Advanced Research + Invention Agency ARIA

Programme Thesis

Massively Scalable Neurotechnologies for Human Health

v0.3

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CONTEXT

This document presents the core thesis underpinning a programme that is currently in development at ARIA. We share an early formulation and invite you to provide feedback to help us refine our thinking.

This is not a funding opportunity, but in most cases will lead to one – sign up **here** to learn about any funding opportunities derived or adapted from this programme formulation.

An ARIA programme seeks to unlock a scientific or technical capability that

+ changes the perception of what's possible or valuable
+ has the potential to catalyse massive social and economic returns
+ is unlikely to be achieved without ARIA's intervention.

PROGRAMME THESIS, SIMPLY STATED

An overview of the programme thesis, accessible & simply stated

Neurological and neuropsychiatric disorders are now the leading cause of ill health and disability worldwide[1]. In Europe and the USA alone, their annual economic cost exceeds USD 1.7 trillion[2]. Technologies that can precisely *sense, interpret and modulate pathological neural activity* could potentially functionally cure many brain disorders. However, state-of-the-art treatments typically require complex surgical procedures, restricting access to only the most severely-affected individuals and excluding the vast majority who could benefit from earlier intervention.

This programme aims to break these bottlenecks. We will develop a new class of *brain surgery-free* neurotechnologies that leverage the body's natural pathways to reach the central nervous system without breaching the skull. These new therapies will be *responsive* — capable of monitoring disease progression, reporting biomarkers to the individual or their clinician, and actively modulating brain activity towards a desired, more physiological state. Our North Star is a responsive neurotechnology that can be delivered systemically or minimally invasively, in less than 30 minutes, in an outpatient setting.

Recent advances at the intersection of biological and electrical engineering now make this vision possible. These advances combine the natural ability of certain biological systems to traverse peripheral pathways and access the central nervous system with sophisticated electronic systems capable of sensing, processing, and reporting biological activity. By radically reducing the procedural burden of deploying advanced neurotechnologies, we can unlock earlier intervention in disease, generate real-world data to identify new and more effective therapeutic targets, and expand access to powerful new brain therapies.

This programme thesis is derived from the ARIA Opportunity Space: Scalable Neural Interfaces.

PROGRAMME THESIS, EXPLAINED

A detailed description of the programme thesis, presented for constructive feedback

Why this programme

We are at a pivotal moment where next-generation therapies for complex, severe and prevalent brain disorders are beginning to demonstrate clinical efficacy. Targeted neuromodulation of deep brain structures is showing promise for a range of otherwise intractable conditions[3], including treatment resistant depression[4], refractory epilepsy[5], addiction[6] and even chronic pain[7]. Concurrently, cell and gene therapies are emerging as credible treatment options for neurodegenerative disorders[8,9].

These early signals highlight the vast potential for neurotechnologies. However, they will struggle to scale to the people who need them most. Consider deep brain stimulation for Parkinson's disease — one of the most well established neurotechnology indications. Annual global procedures only account for 0.1% of the people living with Parkinson's disease[10,11]. Even under conservative eligibility assumptions[12], the vast majority of potential beneficiaries remain untreated. If this is the reality for a therapy which has been FDA-approved for over 20 years, with high response rates[13] and a clear reimbursement pathway then emerging therapies

— with more complex procedures, uncertain reimbursement models and untested patient acceptability — may face even greater barriers to adoption.

While there are many reasons advanced neurotechnologies remain limited in adoption[14,15], two stand out as ripe for technological progress: **efficacy** and **procedural burden**. On the **efficacy** side, most treatments are symptom-modifying rather than disease-modifying, and approaches that target underlying pathology would likely achieve greater uptake. This challenge motivates our Precision Neurotechnologies programme[16], which is developing next-generation *circuit-level* interventions. On the **procedural burden** side, the deployment of high-performance neurotechnologies — such as brain computer interfaces, deep brain stimulators or cell and gene therapies — requires complex surgical procedures that impose a series of stacked, multiplicative barriers, fundamentally limiting scalability (see Appendix 1 for further details). Together, these barriers restrict advanced neurotechnologies to only the most severe, treatment-refractory patients, excluding the vast majority who could benefit from earlier, less risky intervention.

