stimulation[21,22] as compared to tonic 'always-on' DBS. As well as being intuitive from a biological and therapeutic perspective mimicking the endogenous neural ebb and flow, there are also hardware benefits, such as decreased battery usage. The latter results in real-world benefits to the patients such as fewer surgical procedures for battery replacements, and less time spent using inductive recharging with the device in-situ.

The term 'closed-loop' in this regard relates to actively sensing and responding to device-identified brain measure changes, along with therapeutic stimulation. In order to robustly progress these systems into fully responsive 'closed loop BCI', behavioural and clinical features will need to be integrated with physiological markers in a patient-specific fashion.

*Network and connectivity neuromodulation*

Brain regions may function together within brain networks, with multiple brain areas communicating and acting in a coordinated manner. As a result of this, the initial paradigm of single target stimulation and/or interfacing is evolving into global brain network modulation[23]. This has been informed by observation of network level changes in response to DBS[24]. Additionally, neuroimaging studies have shown the distributed and connected nature of specific brain functions, including motor behaviour, language and cognition[25–27].

Optogenetics has provided a principled biological toolkit for dissecting out neural circuits[28–30],stimulating connectivity[31], and informing the first steps towards circuit-driven neuromodulation. At a minimum, network brain measures will need to a become a standard measure of assessing therapeutic neuromodulation, ahead of *a priori* stimulation of multiple network nodes, and white matter connectivity between nodes. Building on this, a future therapeutic aim of neuromodulation will be to shift whole brain networks to a previously defined canonical 'healthy template' established using large normative datasets.

*Non-invasive alternatives*

An overarching principle with implantable BCIs for therapy should be the determination that it is the best option, in the absence of any other treatments, including non-invasive BCIs. A combination of the two approaches may facilitate the best of both worlds. In this scenario, intended target neural tissue and functions could first be 'primed' using a non-invasive approach prior to a definitive surgical implant (See Fig)[32]. The principal benefit of this is that it provides a fully portable solution.

*Triggering plasticity*

Use of neuro-prosthetics as well electroceutical-based stimulation treatments such as DBS, have been shown to produce structural and functional changes in the brain, underpinned by changes in gene expression. These changes have been observed at the sites of stimulation as well as in functionally connected grey and white matter regions. To date these changes have been established retroactively[33–36]. There is therefore a forward-looking opportunity to select specific approaches with the aim of re-establishing functionally relevant connectivity or compensatory plasticity in the damaged central or peripheral nervous system in advance of surgery and stimulation.

