European Innovation Council

PATHFINDER CHALLENGE
Tools to measure and stimulate activity in brain tissue
CHALLENGE GUIDE – PART I

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CONTENT

The Appendices that are referred to in this document are common to the different Challenges and bundled in Part II of the Challenge Guide, published on the Challenge page on the EIC Website https://eic.ec.europa.eu/calls-proposals/eic-pathfinder-challenge-tools-measure-and-stimulate-activity-brain-tissue_en.

1. About this document

The Challenge Guide is the reference document accompanying a Pathfinder challenge along its whole life cycle, from call to achieving its objectives.

The Programme Manager in charge of this Pathfinder Challenge is the editor of the Challenge Guide. The Challenge Guide captures, at any moment, the state of play, achievements and remaining challenges, and documents the process by which the Programme Manager and Portfolio members jointly establish an evolving set of Portfolio objectives and a shared roadmap for achieving them. The most recent version can be found through the corresponding Challenge page on the EIC Website https://eic.ec.europa.eu/calls-proposals/eic-pathfinder-challenge-tools-measure-and-stimulate-activity-brain-tissue_en.

The Challenge Guide starts out as a background document to the initial Pathfinder Challenge call. It details the intention of the call by complementing notably the scope, objectives (see Section 5 - Challenge call text) or criteria (see Appendix 3: EIC 2021 Work Programme – Evaluation criteria) set out in the EIC Work Programme. In no case does it contradict or supplant the Work Programme text. After the call evaluation, the Challenge Guide further documents the initial Challenge Portfolio that resulted from the call.

As the actions in the Portfolio unfold, the Challenge Guide further documents the evolving Portfolio Objective(s) and the progress towards achieving them, notably through the Portfolio Activities that the Programme Manager puts in place.

The Challenge Guide serves as a reference for the common understanding, rules-of-play and obligations for the EIC beneficiaries that are involved in the Challenge Portfolio. Contractual Obligations are further reference material from the EIC Work Programme and are collected in Part II of the Pathfinder Challenge Guide, published on the Challenge page on the EIC Website https://eic.ec.europa.eu/calls-proposals/eic-pathfinder-challenge-tools-measure-and-stimulate-activity-brain-tissue_en.

2. Overall objective of the Pathfinder Challenge

This section sets out the rationale of the Challenge. Building on the state of the art in the relevant scientific and technological domains, it motivates the challenge, sets the boundaries of its scope and explains the overall objectives. This section should be read as further background to the Challenge specific part of the EIC Work Programme text (see work programme extract in Section 5).

Proposals to this Challenge are expected to explain how they relate to and intend to go beyond the state of the art, and how they interpret and contribute to the objectives of the Challenge.

Background – State of the Art - Scope

A broad range of high-prevalence medical conditions are directly or indirectly linked to electrical activity in neuronal tissue, including motor disorders, chronic pain, age-related cognitive decline, epilepsy… but also the immune response, cardiac function, skin health, and so on. The scientific community has gained substantial expertise at monitoring and modifying the electrical content of the Central Nervous System (CNS) and peripheral nerves (PNs) to realise powerful diagnosis and treatment strategies.

Concomitantly, the 21st century has brought a substantial increase in technological know-how in the field of electronics, partly due to market-driven fast-paced advances in miniaturisation, power consumption and wireless communications, but also deeper understanding of the interface between physics and living matter for sensing and stimulation, yielding improved imaging modalities and non-invasive forms of neuromodulation. With sub- 10 nm features, state-of-the-art Extreme UltraViolet lithography (EUV) yields transistors x3 orders of magnitude smaller than a typical 20 µm pyramidal neuron.

Unsurprisingly, the historic confluence of a growing understanding of the electrical basis of brain function, and the advent of new electronics and physics-grounded technological capabilities in the electrical domain, have raised expectations over the creation of new devices and instruments for monitoring or intervening on the electrical brain, reaching the clinic, and revolutionising healthcare.

Despite several success stories attesting to the potential in the field, however, only a limited number of such devices are widely used in clinical practice today.

This call aims at creating new technologies with a focus on projects that can bring new therapeutic tools to clinicians and patients.

There is indeed a need and room for new approaches. The technology used in the clinically accepted devices, e.g. in relation to integration level and electrode density, often lags behind the capabilities of modern microelectronics. Moreover, the first demonstration of the underlying principles can often be traced back decades, suggesting an opportunity for new ideas.

The Cochlear Implant (CI) is a well known classic success case. Used in adults since the 1980s, CIs are currently implanted in Europe in approximately 1 per 1000 newborns (De Raeve et al., 2020) and a total of more than 12.000 CI surgeries, including adults, are performed each year (Eurostats 2015). Relatively low-density electrode arrays in CIs, with less than 30 stimulation sites, are able to produce intelligible speech (Croghan et al., 2017)(Berg et al., 2019). The favourable risk-benefit profile of CIs is also a factor in their success in the newborn population, offsetting the disadvantages, e.g. relatively bulky and visible external modules and the invasiveness of the implantation procedure. Yet less than 10% of the potential adult patients accept state-of-the-art CIs.

Deep Brain Stimulation (DBS) (Lozano, 2019), as for example used for the treatment of Parkinson´s disease by stimulation of the subthalamic nucleus or the globus pallidus, is also a clinically accepted procedure with a history going back over 25 years (Siegfried J, 1994). Here again a limited number of stimulation sites (fewer than 10) and relatively large electrodes (in the order of several mm^2) and large supporting shank (>1mm in diameter) suffice to safely achieve therapeutic effect (Paff M, 2020). The relative simplicity of the electrode geometries and stimulation electronics, and acceptable risk-benefit considering the impact of Parkinson's disease on patient's quality of life, have contributed to DBS's growth in clinical practise. The stimulation electronics modules remain however bulky, typically with a volume of over 20 cm^3 and implanted in the chest below the collarbone. Moreover, clinicians demand higher levels of freedom in the stimulation patterns, which will require leads with smaller electrodes and higher density electrode arrays.