The goal of this new *Massively Scalable Neurotechnologies* programme is to develop high-performance neural interfaces that can be delivered **without the need for transcranial surgery** by leveraging the body's natural pathways into the brain — through systemic or minimally invasive routes (Figure 1). These systems will be capable of sophisticated functionality such as continuous monitoring and reporting of disease-relevant biomarkers and closed-loop neuromodulation to restore physiological states.

Closing-the-loop

The brain is inherently a dynamical system[17] and many brain disorders can be understood as disruptions in the regulation of these dynamics — oscillations that are too strong or weak, or feedback loops that no longer stabilise neural activity or behaviour[18]. To treat such conditions, a therapeutic must do more than deliver a fixed dose of stimulation; it must *sense, compute, and respond on disease relevant timescales*. Closed-loop neuromodulation applies the principles of control theory to the brain, using biological error signals to adjust stimulation so as to restore a desired, more physiological state. This control can be implemented with a user or clinician in the loop — in which case the system must report disease-relevant biomarkers and respond to external control signals — or in a fully autonomous, closed-loop manner. We refer to this class of technologies as *responsive neural interfaces*. This responsive approach has already been successfully applied to treat epilepsy[5], Parkinson's disease[19], chronic pain[7], and mood disorders[20].

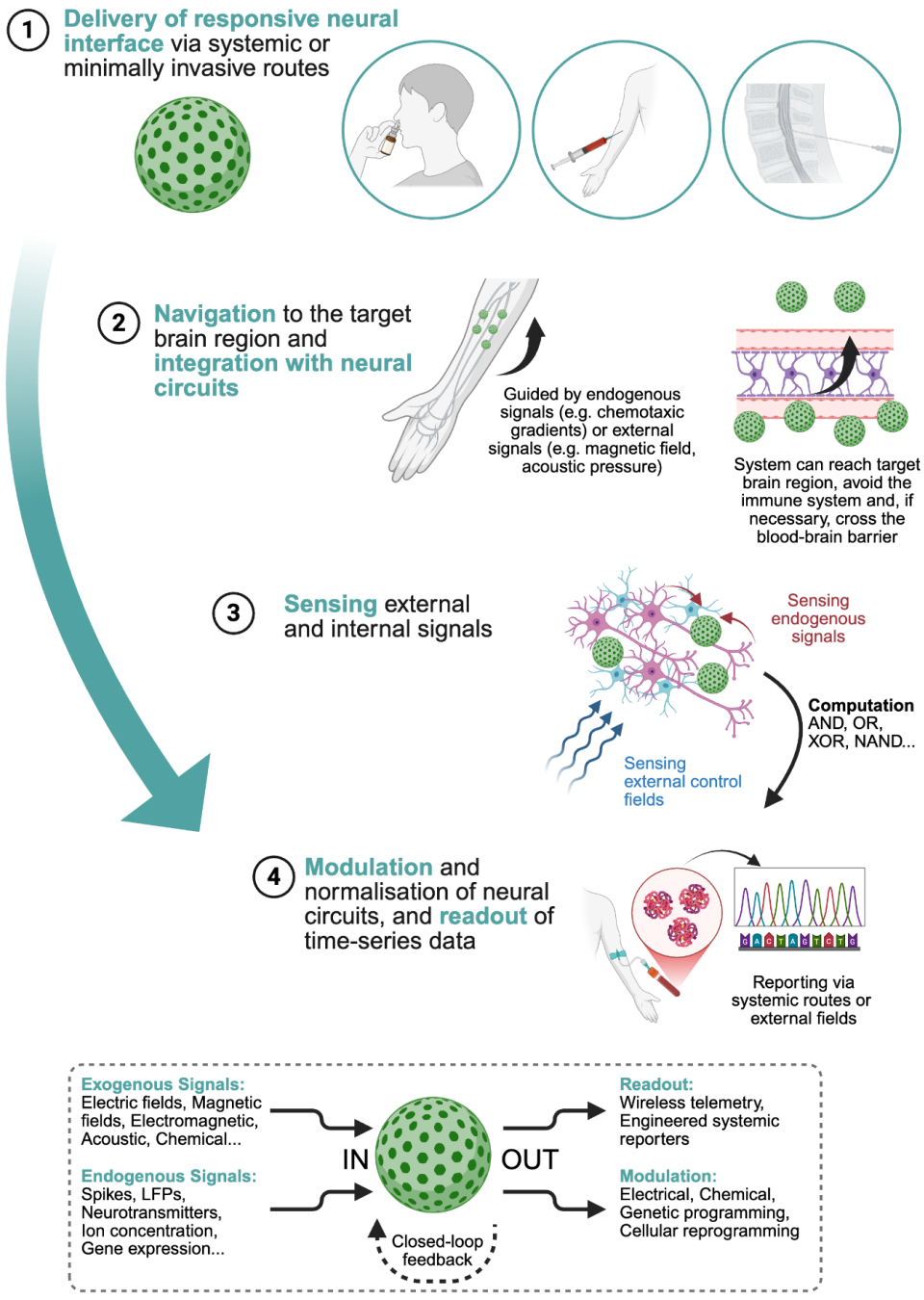

Figure 1. Responsive neural interfaces should be (1) delivered to the body without transcranial surgery, leveraging access points such as direct neural pathways (left), the vasculature (centre) or the CSF (right); (2) navigate to target brain regions; (3) sense endogenous or exogenous signals, and based on these signals (4) modulate and report neural activity. Inset: example signals that may be recorded, modulated or read out by a responsive neural interface.

Our North Star is a responsive neural interface that can be delivered without transcranial surgery. To benefit the greatest number, it should be deployable in an outpatient setting, in