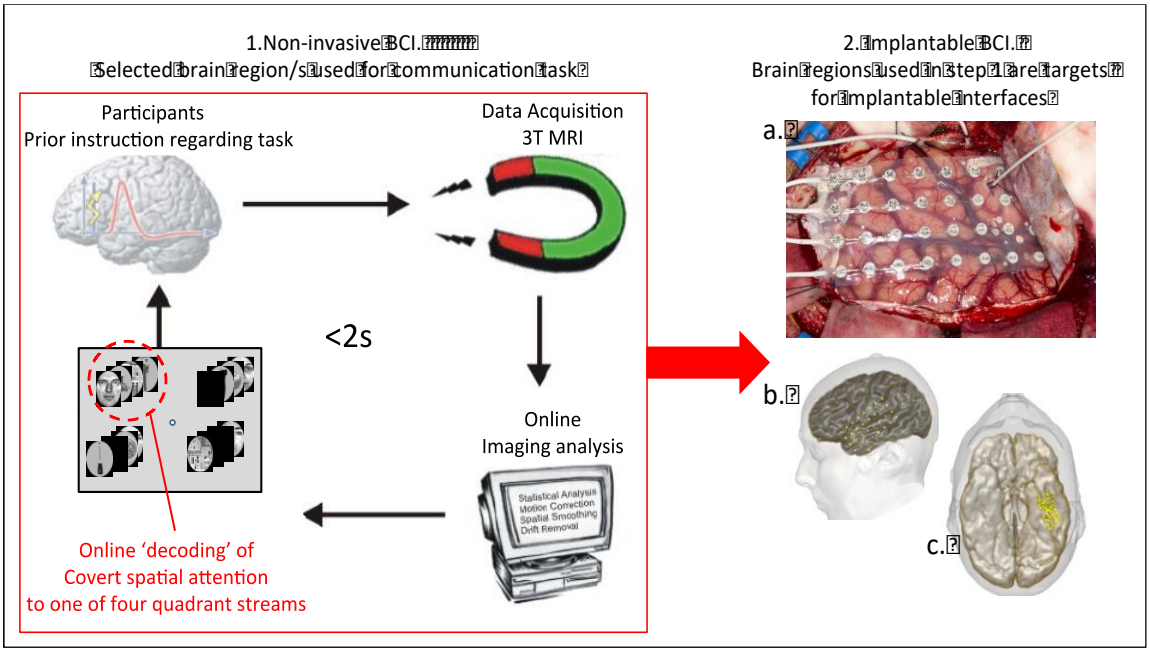


*Fig 1: Conceptual pipeline using a non-invasive BCI interface with rt- fMRI to prime and prepare specific brain regions with a BCI task, prior to surgery for placement of longer-term implantable BCI*

## 2. Implantable Devices

Existing, emerging and future devices are covered below, with a specific focus on implants that are currently being used in the UK's National Health Service for therapy.

### A. Current usage

### i) NHS domain

### Central Nervous System: Brain, spine and cranial nerves

*Deep brain stimulation (DBS)*

Stimulation of deep brain structures for therapeutic effect is produced by the insertion of one or two electrodes at stereo-tactically defined bilateral brain targets using a head-based frame, or a surgical robot. These 'leads' are connected to a battery powered implantable pulse generator (IPG), which is implanted under the skin or muscle, just below the clavicle or in the abdomen. The IPG may or may not be rechargeable, and is systematically programmed to optimise the therapeutic effect, while simultaneously reducing stimulation related side-effects. This fundamental layout is the prototypical template for most stimulation-based implantable devices. Specific industry partners that produce a spectrum of stimulators in this form include Medtronic, and Boston Scientific. A third component to this set-up is the use of 'extension cables', which provide for the option of short-term externalisation of the implanted leads, for externally driven stimulation prior to definitive attachment to the IPG.

DBS of specific brain targets has been approved in the UK for some movement disorders such as Parkinson's disease, dystonia and tremor and for centre-specific use in psychiatric conditions such as Tourette's and obsessive compulsive disorder. Worldwide usage has included chronic pain, treatment-resistant depression and refractory epilepsy.

*Vagus nerve stimulators (VNS)*

In VNS interfaces, the stimulating contacts are collapsible springs which are attached by 'wrapping' them around the vagus nerve – they are then connected via cables to an IPG. VNS activates target neurons, resulting in the release of neurotransmitters such as noradrenaline and GABA leading to changes in brain networks. It has been applied most successfully in the treatment of drug-resistant epilepsy, but also in depression and substance abuse.[20]

*Vestibular implants*

These are used to artificially restore vestibular function in patients with bilateral vestibular loss. Patients suffer with severe imbalance and blurred vision as a result of this vestibulocochlear nerve's ($8^{th}$ cranial nerve) contribution to eye movements. The implant provides electrical stimulation of the vestibular nerve based on its detection of head movement using in-built motion detectors, effectively substituting normal vestibular nerve function[37].

*Cochlear implants*

These implants aim to restore function to the cochlear component of the $8^{th}$ cranial nerve, which facilitates hearing. It is partly implanted directly into the cochlea, the organ chiefly

concerned with hearing, and partly implanted externally in direct contact with the outside world. This external part captures sounds via multiple microphones, and transmits it as an electrical signal to the internal component, which acts as a 'speech processor'. This results in a specific stimulation of the hearing nerve cells in the cochlea, with a reproduction of specific components of the sound, such as loudness, pitch and frequency. These devices have proven to be highly successful in restoring speech in a wide range of age groups from 12 months to 90 years.