Spinal cord stimulation (SCS) for pain indications, was first developed five decades ago and has since increasingly gained recognition in clinical practise (Mekhail N, 2018). Ongoing research aims at increasing the number of electrodes beyond 30 and reducing footprint and invasiveness (Lempka SF, 2018). Similarly Vagus Nerve Stimulation (VNS) for the treatment of drug-resistant epilepsy has been used for decades (Marras CE, 2020), yet clinically used VNS leads contacting the nerve remain passive elements, devoid of integrated electronics, requiring a separate implanted pulse generator (IPG).

CI, DBS, SCS and VNS are used here merely as examples suggesting the need for new implantable devices fully leveraging state of the art microelectronics technology, with higher levels of integration, lower invasiveness, improved reliability, etc.

In other cases, such as for example Retinal Prosthesis (RPs) for the blind, substantial technological progress is still needed. Several RP devices have been developed and tested in

humans over the past years (Ayton et al., 2020) with limited success. Direct stimulation of the retina or the visual cortex have not yet succeeded in creating sufficiently high-resolution images, which is critical for RP devices to impact patients´ lives.

Non-invasive technologies are also gaining traction, and facing challenges of their own.

Transcranial Magnetic Stimulation (TMS), with over three decades of history (Ziemann, 2017), has received CE mark or is actively researched for multiple indications, such as major depressive disorder, OCD, chronic pain, smoking addiction and even Alzheimers'. TMS is increasingly recognised as clinically useful (Leung et al., 2020). However, the neurophysiological basis of its broad therapeutic action is not fully understood. Moreover, TMS suffers from several technical limitations, including its poor spatial resolution, compared to electrical stimulation with implanted electrodes, and the impracticality of targeting specific neuronal subtypes. Safety concerns, e.g. TMS-triggered epileptic seizures, also remain an active topic of research (Rossi et al., 2020).

Electro-convulsive therapy (ECT), a technique researched and practiced for over 50 years, uses high-intensity transcranial currents and has also been demonstrated effective against depression (Kellner et al., 2020). Its use remains limited, partly due to stigma, and as other neuromodulation approaches is not considered first-line treatment (Borrione et al., 2020).

Currently more popular are the techniques known as transcranial Direct Current Stimulation (tDCS) and transcranial Alternate Current Stimulation (tACS), related to ECT and re-discovered nearly 20 years ago. A recent surge of new studies on tDCS and tACS have demonstrated that transcranial current intensities at much lower intensities (several mA) than those used in ECT can be used for neuromodulation (Stagg et al., 2018). Neuronal excitability can be in this way decreased or increased depending on current polarity and numerous clinical applications are being explored (Lefaucheur et al., 2017). Approval in the EU for major depressive disorder has been granted. Despite the undoubtable cost-benefit of tDCS and tACS they have not become first-line treatments.

Other techniques target nerves for indirect brain neuromodulation such as transcutaneous auricular or neck vagus nerve stimulation for indications such as tinnitus, migraine and pain (Yap et al., 2020).

Ultrasound-based neuromodulation has also emerged as a novel non-invasive alternative, both for stimulation and imaging of activity, but it is also far from becoming widely accepted in clinical practice (Urban et al, 2015)(Puleo & Cotero, 2020).

Overall, despite the wealth of existing devices and instruments, both invasive and non-invasive, the fraction of neuro-related disorders successfully tackled by these, particularly as first-line treatments, remains small. A number of barriers still remain.

Remaining barriers and possible approaches

The nature and relative weight of the various obstacles to overcome are dependent on the technology modality, i.e. invasive versus non-invasive.

Barriers faced by invasive technologies

- *Device size, complexity of surgery and implantation risk.*

The general trend in surgery is towards minimizing invasiveness. A plethora of laparoscopic, endoscopic port access surgeries, as well as endovascular procedures in cardiac (e.g. valve replacement) and brain surgeries (e.g. for the treatment of aneurysms and stroke), attest to the importance of limiting tissue disruption in the operating room.

Indeed, single module compact devices are easier to implant than assemblies including separate electrodes, connecting wires and an electronics pulse-generator module. And as robotic surgery grows (Leal Ghezzi & Campos Corleta, 2016), these single-element devices designed with in-built compatibility with robotic laparoscopy are more likely to impact clinical practice.

Consider for example the potential impact of a future fully-implantable and invisible Cochlear Implant (Mitchell-Innes et al., 2018). The opportunities for fully-integrated one-part stimulators are enormous, as are the challenges involved.

Battery size and power budget are limiting factors. The experience gained with state-of-the-art cardiac leadless pacemakers, currently achieving over 10 years of heart stimulation with a device size under 1 cm^3 (Acha et al., 2020) suggests that low power circuit design, optimised stimulation duty cycles and miniature batteries could enable sufficient life-span of fully-integrated neurostimulators. Further, various types of wireless power transfer (WPT) can be used to extend battery life and decrease battery volume (Khan et al., 2020) or even support battery-less designs (Lin et al., 2016).

- *Gliosis and long-term stability of device-tissue interface.*

Post-mortem studies suggest that the life span of existing DBS electrodes does not seem to be negatively impacted by gliosis (Vedam-Mai et al., 2018). However, as electrode density increases and electrode surface decreases, e.g. as required for retinal prosthesis, gliosis might indeed render stimulation less effective due to impedance increase.

Future technologies should pay attention to minimising tissue response by appropriate material selection and development of biocompatible enclosure coatings.

- *Objective and subjective risk-benefit profile of invasive technologies*

Invasive approaches to neuromodulation might offer clinical advantages, but undoubtedly lead to the perception of higher risk. From both the clinician’s and patient´s perspectives, the possibility of adverse events associated with device implantation, post-operative care

and long-term device use, is generally unacceptable, unless alternative treatment options are clearly less effective.