less than 30 minutes, by a broad range of clinical (and potentially non-clinical) staff (see Box 1).

Our theory of change is that by drastically reducing the procedural burden required to deploy high-performance neurotechnologies, we will unlock: (1) **earlier intervention in disease** which has been shown to significantly improve long-term outcomes across a broad array of brain disorders[21–23]; (2) **identification of new therapeutic targets**, as broader clinical deployment generates real-world neural data that cannot be replicated in pre-clinical models, improving our understanding of disease mechanisms and the predictive validity of future interventions[24]; and (3) **significantly increased access**, by enabling outpatient or community-level delivery and reducing dependence on highly specialised urban medical centres.

Box 1 — North Star Goals

Non-transcranial access: Similar to how solving surgical and procedural burden drove wide adoption in cardiac pacemakers[25], systems developed under this programme should reach the brain without the need for transcranial surgery, using systemic delivery or natural access routes such as the vasculature or cerebrospinal fluid. We define 'transcranial surgery' as any surgical procedure that removes or destroys cranial bone.

Clinical efficacy at validated targets: To overcome entrenched barriers to adoption, technologies must demonstrate functional impact (e.g. therapeutic efficacy or readout performance) at least equivalent to, and ideally exceeding, today's best-in-class interventions. This includes targeting clinically validated stimulation targets such as the subthalamic nucleus (Parkinson's disease), anterior nucleus of the thalamus (refractory epilepsy) or subcallosal cingulate (treatment-resistant depression).

Radical simplicity: The procedure should be performed by a range of clinical (and potentially non-clinical) staff, with minimal training, in under 30 minutes, within a standard outpatient or catheterisation setting. Procedure time is defined as the *active procedural duration* required to administer the therapeutic. This excludes anaesthesia induction, patient preparation, post-procedure recovery and time to efficacy. Achieving this level of simplicity is essential to break the bottleneck of limited expertise and centralised surgical infrastructure.