*Retinal implants*

These are arrays of micro-electrodes, typically 25-100 surgically attached on the surface (epiretinal) or beneath (subretinal) the retina. They provide a direct interface with visual pathways to the brain, either via cells of the inner retina, or from within the coloured part of the retina. They enable partial vision restoration, comparable to converting a darkened TV screen into a hazy black and white real-world image. Rudimentary light perception is currently possible, with measures including pixel number, density and field of vision[38].

*Intracranial pressure (ICP) bolts /Cerebrospinal fluid (CSF) diversion systems*

CSF is a naturally circulating fluid within the brain and around the spinal cord which may be pathologically increased. Access to this fluid compartment can be used to gauge intracranial pressure, a marker for brain health in some conditions, as well as providing a more direct means of delivering drugs, such as 'intrathecal' (within the CSF compartment of the spinal cord) medication for cancer.

Traditionally, intracranial pressure bolts (ICP) have been simple screw-in access points via a skull entry to enable passive recording of intracranial pressure. Similarly, CSF 'diversion' devices such as ventriculo-peritoneal (VP) shunts have until recently only provided CSF flow regulation, albeit with a programmable function via an in-built valve.

A recent innovation has been the inclusion of electrical chips, which can wirelessly send information revealing changes in CSF flow dynamics and/or ICP. Currently this is being used for data collection, although 'active modes' have been trialled, including neurofeedback related control of ICP[39], and 'intelligent VP shunts' which self-tune in response patient-specific shifts in ICP or CSF flow[40]. Further, Medtronic have a prototype biofeedback pump for the monitoring and delivery of intrathecal chemotherapy in patients with widespread cancer[41].

*Spinal cord stimulation (SCS)*

SCS is an implantable treatment for treatment-refractory chronic pain. Rather than removing the source of the pain, SCS modulates the perception of nerve-related and ischaemic pain, by stimulating the part of the spinal cord involved in the carriage of pain sensation, namely the dorsal column. There are a number of devices that have been authorised for use. All involve a surgically implanted electrode placed on the surface of the coverings of the spinal cord, directly or via skin puncture (percutaneous). This is connected via a lead to battery source, which may be rechargeable, such as an IPG, and is implanted into the abdomen or back. Alternatively the device may connect to an externally driven radiofrequency device.

**Peripheral nervous system**

*Occipital nerve stimulation (ONS)*

Single or bilateral electrodes are placed in a surgically created pouch under the skin, directly over the greater occipital nerve. The electrodes are connected to an IPG placed underneath skin or muscle, just below the clavicle. With ONS insertion, a trial phase may be performed with externalised electrodes to confirm a therapeutic effect prior to definitive IPG implantation. ONS stimulation is used for chronic migraine.

*Sphenopalatine ganglion stimulation*

This is a recent addition to the pain stimulation portfolio, and is used to treat cluster headaches. The stimulator is inserted under X-ray guidance into a region of the face just behind the upper jaw, into direct contact with a nerve centre implicated in cluster headache pain. The main part of the stimulator is affixed to part of the cheek-bone. Unlike the other stimulators discussed in this article, the patient holds a hand-held device over the stimulator and triggers stimulation.

**ii) Non-NHS clinical domain**

*NeuroPace*

This is currently the most technically advanced stimulation system on the market, and is produced exclusively by NeuroPace for the treatment of refractory epilepsy. The device set-up includes stimulating electrodes, which may be placed on the surface of the brain, and/or into deep-brain targets. They connect to a battery-powered sensor that fits into a depression made in the skull, facilitating a 'head-only surgical implantation' procedure. The device is able to monitor brain activity from both electrode locations, triggering stimulation when it detects abnormal brain activity linked to seizure onset. This closed-loop 'responsive neurostimulation' system in its most recent iteration additionally stores brain activity data, which can then be wirelessly downloaded for offline assessment.

The NeuroPace system is currently not approved for usage by NICE, although this may change given the overall shift towards adaptive or intelligent stimulation, and recent promising long-term follow-up data.