As a result, to overcome this barrier and realise clinical impact with a new technology, a systematic evidence-based evaluation of its benefits and a realistic analysis of its risks should be carried out before committing to a full technology development programme (Fisher et al., 2018). The patient´s perspective should be taken into consideration at this stage, in addition to purely medical considerations.

Barriers for non-invasive technologies

- *Coarse stimulation granularity, poor selectivity and diffuse boundaries of stimulated regions.*

While an implanted (micro) electrode can in principle offer fine granularity, i.e. stimulating small spherical volumes (radius ≈100 μm) in the proximity of the tip of the electrode, similar specifications are difficult to achieve with non-invasive methods acting through the skull.

The state of the art figure-8 TMS coils modulate activity in regions centimetres across, with even coarser stimulation resulting from TES. Yet consider the potential advantages of achieving resolutions comparable to single cortical columns, with stimulation voxels in the hundreds micrometres.

A possible strategy to achieve finer stimulation granularity is the simultaneous use of neuromodulation and sensory stimuli to trigger associative plasticity. For example, presentation of images with a specific orientation and simultaneous TMS stimulation can selectively induce plasticity in the visual cortex selectively on the neuronal population with the desired orientation preference (Kozyrev et al., 2018).

Further, micro-coil TMS arrays could also be explored as a promising strategy for focalised magnetic stimulation (Colella et al., 2021) and, similarly, high-definition (HD) TES with multiple concentric surface electrodes for electrical stimulation (Perceval et al., 2017).

More speculative hybrid modalities could also be explored such as combinations of TES and multi-beam focused ultrasound, magneto-acoustic effect or light sources for stratification or focalisation of neurostimulation.

- *Limited access to deep brain structures*

Non-invasive technologies such as tDCS, High Definition (HD)-tDCS and tACS use surface electrodes to pass currents through the scalp, soft tissue and skull. The patch of cortex immediately beneath the electrodes experiences a higher electric field magnitude, compared to deeper regions, which are therefore less amenable to stimulation (Thomas et al., 2019). State-of-the-art TES techniques could be substantially enhanced as therapeutic tools if endowed with stimulation selectivity for deep brain structures such as the brain

stem, thalamus and basal ganglia. Clinically important disorders, such as Parkinsons´ disease, which requires stimulation of the Subthalamic nucleus (STN) or the globus pallidus internus (GPi), would then be treatable non-invasively by neuromodulation.

Various routes could be explored to overcome these limitations. Multi-electrode TES montages, for example, have demonstrated the viability of an interference-like strategy to stimulate regions below the cortex, with little cortical stimulation (Grossman et al., 2017). Further, deep and focused tissue access by new generation TMS using multi-coil arrays is also a promising strategy, potentially realising hot-spots several centimetres below the skull (Gomez et al., 2013). And focused ultrasound, for deep ablation (irreversible) but also (reversible) modulation has been demonstrated (Fini & Tyler, 2017)(Quadri et al., 2018).

Finally, radically novel deep and focused neurostimulation modalities could be explored. For instance, the functional impact of ionising radiation on the CNS has historically been studied mostly in the context of radiation damage, e.g. as a side-effect of oncological radiotherapy. However, it is conceivable, but admittedly speculative, that low-dose multi-beam technologies, akin to gamma knifes for stereotactic radiosurgery (Fanous et al., 2019), possible used in conjunction with novel radiation sensitisers, could lead to new strategies for focalised functional modulation.

Barriers common to invasive and non-invasive technologies

- *Limited understanding of the electrical activity subserving brain function. Better activity-measurement technologies are needed.*

The development of a novel neuro-technology hinges on our understanding of the electrical basis of function in the targeted brain region. Sufficient knowledge of the differences between healthy and anomalous electrical patterns is a pre-requisite to design effective stimulation devices and optimal stimulation sequences.

Unfortunately, the spatial resolution afforded by state of the art functional imaging technologies such as EEG, fMRI, PET, MEG, etc. is far from single-cell. Moreover, observation at the time scale of the action potential (1 to 10 ms) requires also relatively high temporal resolution. To a large extent, as a result of the limitations of current imaging modalities, the complex electrical interplay of neurons in the circuits remain poorly understood: elaborate thought speech cannot yet be reliably decoded by cortically implanted electrodes to help patients with loss of speech motor function, we are not yet able to create high-resolution images by multi-pixel stimulation of the visual cortex of the blind and it remains a formidable challenge to untangle the spinal cord messages carrying precise motor actions or conveying complex touch and pain information.

Novel principles towards single-cell and single-action potential resolutions should be explored and new functional imaging technologies developed. Opportunities abound including new contrast mechanisms for MRI, multimodality approaches which combine high-

resolution anatomical imaging, e.g. Diffusion Tensor Imaging, and low-resolution functional connectome information, e.g. from EEG or Magnetoencephalography (MEG), to increase overall effective resolution, beyond state-of-the-art ultra-high-field fMRI, novel ultrasound functional imaging, enhanced fNIRS, expanding the use of optogenetics for probing and response imaging for neuronal circuit characterisation, or even exploring radically novel imaging modalities, for example ideas stemming from high-energy physics and new knowledge on interaction between high-energy particles and living matter.

- *Limited knowledge of the optimal electrical stimulation sequences. Need for more sophisticated stimulation patterns.*

Historically electrical stimulation of neuronal tissue resorted first to simple current or voltage stimulation patterns, e.g. single current pulses, biphasic pulses, bursts of pulses, etc. However, it is increasingly evident that more complex current patterns can induce richer, more elaborate effects, particularly when multi-channel stimulation is available to create a wealth of spatial and temporal current profiles.