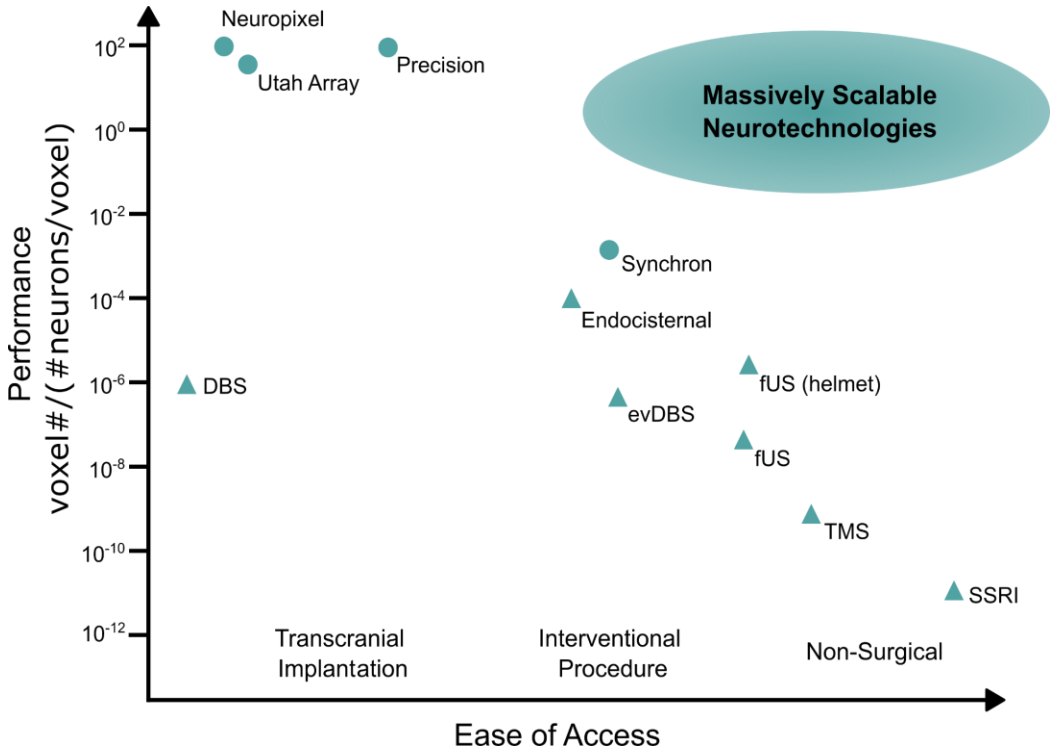

Figure 2. A plot of spatial performance for a variety of current neurotechnologies[1]. Our existing technology paradigm trades performance against ease of access. Massively Scalable Neurotechnologies aim to break this trade-off by developing high performance, responsive neural interfaces that can be delivered without transcranial surgery. Triangle and circular symbols represent modulation and readout respectively.

Why now

Our current paradigm of neurotechnologies typically trades off performance against ease of deployment (Figure 2). We believe a confluence of advances across molecular and cellular biology, nanoscience and bioengineering now makes it possible to create neurotechnologies that can both *scalably access* the central nervous system and deliver *high performance*.

Biology offers unique opportunities for access to the brain. There are several natural pathways to the central nervous system, including the vasculature[26], the cerebrospinal fluid system[27] and direct neural pathways[28]. Certain biological systems, such as cells or AAVs, possess tropisms that enable them to be administered peripherally, cross biological barriers[29] and deliver

[1] Spatial performance is shown for illustration purposes and is not the exclusive focus of the programme. This programme seeks technologies that are performant across various dimensions — e.g. spatial, temporal, circuit, volumetric coverage — towards the ultimate goal of clinical efficacy.

therapeutic payloads[30,31]. These systems can also be engineered to perform sophisticated functions — such as responding to external cues[32,33], regulating pathological neural activity[34] and reporting disease-relevant biomarkers[35]. Both access and performance will be further advanced by AI-driven protein design, improving targeting efficiency and minimising immune responses[15].

In parallel, advances in electronic engineering are enabling sophisticated circuitry at biological length scales — from the cellular-scale (μm)[36] to blood-vessel-scale (sub-mm)[37]. These systems can be delivered to the central nervous system via interventional procedures[38] and wirelessly powered[39] to perform neuromodulation, readout and local computation[40]. Increasingly complex functionalities can also be achieved by self-assembling smaller, less complex, systems *in vivo*[41,42].

It is now possible to combine biological and inorganic systems to create *biohybrids*[43,44] that merge the advantages of both paradigms. These hybrid systems can access the central nervous system via peripheral routes[45], exploit the natural tropism of biological systems to target specific brain regions and cell types[46], and be precisely and remotely modulated[47].

What we expect to fund

This programme aims to establish the foundations for an entirely new paradigm of massively scalable neurotechnologies. We are therefore seeking radically new solutions — rather than incremental improvements of existing approaches — to overcome the bottlenecks of access and functionality. To achieve this, we anticipate funding a diverse portfolio of early-stage technologies across the following technical areas:

+ **Technology Area 1 (TA1) — Access + Function:** Develop responsive neural interfaces that can reliably reach deep brain targets or other clinically validated brain targets, without transcranial surgery.
+ **Technology Area 2 (TA2) — Prototyping + Adoption:** Support a network of 'Neuro-Acceleration Partners' to accelerate development, translation and adoption of technologies developed through this programme.