**iii) Research domain**

**Central Nervous System: Brain, spine and cranial nerves**

*Cortical implants for the restoration of vision*

Currently no cortical implant for vision restoration system is in active use for humans. There was some historical success, initially in the UK, with early investigations into a wireless device that provided phosphene stimulation. This was followed by the 'Dobelle eye', a cortical implant placed directly onto the visual cortex, with a transcutaneous external connector to enable externally-driven stimulation. The device was reported to enable previously blind patients to read and drive a car, with long-term stability over 20 years. However, complications were reported from some patients including seizures, and device failure. The system continues to be developed, although no further reports have been forthcoming since 2004.

*Braingate*

This system has been extensively used to explore BCI control for motor prostheses in patients who lost over motor function[42–50]. It incorporates a Utah microelectrode array[51] consisting of 100 silicon hair-thin microelectrodes, connected to an external recording device. This external connection is cumbersome, and remains a potential obstacle to operational translation of this device as a mainstream restorative rehabilitation tool. The array is implanted over the hand motor cortex of tetraplegic patients with high spinal cord injury, and has demonstrated long-term BCI functioning[52].The Braingate team initially used it to show control of neural spiking, and then for control of 2D movement of a computer cursor. The same system was used to control a QWERTY keyboard as well as for communication using text-to-speech[43,46,48]. Aside from intracortical spike-based BCI signals, the implant has also provided LFP-based communication in locked-in-syndrome patients[49]. Most recently, the system has been used for reaching and grasping movements with 3D virtual arms and real-world robotic limbs[53].

A hybrid interface has recently been reported[44], combining the Braingate cortical implant with a peripherally implanted functional electrical stimulation (FES) system for high precision multi-joint control (eg shoulder, arm and hand). This was performed in a tetraplegic patient, enabling him to drink from a mug. External peripheral stimulation has previously been successfully paired in this fashion, although not in a patient with complete loss of limb function[54].

*Michigan probe*

The other key silicon-based microarray system is the Michigan probe. It is formed of a small square platform with needle-like electrodes, Unlike the Utah electrode array, which records only from the tips of its electrodes, the Michigan probe has a thin-film planar array with recording sites spaced along the electrode shank. There are some technical advantages to the probe, which has been recently modified to include microscopic light emitting diodes onto the electrodes. This has been applied to deep brain structures in mice to stimulate neurones 50 microns apart using light e.g. optogenetics (see below), while simultaneously recording electrophysiological data[55]. The potential power of this device i the precision provided by cellular level circuit neuromodulation using optogenetics, although this application is currently limited to animal studies[56,57].

**Peripheral nervous system**

*Functional electrical stimulation (FES)*

The fundamental premise of FES is the implantation of stimulating electrodes in contact with specific nerves or target muscles to produce functional contractions. The electrodes are connected to an external or internal control unit; the latter can be under volitional central control. Neuromuscular stimulation is a specific discipline within this, and has received scientific and general press coverage in recent high profile publications[44,54], with focused funding investments by the NIHR, the research body linked to UK's National Health Service. It has been successfully used in a number of different applications[58]. They include: 1) cardiac, phrenic nerve and diaphragmatic pacing; 2) cough stimulation; 3) upper limb and lower limb muscular stimulation for movement; 4) axial muscle stimulation for trunk stability; 5) bladder, bowel and sexual function.

## B. Emergent applications

*Optogenetic neuromodulation*

This is a powerful technology that is poised to revolutionise BCI and clinical neuromodulation[30,59]. It involves facilitating the expression of light-activated microbial opsin proteins in a target neural or non-neural cell population. The opsins can be delivered by cellular transplantation, transgenesis or viral transfection. Light delivery to the cells then results in an opsin-specific activation, producing a temporally precise (over milliseconds) activation at a cellular level. Within a clinical context, this typically involves opsin activated ion channels generating action potentials in a circuit or network-specific manner. This may be activating a compensatory physiological response - 'switching on' or 'switching off' of a pathological activity such as seizures. The approach has a number of useful properties, including specificity for neuronal populations, flexibility due to the range of opsins available, and precision of spatiotemporal control. The two principal applications are circuit-driven neuromodulation by allowing tailored cellular stimulation, currently demonstrated only in animal models[28,60].