Consider for example cortical stimulation in the context of visual prosthesis. Multiple electrodes activated in sequence, with optimal inter-electrode time lags, has recently been demonstrated to produce images with higher resolution as compared to simultaneous stimulation of all the pixels (electrodes) making up the full shape (Beauchamp et al., 2020). And repetitive TMS (rTMS) compared to traditional (single-pulse) TMS is a trivial but illustrative example of how more elaborate stimulation patterns can lead to therapeutic value (Lefaucheur et al., 2020) .

Further, Transcranial Electrical Stimulation (TES) with brief and rapidly rotating fields has been demonstrated recently to realise immediate modulation of activity without pain or other side-effects, e.g. phosphenes, despite using relatively high currents of up to 6mA (Vöröslakos et al., 2018)

It is therefore likely that the large parameter space of stimulation sequences compatible with existing hardware, contains therapeutically useful regions that remain unexplored.

- *Insufficiently personalised stimulation. Need for novel closed-loop measure-stimulate architectures.*

Time-locking stimulation to patient-specific signatures, e.g. within monitored neuronal activity, is expected to offer superior therapeutic potential than open-loop stimulation (Zanos, 2019), and yet this strategy is rare amongst existing clinical neuro-devices.

Considering today's CPU clock speeds in the 100MHz to GHz range, operating in the multi-GFLOP per Watt region (Sun et al., 2019), it is conceivable that function-rich low-power implantable devices could monitor local neuronal activity, perform signal processing and stimulate upon discovery of specific activity patterns, all within a limited power budget. Sub-

millisecond latency in the loop is within reach for many applications. Moreover, such closed-loop fast-response architectures can also benefit non-invasive technologies, for example by combining TMS and EEG (Tremblay et al., 2019).

Beyond electrical signatures, closed-loop technologies could make use of neurochemical information, e.g. local ion or neurotransmitter concentrations, motion sensing for motor disorders, oxygen saturation, temperature, heart rate and heart rate variability, autonomic activation, wearable IoT-gathered behavioural patterns for psychiatric indications, etc.

Objectives of the Call

The proposals submitted to this Call should target at least one of the following two sub-challenges: 1) the development of a full device or 2) the exploration of new physical principles for sensing/stimulation towards future devices.

Sub-challenge 1. A new device or instrument.

Main objective of sub-challenge 1: Develop a fully functional prototype device or instrument and, if relevant, demonstrate efficacy and safety in animal models. The targeted device or instrument will address one or more of the barriers described above and will tackle an important clinical need.

Proposals of an exploratory nature are not within the scope of sub-challenge 1. For instance, a proposal targeting the invention of a new clinical neuro-stimulation system is expected to rely on existing data, which convincingly describe the location and type of stimulation that will cause the desired therapeutic effect. Sub-challenge 1 does not address basic research on neuronal circuits or completely untested stimulation patterns. The proposal should build on existing scientific evidence, and implement a credible technology-focused workplan towards the end deliverable, i.e. a fully functional proof-of-concept prototype, within the time span of the project.

Demonstrate clinician/patient acceptability of the proposed technology.

Proposals submitted to sub-challenge 1 need to address the following questions: Is the proposed technology clinically advantageous compared to competing (e.g. pharmacological) solutions? Will it fare well in a cost-effectiveness analysis? Are patients likely to accept it?

Further, decision-making milestones in the workplan should trigger re-evaluation of the potential impact on future Health Technology Assessments (HTA) and patient acceptance. For example, a mid-project modification of the form factor of the device to allow for enhanced battery-life, at the expense of increased invasiveness, should not be implemented without assessment of the implications in relation to surgeon adoption.

Shortest technological path from idea to a functional proof-of-concept device.

Proposals submitted to sub-challenge 1 should strive to identify and follow a time-efficient path to the target device. For example, when off-the-shelf components exist or prior research in academia or industry can be re-used through collaboration, the workplan must be designed accordingly.

Lack of focus on rapid progress towards the end deliverable will deem the proposal inadequate for sub-challenge 1.

Plausibility of time and funding requirements.

Proposals addressing sub-challenge 1 should convincingly demonstrate a high probability of achieving each deliverable in the estimated time-frame and within the allocated funding.

Keep future regulatory needs in mind while designing the workplan

A proposal that addresses sub-challenge 1 should tackle a technology with reasonable likelihood of eventual use in humans.

Therefore the proposers are advised to consider future regulatory approval, e.g. CE marking, in justifying the relevant technical decisions. Whenever possible, the workpackages should be designed to facilitate future compliance with IEC60601, MDD/MDR medical devices regulation, ISO10993 materials biocompatibility standards, ISO13485, IEC 62304 medical software standard, etc.

Proposers are NOT requested to carry out an in depth regulatory analysis in the proposal, but to demonstrate attention to details relevant for eventual device approval. For example, if the use of non-medical grade materials (or processes) is proposed for prototyping, a justification is needed and a credible path for future migration to medical grade alternatives should exist and be practical.

Plan for safety tests to build trust on the technology

Workplans under sub-challenge 1 must include experimental proof of safety, in addition to efficacy, as the project progresses. The objective must be to build trust in the technology demonstrating that potential safety issues have been considered and addressed during early development stages.

Sub-Challenge 2. Explore novel physical principles for sensing and/or stimulation.

While sub-challenge 1 targets the development of a full device relying on known physical principles, sub-challenge 2 aims at the discovery of new principles for monitoring or

modulation of function for therapeutic purposes. These will enable future devices with radically improved features.

A sub-challenge 2 proposal must seek substantial improvements with respect to existing technologies, for example an improvement in the spatial resolution of non-invasive techniques (e.g. to attain the millimeter-range, single-column, single-cell or single-compartment), temporal resolution (e.g. single-spike), cell type-selectivity, deep-brain access at fine granularity, monitoring of metabolic-function correlations, or other unique features in line with the barriers described above.