To achieve the ambitious goals of the programme, we anticipate that project teams will be highly interdisciplinary and drawn from diverse institutions, spanning fields from synthetic biology and molecular neuroscience to nanotechnology and electrical engineering, and including academic groups, start-ups, non-profits, and established industry partners. To support this, we have launched a **teaming platform** ahead of the programme call to connect

researchers and organisations. During the programme, ARIA will support teams in sharing methodologies, validation techniques, and performance benchmarks to accelerate collective progress and ensure that results remain comparable across technical areas.

Technology Area 1 (TA1) — Access + Function

This technical area will form the core technology development activity of the programme, comprising three sub-areas defined by functionality: readout and biomarkers (TA1.1), remote modulation (TA1.2) and closed-loop control (TA1.3). Our central thesis is that delivery is the gating factor for scale: *access to the brain without transcranial surgery must be achieved before advancing performance*. Each sub-area will therefore run in two phases. Phase 1 establishes safe, targeted access to the brain and baseline performance — demonstrating readout, modulation or closed-loop control. Phase 2 builds on this foundation to advance performance (e.g. spatiotemporal resolution) and capabilities (e.g. multiplexed read/write, reprogrammable closed-loop control). In addition, Phase 2 will apply technologies in a disease context to demonstrate pre-clinical therapeutic evidence towards establishing a pathway for clinical translation. See Table 1 for an overview of possible activities.

All projects in TA1 must solve the access challenge — achieving safe, reliable access to the brain without transcranial surgery. Example activities may include, but are not limited to:

+ **Systemic delivery** of engineered cells capable of navigating to the CNS, crossing blood-brain barrier[30], integrating with neural tissue[31] and delivering cargo[47].
+ **Direct neural delivery** of genetic material via peripheral nerves, leveraging engineered viruses capable of trans-synaptic transmission[48].
+ **Intranasal delivery** of biological systems[49] or nanotransducers[50].
+ **Intra-CSF or intravasculature delivery** of magnetically, acoustically or chemically guided bioelectronic devices.
+ **In vivo clearing** of biological barriers to increase access to deep targets[51,52].
+ **Entirely new approaches to access the brain...**

Safety

Throughout the course of the programme teams will have to report critical safety metrics such as peripheral accumulation, toxicity and tissue damage. We are also interested in approaches that incorporate novel safety mechanisms — such as biological off-switches[53] or bioreabsorbable electronics[54] — and delivery strategies that enhance targeting specificity and reduce systemic exposure.

Scope

The following activities are likely to be out of scope for this programme: approaches that rely fundamentally on large-scale or capital-intensive equipment; fully non-invasive systems that do not incorporate any implantable or biological component (though external devices for monitoring, power delivery or control are acceptable); and technologies that are not responsive — for example, those delivering a fixed therapeutic dose rather than one that can be tuned by endogenous or exogenous signals.

	Phase 1	**Phase 2**
Target	Reliable access to the brain in a 30 minute procedure, without transcranial surgery.	Rescue disease state, or equivalent physiological response, in a large-animal model system (e.g. ovine, porcine).
TA1.1 Readout & Biomarkers	Demonstrate readout and reporting of time-series biological data from a well defined brain region.	Achieve advanced performance in e.g. signal fidelity, spatiotemporal resolution, field-of-view. Demonstrate multiplexed readout of multiple biomarkers using systemic or remote readout.
TA1.2 Remote Modulation	Demonstrate user-controlled modulation of neural activity at a validated deep-brain target.	Achieve advanced performance in e.g. efficiency, spatiotemporal resolution, selectivity. Demonstrate multiplexed modulation of distinct neural populations (e.g., excitatory, inhibitory, different brain regions).
TA1.3 Closed-loop Control	Demonstrate closed-loop control of at least one biomarker-based input to restore or maintain a physiological state.	Achieve advanced performance in e.g. latency, spatiotemporal resolution. Achieve programmable closed-loop operation integrating multiple inputs and outputs.
Safety	Report key safety parameters e.g. toxicity, peripheral accumulation, tissue damage.	Validate long-term safety, performance, and biocompatibility. Explore methods for reversibility.

Table 1. Example activities across Phase 1 and Phase 2 of the programme.

To maximise the scientific and translational impact of the programme, all applicants will be asked to address several key areas in their proposals:

+ Describe the intended clinical context — specifying the condition(s) targeted, how the technology could be deployed in outpatient or community settings, and how non-specialist staff could deliver or monitor its use.
+ Based on the target condition, propose relevant performance metrics (e.g. spatial precision, temporal resolution, closed-loop latency).
+ Describe the validation methods to be used, including any ground-truth measurements for verifying performance.
+ Justify the model system to be used and explain its translational relevance to human applications (noting that all ARIA-funded animal research must comply with the 3Rs).