Optogenetics has been used in animal models for a range of conditions including chronic pain, depression, obsessive compulsive disorder, Parkinson's disease, epilepsy, addiction and laryngeal paralysis, and has been proposed as an optimal technique for spinal cord and PNS neuromodulation[61]. Most recently, first-in-human clinical trials have been planned, with orphan status being granted to a viral-vector based optogenetic therapy (RetroSense Therapeutics) for retinitis pigmentosa.

The US Food and Drug Administration (FDA) has approved adeno-associated viruses for viral transfection, and deep brain optical electrodes or 'optrodes' (analogous to deep brain electrodes) have been developed. Nonetheless, a number of challenges related to clinical translation remain. These include opsin choice, opsin delivery, optical actuators and illumination strategies, particularly for deep brain tissue[62].

## C. Future device approaches- Smaller, scalable, smarter, and faster

The integral role of the nervous system is an evolving theme in the pathogenesis of disease, potentially increasing the scope and remit of neural-interface devices as therapeutic tools. Examples of this include: (1) occipital nerve stimulation for autonomic cephalgias, (2) deep brain stimulation for traumatic brain injury, disorders of consciousness and hypertension (3) cholinergic-based therapies for inflammatory diseases (4) stimulating the action of gut-based ('enteric') neurones and neurotransmitters in the gut-brain axis.

To realise the full potential of bioelectronic BCIs and 'electroceuticals' and achieve the integration achieved by pharmaceuticals, a number of form, signal extraction and design challenges need to be addressed. The current state-of-the-art, with some notable exceptions (e.g. Sphenopalatine ganglion stimulation[17]), requires bulky, wired implants with poor cosmetic profiles, powered by relatively large, surgically implanted batteries. The devices themselves record or stimulate at a comparatively crude resolution , with low channel count devices applied to macroscopic areas of brain or spinal cord. Finally, rather than being 'intelligent' devices which adaptively self-govern in response to biological and pathological fluctuations, the devices are 'open-loop', requiring adjustment by a third party such as the treating clinician, often by trial-and-error.

Much of the high concept work in implantable BCI is geared towards a wireless, scalable reduction in implant size, an improvement in signal quality by selectively interfacing with nervous tissue at the sub-millimetre scale– smaller, smarter, scalable and faster. We conclude by briefly examining four preliminary but promising technologies that seek to address these challenges:

1. Neural dust: Neural dust motes, made up of sub millimetre piezocrystals, can be used as wireless, battery-free, scalable implants. Nervous tissue action potentials are read by showering the implanted motes with pulses of ultrasound, which additionally power the motes. The resulting back scatter is read wirelessly and externally[13].

2. Neural lace/injectables: Highly flexible macroporous microelectronic mesh interfaces are being developed by companies such as Elon Musk's Neuralink, which can be precisely delivered by syringe injection to the target site. The tightly folded mesh then relaxes, settles and penetrates into neural tissue. Chronic recordings over 8 months in mice brains have been demonstrated[14,63].

3. Neuropixels: This microelectrode technology massively increases the number of recording sites at the electrode tip, with up to 1000 sites over a 1centimetre (70-micron diameter) shank, as compared with the typical 100 sites used by existing electrode arrays. Further iterations are expected, with plans for reducing their size and combining them with optical recordings. The main benefits of this system are its hyper-dense, ultra-low noise recordings with an on-device, self-contained recording and processing system[64].

4. Endovascular EEG: Endovascular access to the brain provides a minimally invasive approach, avoiding the need for a skull opening. Endovascular EEG has been previously demonstrated with large intra-arterial wires[65]. More recently nanowires and stentrodes have increased the density of the recording, as well as providing access to cerebral blood flow dynamics. The latter is exquisitely linked to neural function, as well as serving as a direct target in pathologies such as stroke, and cerebral vasospasm Endovascular BCIs are a rapidly developing field, with testing in large animal models[66], although key challenges such as maintaining the patency of cerebral vasculature and avoiding clot formation remain outstanding.

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