Under sub-challenge 2, proposers are expected to:

a) Provide in the proposal a scientific rational for the new approach. This could rely on existing experimental data or on a solid theoretical analysis.
b) Develop the technology required to test the proposed concept, if specific new hardware is necessary.
c) Execute experimental work seeking to demonstrate that monitoring or modulation of activity in neuronal tissue is viable with the proposed methodology.
d) Optimise the methodology and deliver the technology to the community in a form that facilitates replication and re-use for future device-targeted projects.

The end deliverable of proposals or workpackages targeting sub-challenge 2 must be a description of the technique, data sets and demonstrator hardware as/if required by the novel technique.

De-risking Sub-Challenge 2

Despite the admittedly exploratory nature of sub-challenge 2, the proposers are requested to de-risk this sub-challenge:

- Proposals tackling sub-challenge 2 only: the consortium should be formed by assembling multiple partners each exploring different novel principles in parallel. The goal is to maximise the likelihood of demonstrating at least one successful principle by the end of the project.
- Proposals targeting simultaneously sub-challenge 1 and sub-challenge 2: exploratory tasks should not be critical for the success of the device or instrument development workplan. It would not be acceptable to propose the development of a new device, which hinges on a yet unproven novel principle for sensing or stimulation. However, it would be acceptable to include a task in the workplan on the testing of a new principle, which, in case of failure, would not invalidate the objectives of the project, i.e. the development of the device.

References

Acha, M. R., Soifer, E., & Hasin, T. (2020). Cardiac implantable electronic miniaturized and micro devices. In *Micromachines*. https://doi.org/10.3390/mi11100902

Ayton, L. N., Barnes, N., Dagnelie, G., Fujikado, T., Goetz, G., Hornig, R., Jones, B. W., Muqit, M. M. K., Rathbun, D. L., Stingl, K., Weiland, J. D., & Petoe, M. A. (2020). An update on retinal prostheses. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *131*(6), 1383–1398. https://doi.org/10.1016/j.clinph.2019.11.029

Beauchamp, M. S., Oswalt, D., Sun, P., Foster, B. L., Magnotti, J. F., Niketeghad, S., Pouratian, N., Bosking, W. H., & Yoshor, D. (2020). Dynamic Stimulation of Visual Cortex Produces Form Vision in Sighted and Blind Humans. *Cell*. https://doi.org/10.1016/j.cell.2020.04.033

Berg, K., Noble, J., Dawant, B., Dwyer, R., Labadie, R., Richards, V., & Gifford, R. (2019). Musical Sound Quality as a Function of the Number of Channels in Modern Cochlear Implant Recipients. *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2019.00999

Borrione, L., Bellini, H., Razza, L. B., Avila, A. G., Baeken, C., Brem, A. K., Busatto, G., Carvalho, A. F., Chekroud, A., Daskalakis, Z. J., Deng, Z. De, Downar, J., Gattaz, W., Loo, C., Lotufo, P. A., Martin, M. da G. M., McClintock, S. M., O'shea, J., Padberg, F., … Brunoni, A. R. (2020). Precision non-implantable neuromodulation therapies: A perspective for the depressed brain. *Brazilian Journal of Psychiatry*. https://doi.org/10.1590/1516-4446-2019-0741

Colella, M., Liberti, M., Apollonio, F., & Bonmassar, G. (2021). A Miniaturized Ultra-Focal Magnetic Stimulator and Its Preliminary Application to the Peripheral Nervous System. In *Brain and Human Body Modeling 2020*. https://doi.org/10.1007/978-3-030-45623-8_9

Croghan, N. B. H., Duran, S. I., & Smith, Z. M. (2017). Re-examining the relationship between number of cochlear implant channels and maximal speech intelligibility. *The Journal of the Acoustical Society of America*. https://doi.org/10.1121/1.5016044

De Raeve, L., Archbold, S., Lehnhardt-Goriany, M., & Kemp, T. (2020). Prevalence of cochlear implants in Europe: trend between 2010 and 2016. *Cochlear Implants International*. https://doi.org/10.1080/14670100.2020.1771829

Fanous, A. A., Prasad, D., Mathieu, D., & Biano, A. J. (2019). Intracranial stereotactic radiosurgery. In *Journal of Neurosurgical Sciences*. https://doi.org/10.23736/S0390-5616.17.04210-2

Fini, M., & Tyler, W. J. (2017). Transcranial focused ultrasound: a new tool for non-invasive neuromodulation. In *International Review of Psychiatry*. https://doi.org/10.1080/09540261.2017.1302924

Fisher, L. M., Martinez, A. S., Richmond, F. J., Krieger, M. D., Wilkinson, E. P., & Eisenberg, L. S. (2018). Assessing the Benefit-Risk Profile for Pediatric Implantable Auditory Prostheses. *Therapeutic Innovation and Regulatory Science*. https://doi.org/10.1177/2168479017741111

Gomez, L., Cajko, F., Hernandez-Garcia, L., Grbic, A., & Michielssen, E. (2013). Numerical analysis and design of single-source multicoil TMS for deep and focused brain stimulation. *IEEE Transactions on Biomedical Engineering*. https://doi.org/10.1109/TBME.2013.2264632

Grossman, N., Bono, D., Dedic, N., Kodandaramaiah, S. B., Rudenko, A., Suk, H. J., Cassara, A. M., Neufeld, E., Kuster, N., Tsai, L. H., Pascual-Leone, A., & Boyden, E. S. (2017). Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields. *Cell*. https://doi.org/10.1016/j.cell.2017.05.024

Kellner, C. H., Obbels, J., & Sienaert, P. (2020). When to consider electroconvulsive therapy (ECT). *Acta Psychiatrica Scandinavica*. https://doi.org/10.1111/acps.13134

Khan, S. R., Pavuluri, S. K., Cummins, G., & Desmulliez, M. P. Y. (2020). Wireless power transfer techniques for implantable medical devices: A review. In *Sensors (Switzerland)*. https://doi.org/10.3390/s20123487