TA1.1 — Readout and biomarkers

This technical area will develop neural interfaces capable of reading out and reporting time-series biological data, such as neural firing patterns, gene expression, or other disease-relevant biomarkers, including biomarkers of integration and survival of the delivered system. We are particularly interested in approaches that can record signals from well defined regions of the brain — rather than integrating signals across the entire brain — and report these signals to external systems[35,55,56]. These capabilities will enable minimally invasive monitoring of disease state and therapeutic response, forming the foundation for closed-loop control in later phases.

TA1.2 — Remote modulation

This technical area will develop neural interfaces capable of remotely modulating neural activity through electrical, chemical, or genetic actuation, including cellular reprogramming[57]. We are particularly interested in approaches that can target and modulate clinically validated deep brain regions, or other clinically validated brain targets. Possible activities may include, but are not limited to, genetically encoded actuators enabling wireless modulation of targeted deep brain circuits[32,33], wireless nanotransducers[40], micron-to-millimeter scale bioelectronic implants capable of delivering localised, programmable stimulation. These systems will provide the actuation layer required for closed-loop control.

TA1.3 — Closed-loop control

This technical area will develop closed-loop neural interfaces that can sense their environment, compare signals to a physiological baseline, and modulate local activity to restore or maintain a desired neural state. These approaches may draw on tools from synthetic biology[58], molecular biology[34] or CMOS engineering[59] to enable programmable control of neural circuits, providing a foundation for dynamic, self-regulating therapies.

TA2 — Prototyping + Adoption

To accelerate the translation and deployment of technologies developed through this programme, ARIA will launch a broad call for Neuro-Acceleration Partners — specialist organisations that can collaborate with project teams to provide targeted technical and translational support.

As Phase 1 requires rapid technical progress, a first call, launched in conjunction with TA1, will identify partners with capabilities in rapid prototyping, electronics and mechanical design, and novel models for safety testing — helping teams to iterate rapidly and accelerate R&D. We also believe that AI will play a crucial role in scientific research and are therefore soliciting potential AI partners to work across funded teams to accelerate critical parts of their technology development pipeline. This may include supporting TA1 teams with AI assisted biological or materials engineering, *in silico* safety testing, biomarker analysis or novel closed-loop control strategies.

Phase 2 will focus on translation. At the time of the Phase 2 transition, ARIA will launch a second call to identify partners who can support all aspects of the translational pipeline, enabling the most promising approaches from Phase 1 to progress efficiently toward real-world deployment. This call will build on learnings from Phase 1 and may include partners providing regulatory support, target product profile development, lived-experience engagement, GMP manufacturing, and preclinical GLP testing. We anticipate a diverse set of collaborators, ranging from industry partners to charities.

Together, these partnerships will create a continuum of support — from early technical acceleration to translational readiness — maximising the programme's impact and reducing the time from discovery to the clinic.

What we are still trying to figure out

+ We anticipate funding a diverse portfolio of early-stage technologies. How can we define a unified framework of metrics for "access" that allows us to rigorously compare performance and track progress longitudinally, despite the differences in the underlying physical and biological mechanisms?
+ We have currently scoped Phase 1 as a two-year sprint to establish access and baseline function. Given the complex design-build-test cycles inherent to biological engineering, is this realistic? Would extending Phase 1 to three years significantly increase the probability of success?
+ What is a realistic budget range for a Phase 1 project, particularly given the need for interdisciplinary teams, *in vivo* testing, and iterative prototyping?
+ What specific shared capabilities or tools (e.g., standardised validation pipelines, specific manufacturing capabilities, or computational models) would provide the highest leverage to accelerate the entire cohort simultaneously?
+ We need to demonstrate delivery in a system that translates to humans. What is the right model system? Is it valuable to validate non-transcranial access in rodents, or are large-animal models (or sophisticated *in vitro* models) strictly necessary from Day 1 to prove the core thesis?

ENGAGE

*Our next step is to launch a funding opportunity derived or adapted from this programme formulation. Click **here** to register your interest, or to provide feedback that can help improve this programme thesis.*

Appendix 1: Procedural Burden Factors

This appendix outlines the key procedural factors that currently limit the scalability of advanced neurotechnologies. Each represents a compounding barrier — in workforce, infrastructure, complexity and risk — that collectively constrains access and slows the rate at which effective therapies can reach patients.