Kozyrev, V., Staadt, R., Eysel, U. T., & Jancke, D. (2018). TMS-induced neuronal plasticity enables targeted remodeling of visual cortical maps. Proceedings of the National Academy of Sciences of the United States of America. https://doi.org/10.1073/pnas.1802798115

Leal Ghezzi, T., & Campos Corleta, O. (2016). 30 Years of Robotic Surgery. World Journal of Surgery. https://doi.org/10.1007/s00268-016-3543-9

*Lefaucheur, J. P., Aleman, A., Baeken, C., Benninger, D. H., Brunelin, J., Di Lazzaro, V., Filipović, S. R., Grefkes, C., Hasan, A., Hummel, F. C., Jääskeläi*nen, S. K., Langguth, B., Leocani, L., Londero, A., Nardone, R., Nguyen, J. P., Nyffeler, T., Oliveira-Maia, A. J., Oliviero, A., … Ziemann, U. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). In *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2019.11.002

Lefaucheur, J. P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M. A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Schecklmann, M., … Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). In *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2016.10.087

Lempka, S. F., Patil, P.G. (2018) Innovations in spinal cord stimulation for pain. Current Opinion in Biomedical Engineering. https://doi.org/10.1016/j.cobme.2018.10.00

Leung, A., Shirvalkar, P., Chen, R., Kuluva, J., Vaninetti, M., Bermudes, R., Poree, L., Wassermann, E. M., Kopell, B., Levy, R., Leung, A., Saitoh, Y., Lefaucheur, J. P., Khedr, E., de Andrade, D. C., Schuster, N. M., Salmasi, V., Leung, A., Adamson, M. M., … Leung, A. (2020). Transcranial Magnetic Stimulation for Pain, Headache, and Comorbid Depression: INS-

NANS Expert Consensus Panel Review and Recommendation. In *Neuromodulation*. https://doi.org/10.1111/ner.13094

Lin, Y. P., Yeh, C. Y., Huang, P. Y., Wang, Z. Y., Cheng, H. H., Li, Y. T., Chuang, C. F., Huang, P. C., Tang, K. T., Ma, H. P., Chang, Y. C., Yeh, S. R., & Chen, H. (2016). A Battery-Less, Implantable Neuro-Electronic Interface for Studying the Mechanisms of Deep Brain Stimulation in Rat Models. *IEEE Transactions on Biomedical Circuits and Systems*. https://doi.org/10.1109/TBCAS.2015.2403282

Lozano, A. M., Lipsman, N., Bergman, H., Brown, P., Chabardes, S., Chang, J.W., Matthews, K., McIntyre, C. C., Schlaepfer, T. E., Schulder, M. Temel, Y., Volkmann, J., Krauss, J. K. (2019) Deep brain stimulation: current challenges and future directions. Nature Reviews Neurobiology. https://doi.org/10.1038/s41582-018-0128-2

Marras C., Colicchio G., De Palma L., De Benedictis A., Di Gennaro G., Cavaliere, M., Cesaroni, E.,Consales, A.,Asioli, S.,Caulo, M.,Villani, F.,Zamponi, N. (2020) Health technology assessment report on vagus nerve stimulation in drug-resistant epilepsy. International Journal of Environmental Research and Public Health. https://doi.org/10.3390/ijerph1717615

Mekhail, N., Visnjevac, O., Azer, G., Mehanny, D.S., Agrawal, P., Foorsov, V. (2018) Spinal Cord Stimulation 50 Years Later: Clinical Outcomes of Spinal Cord Stimulation Based on Randomized Clinical Trials - A Systematic Review. Regional Anesthesia and Pain Medicine. https://doi.org/10.1097/AAP.0000000000000744

Mitchell-Innes, A., Saeed, S. R., & Irving, R. (2018). The future of cochlear implant design. *Advances in Oto-Rhino-Laryngology*. https://doi.org/10.1159/000485540

Paff, M., Loh, A., Sarica, C., Lozano, A. M., Fasano, A. (2020) Update on current technologies for deep brain stimulation in parkinson's disease. Journal of Movement Disorders. https://doi.org/10.14802/jmd.20052

Perceval, G., Martin, A. K., Copland, D. A., Laine, M., & Meinzer, M. (2017). High-definition tDCS of the temporo-parietal cortex enhances access to newly learned words. *Scientific Reports*. https://doi.org/10.1038/s41598-017-17279-0

Puleo, C., & Cotero, V. (2020). Noninvasive neuromodulation of peripheral nerve pathways using ultrasound and its current therapeutic implications. *Cold Spring Harbor Perspectives in Medicine*. https://doi.org/10.1101/cshperspect.a034215

Quadri, S. A., Waqas, M., Khan, I., Khan, M. A., Suriya, S. S., Farooqui, M., & Fiani, B. (2018). High-intensity focused ultrasound: Past, present, and future in neurosurgery. *Neurosurgical Focus*. https://doi.org/10.3171/2017.11.FOCUS17610

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., Carpenter, L. L., Cincotta, M., Chen, R., Daskalakis, J. D., Di Lazzaro, V., Fox, M. D., George, M. S., Gilbert, D., Kimiskidis, V. K., Koch, G., Ilmoniemi, R. J., Pascal Lefaucheur, J., Leocani, L., … Hallett, M. (2020). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. In *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2020.10.003

Siegfried, J., Lippitz, B. (1994) Bilateral chronic electrostimulation of ventroposterolateral pallidum: A new therapeutic approach for alleviating all parkinsonian symptoms. Neurosurgery. https://doi.org/ 10.1227/00006123-199412000-00016

Stagg, C. J., Antal, A., & Nitsche, M. A. (2018). Physiology of Transcranial Direct Current Stimulation. In *Journal of ECT*. https://doi.org/10.1097/YCT.0000000000000510Sun, Y., Agostini, N. B., Dong, S., & Kaeli, D. (2019). Summarizing CPU and GPU design trends with product data. In *arXiv*.

Thomas, C., Huang, Y., Faria, P. C., & Datta, A. (2019). High-resolution head model of transcranial direct current stimulation: A labeling analysis. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*. https://doi.org/10.1109/EMBC.2019.8857181

Tremblay, S., Rogasch, N. C., Premoli, I., Blumberger, D. M., Casarotto, S., Chen, R., Di Lazzaro, V., Farzan, F., Ferrarelli, F., Fitzgerald, P. B., Hui, J., Ilmoniemi, R. J., Kimiskidis, V. K., Kugiumtzis, D., Lioumis, P., Pascual-Leone, A., Pellicciari, M. C., Rajji, T., Thut, G., … Daskalakis, Z. J. (2019). Clinical utility and prospective of TMS–EEG. In *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2019.01.001

Urban, A., Dussaux, C., Martel, G., Brunner, C., Mace, E., Montaldo, G. (2015) Real-time imaging of brain activity in freely moving rats using functional ultrasound. Nature Methods. https://doi.org/10.1038/nmeth.3482

Vedam-Mai, V., Rodgers, C., Gureck, A., Vincent, M., Ippolito, G., Elkouzi, A., Yachnis, A. T., Foote, K. D., & Okun, M. S. (2018). Deep Brain Stimulation associated gliosis: A post-mortem study. *Parkinsonism and Related Disorders*. https://doi.org/10.1016/j.parkreldis.2018.04.009

Vöröslakos, M., Takeuchi, Y., Brinyiczki, K., Zombori, T., Oliva, A., Fernández-Ruiz, A., Kozák, G., Kincses, Z. T., Iványi, B., Buzsáki, G., & Berényi, A. (2018). Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nature Communications*. https://doi.org/10.1038/s41467-018-02928-3

Yap, J. Y. Y., Keatch, C., Lambert, E., Woods, W., Stoddart, P. R., & Kameneva, T. (2020). Critical Review of Transcutaneous Vagus Nerve Stimulation: Challenges for Translation to Clinical Practice. In *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2020.00284

Zanos, S. (2019). Closed-loop neuromodulation in physiological and translational research. *Cold Spring Harbor Perspectives in Medicine*. https://doi.org/10.1101/cshperspect.a034314

Ziemann, U. (2017). Thirty years of transcranial magnetic stimulation: where do we stand? In *Experimental Brain Research*. https://doi.org/10.1007/s00221-016-4865-4

Proactive portfolio management

This section describes the EIC proactive management as applied to this Pathfinder Challenge. It starts by building the portfolios; i.e. by allocating projects into portfolios (a). Based on the composition of each portfolio, the objectives of each portfolio will then be refined and laid out in the form of a portfolio roadmap (b). Throughout the execution of the projects, portfolio members will benefit from portfolio-level activities and from the access to the EIC Market Place (c).

a. Allocation of projects into the Challenge Portfolio

This section provides the Challenge specific elements of the way in which the evaluation results in a coherent Challenge Portfolio. It should be read in conjunction with the overall evaluation process as described in the EIC Work Programme text (Appendix 3).This section provides guidance to proposers on how to align their proposal with the architecture of the Challenge Portfolio as envisaged by the Programme Manager.

At the second evaluation step, the evaluation committee, chaired by the Programme Manager, builds a consistent Challenge portfolio, i.e. a set of projects which contribute to the same EIC Pathfinder Challenge. In order to do so, the evaluation committee will first allocate proposals into categories. These categories define the overall architecture of the targeted portfolio.

For this specific Challenge, the evaluation committee will consider the following categories:

- Sub-challenge being addressed (1 or 2).
- Likelihood of take up by clinicians and patients.
- Time-frame to reach clinical practise.
- Medical indications being addressed.
- Barriers being addressed (see section 2).

Each proposal will be allocated within each of these categories. For selecting proposals and creating portfolios, the evaluation committee will use this classification and the following considerations:

- Achieving a balanced portfolio in relation to potential for clinical benefit, technological risk and time to patient. Successfully bringing novel technologies and devices to patients is a critical objective of the medical technologies and medical devices programme. This Pathfinder challenge-driven call is key to fulfil this endeavour and therefore the evaluation committee will be addressing the question: what is the combination of proposals that maximises the probability of reaching clinical practice in the foreseeable future?

- Avoiding excessive focus on one clinical indication and favouring a wide coverage of medical needs across the portfolio.
- Targeting the largest possible number of barriers (see Section 2).

The selected proposals, once funded, will be included in the EIC Challenge Portfolio (see Section 4).

The contractual obligations resulting from the participation of a project in a Challenge Portfolio are described in Appendix 1.

b. Portfolio objectives and roadmap

Portfolio Objectives are overarching objectives for the collection of projects in the portfolio, to be achieved by joint activities among the projects' participants. They are set by the Programme Manager, in close discussion with the participants. They will be updated following discussion with beneficiaries, and revised on a regular basis, for instance based on projects' achievements, new technology trends, external inputs (other projects, new calls…), and discussions with stakeholders/communities.

The EIC Programme Manager will propose to the granting authority the Challenge Portfolio's objectives and roadmap, building on:

- the overall objective set out in the relevant call text (see Section 5 – Challenge call text),
- the overall objective of the Pathfinder Challenge (see Section 2)
- other actions selected in consultation with beneficiaries, other interested members of the EIC Community and other third parties.

The initial Portfolio Objectives for this Challenge are the following (others may be added once the portfolio is established, in cooperation with the beneficiaries):

1. Position statement on challenges and opportunities in the field addressed by the portfolios. This will start from the material in this Guide and expand with the expertise gathered in the portfolio. It can take the form of a journal paper, book, presentation, etc.
2. Portfolio benchmarking at end-of-project: systematic documentation of the technological solutions realised by the portfolio and comparison/benchmarking inter-portfolio, intra-portfolio and with other state of the art solutions.
3. Portfolio demonstration: for instance through a joint workshop/event, preferably embedded in a high-profile relevant scientific/professional gathering, demonstrating the concrete technologies and devices developed.