+ **Human capital:** The number of clinicians who can perform these procedures is limited and increasing only modestly[60]. Solving the human capital challenge has a decadal time constant.
+ **Infrastructure:** The number of locations where these procedures can be performed is also limited and the infrastructure is expensive to build[61] and operate[62]. This limits access to a handful of urban medical centres, creating geographic and economic inequities where treatment is simply unavailable[63].
+ **Procedural complexity:** The deployment of advanced neurotechnologies often involves multi-step, technically demanding procedures requiring complex patient selection, imaging and navigation[64]. Each layer of manual intervention adds time, cost, and potential failure points, creating a cumulative barrier to throughput and large-scale deployment.
+ **Surgical risk:** Breaching the dura mater and implanting a medical device carries a non-negligible risk of adverse events[65]. This can give rise to clinician and patient hesitancy[66] and, at a population level, would place a further burden on already stretched healthcare systems.

SOURCES

References cited in this document.

1. GBD 2021 Nervous System Disorders Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol.* **23**, 344–381 (2024).
2. Feigin, V. L. The evolution of neuroepidemiology: Marking the 40-year anniversary of publishing studies on epidemiology of neurological disorders. *Neuroepidemiology* **56**, 2–3 (2022).
3. Harmsen, I. E. *et al.* Clinical trials for deep brain stimulation: Current state of affairs. *Brain Stimul.* **13**, 378–385 (2020).
4. Alagapan, S. *et al.* Cingulate dynamics track depression recovery with deep brain stimulation. *Nature* **622**, 130–138 (2023).

5. Nair, D. R. *et al*. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. *Neurology* **95**, e1244–e1256 (2020).
6. Bach, P. *et al*. Deep brain stimulation of the nucleus accumbens in treatment-resistant alcohol use disorder: a double-blind randomized controlled multi-center trial. *Transl. Psychiatry* **13**, 49 (2023).
7. Shirvalkar, P. *et al*. Personalized, closed-loop deep brain stimulation for chronic pain. *medRxiv* (2025).
8. Dolgin, E. Huntington's disease treated for first time using gene therapy. *Nature* **646**, 15 (2025).
9. Fraint, A. *et al*. Safety, tolerability, and efficacy of intracranial delivery of autologous iPSC-derived dopaminergic precursors in moderate to advanced Parkinson's Disease. *Parkinsonism Relat. Disord*. **134**, 107630 (2025).
10. Lee, D. J., Lozano, C. S., Dallapiazza, R. F. & Lozano, A. M. Current and future directions of deep brain stimulation for neurological and psychiatric disorders: JNSPG 75th Anniversary Invited Review Article. *J. Neurosurg*. **131**, 333–342 (2019).
11. Su, D. *et al*. Projections for prevalence of Parkinson's disease and its driving factors in 195 countries and territories to 2050: modelling study of Global Burden of Disease Study 2021. *BMJ* **388**, e080952 (2025).
12. Stein, A. & Gericke, C. A. PND23 treatment gaps in deep brain stimulation for patients with Parkinson's disease: A comparative analysis of nine high-income countries. *Value Health Reg. Issues* **22**, S78–S79 (2020).
13. Deuschl, G. *et al*. A randomized trial of deep-brain stimulation for Parkinson's disease. *N. Engl. J. Med*. **355**, 896–908 (2006).
14. Lange, M. *et al*. Underutilization of deep brain stimulation for Parkinson's disease? A survey on possible clinical reasons. *Acta Neurochir. (Wien)* **159**, 771–778 (2017).
15. Borton, D. A., Dawes, H. E., Worrell, G. A., Starr, P. A. & Denison, T. J. Developing collaborative platforms to advance neurotechnology and its translation. *Neuron* **108**, 286–301 (2020).
16. Precision Neurotechnologies. https://www.aria.org.uk/opportunity-spaces/scalable-neural-interfaces/precision-neurotechnologies.
17. Breakspear, M. Dynamic models of large-scale brain activity. *Nat. Neurosci*. **20**, 340–352 (2017).
18. Uhlhaas, P. J. & Singer, W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron* **52**, 155–168 (2006).
19. Bronte-Stewart, H. M. *et al*. Long-term personalized adaptive deep brain stimulation in Parkinson disease: A nonrandomized clinical trial: A nonrandomized clinical trial. *JAMA Neurol*. (2025) doi:10.1001/jamaneurol.2025.2781.
20. Scangos, K. W. *et al*. Closed-loop neuromodulation in an individual with treatment-resistant

depression. *Nat. Med.* **27**, 1696–1700 (2021).