Further objectives, notably technological ones, may be agreed at a later stage with the participants of the projects in the Portfolio.

For this specific Challenge, the roadmap to reach the Portfolio objectives will be co-designed and agreed between the Programme Manager and the participants of the projects in the Portfolio, once established.

c. Portfolio activities and EIC Market Place

Portfolio activities are proposed and designed by the EIC Programme Manager in consultation with the beneficiaries, and where appropriate with other interested EIC Community members and other third parties. They aim at developing the cooperation within the EIC Portfolio in order to:

- achieve the objectives of the Portfolio and the objectives of the individual projects,
- enhance research,
- prepare transition to market,
- stimulate business opportunities,
- and strengthen the EIC Community.

Such activities may cover - notably but not only - participation to conferences, workshops or any EIC Portfolio or networking meetings, experience and data sharing, as well as participation in any relevant EIC Business Acceleration Services events.
The responsible Programme Manager will manage the portfolio through actions, he or she sees most fitting to advise the participants in the orientations of their work, or exploring potential synergies with others, including with businesses and start-ups, for mutual benefit.

To enhance cross-fertilization activities, and to stimulate potential innovation, the EIC Programme Manager may request any beneficiary to make available - through the EIC Market Place - information on preliminary findings and results generated by the action, with the aim to probe their potential for further innovation. The EIC Market Place allows the Programme Manager to have an overview of the actions, their preliminary findings and potential links between those, thanks to the underlying Artificial Intelligence tool.

The Programme Manager will accelerate the most promising portfolio projects based on work progress against previously set milestones. To accomplish that, the Programme Manager will make use of EIC tools such as, fast tracking a project to Accelerator (see Appendix 2, Active management section) and a 50K grant that can be used more than once, to the benefit of a beneficiary (see Appendix 4). Regarding the latter, the beneficiary must provide to the Programme Manager convincing and fully documented evidence that the project has arrived at a new, rather unexpected outcome that opens new opportunities and, therefore, new or additional activities are needed.

For this specific Challenge, the Programme Manager is currently planning the following Portfolio Activities (table to remain up-to-date):

Date	Description
Tbd	Portfolio Kick-Off meeting
Tbd	Plenary Portfolio meetings to explore synergies amongst projects
Tbd	

Table 1: Portfolio Activities for the Pathfinder Challenge 'Tools to measure and stimulate activity in brain tissue'.

4. List of projects in this Pathfinder Challenge Portfolio

(to be updated after the portfolio selection)

5. Challenge call text

(extract from
https://eic.ec.europa.eu/system/files/2021-03/EIC%20Work%20Programme%202021.pdf)

Medical devices to measure and stimulate brain activity are emerging as tremendously powerful therapeutic tools that could revolutionise the treatment of brain diseases. Anomalous neuronal electrical signals are present in a wide range of disorders including memory impairment (Alzheimer's), epilepsy, chronic pain, mood disorders, movement disorders (Parkinson's), ischemic cognitive decline (post-heart attack), sensory disorders (hearing loss, tinnitus),cerebrovascular events, aging related neurodegeneration, traumatic brain injury amongst many others.

Unfortunately, existing devices to restore normal patterns of brain activity by stimulation have serious limitations. Invasiveness, limited miniaturisation, poor resolution (with only coarse measurement and stimulation available), limited spatial coverage (not able to monitor or stimulate a sufficient number of neurons) hamper the therapeutic effect or render these solutions unattractive for clinicians and patients.

Yet today's state-of-the art microelectronics and microfabrication are potentially conducive to novel neuro-devices with high levels of miniaturisation, ultra-low power consumption, multi-site sensor/stimulator arrays (linear, planar or 3D with a wealth of geometries) and wireless architectures, leading to lower risk, shorter recovery times and better patient acceptance.

Further, progress can also be achieved by the discovery of new physical principles for activity monitoring (invasive or non-invasive) and activity modulation. These could explore ultrasound, light (optogenetics or otherwise), mechanical stimulation, local release of neuroactive compounds, ionising radiation, etc.

It is the right time to explore these opportunities and develop novel neuro-devices that can be rapidly accepted by clinicians and patients.

Proposals submitted to this call should tackle at least one of the following two challenges:

1. A full device with unique features, e.g. targeting a currently untreated disorder, offering unprecedented miniaturisation, low latency closed-loop monitoring-stimulation feedback (if necessary), ultra-low power consumption, low/moderate invasiveness (e.g. compatible with implantation with endoscopic techniques), high-resolution, sustainable, etc.

or

2. New or nascent physical principles or methodologies that could be the basis for future brain sensing and/or stimulation technologies, with clear and quantifiable

advantages. Focus is on techniques that can offer unprecedented data on brain function or that allow unprecedented modulation of brain activity for therapeutic purposes or brain-computer interfacing.

Specific conditions for this challenge

Proposals targeting a full device are strongly encouraged to establish a plausible work plan to realise by the end of the project at least 1) a working prototype device or instrument and 2) pre-clinical data with proof of therapeutic action.

Proposals targeting the discovery of a new mechanism for monitor and/or stimulate are advised to de-risk the work plan by exploring multiple strategies in parallel, merging competing strategies into a single proposal for cost efficiencies and increased likelihood of success.

Consortia considering both targets in a single proposal are advised to carefully analyse whether the high risk inherent to the discovery of new mechanisms or principles could hamper the plausibility of completing a full device hinging on said principles.

All proposals must fully justify the clinical need for the targeted development, and structure the work plan accordingly, towards credible future transition to market. Proposals need to consider the cost-benefit of the targeted technology and demonstrate that the outcome will be acceptable by clinicians and patients.

The gender dimension in research content should be taken into account, where relevant.