21. Penttilä, M., Jääskeläinen, E., Hirvonen, N., Isohanni, M. & Miettunen, J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br. J. Psychiatry* **205**, 88–94 (2014).
22. Eriksson, M. H. *et al.* Long-term neuropsychological trajectories in children with epilepsy: does surgery halt decline? *Brain* **147**, 2791–2802 (2024).
23. Schuepbach, W. M. M. *et al.* Neurostimulation for Parkinson's disease with early motor complications. *N. Engl. J. Med.* **368**, 610–622 (2013).
24. Scannell, J. W. *et al.* Predictive validity in drug discovery: what it is, why it matters and how to improve it. *Nat. Rev. Drug Discov.* **21**, 915–931 (2022).
25. Jeffrey, K. & Parsonnet, V. Cardiac pacing, 1960-1985: a quarter century of medical and industrial innovation: A quarter century of medical and industrial innovation. *Circulation* **97**, 1978–1991 (1998).
26. Neudorfer, C. *et al.* Endovascular deep brain stimulation: Investigating the relationship between vascular structures and deep brain stimulation targets. *Brain Stimul.* **13**, 1668–1677 (2020).
27. Wichmann, T. O., Damkier, H. H. & Pedersen, M. A brief overview of the cerebrospinal fluid system and its implications for brain and spinal cord diseases. *Front. Hum. Neurosci.* **15**, 737217 (2021).
28. Lochhead, J. J. & Thorne, R. G. Intranasal delivery of biologics to the central nervous system. *Adv. Drug Deliv. Rev.* **64**, 614–628 (2012).
29. Chuapoco, M. R. *et al.* Adeno-associated viral vectors for functional intravenous gene transfer throughout the non-human primate brain. *Nat. Nanotechnol.* **18**, 1241–1251 (2023).
30. Shields, C. W., 4th *et al.* Cellular backpacks for macrophage immunotherapy. *Sci. Adv.* **6**, eaaz6579 (2020).
31. Chadarevian, J. P. *et al.* Harnessing human iPSC-microglia for CNS-wide delivery of disease-modifying proteins. *Cell Stem Cell* **32**, 914–934.e8 (2025).
32. Zhao, L. *et al.* Human TRPV4 engineering yields an ultrasound-sensitive actuator for sonogenetics. *Biophysics* (2024).
33. Abrahams, G. *et al.* Quantum Spin Resonance in Engineered Magneto-Sensitive Fluorescent Proteins Enables Multi-Modal Sensing in Living Cells. *bioRxiv* (2024).
34. Qiu, Y. *et al.* On-demand cell-autonomous gene therapy for brain circuit disorders. *Science* **378**, 523–532 (2022).
35. Lee, S. *et al.* Engineered serum markers for non-invasive monitoring of gene expression in the brain. *Nat. Biotechnol.* **42**, 1717–1725 (2024).
36. Lee, J. *et al.* Neural recording and stimulation using wireless networks of microimplants. *Nat. Electron.* **4**, 604–614 (2021).

37. Zhang, Y. *et al*. Millimetre-scale bioresorbable optoelectronic systems for electrotherapy. *Nature* **640**, 77–86 (2025).
38. Chen, J. C. *et al*. Endocisternal interfaces for minimally invasive neural stimulation and recording of the brain and spinal cord. *Nat. Biomed. Eng.* **9**, 896–904 (2025).
39. Nair, V. *et al*. Miniature battery-free bioelectronics. *Science* **382**, eabn4732 (2023).
40. Seo, D. *et al*. Wireless recording in the peripheral nervous system with ultrasonic neural dust. *Neuron* **91**, 529–539 (2016).
41. Davoodi, E. *et al*. Imaging-guided deep tissue in vivo sound printing. *Science* **388**, 616–623 (2025).
42. Zhang, Y., Tan, C. M. J., Toepfer, C. N., Lu, X. & Bayley, H. Microscale droplet assembly enables biocompatible multifunctional modular iontronics. *Science* **386**, 1024–1030 (2024).
43. Boufidis, D., Garg, R., Angelopoulos, E., Cullen, D. K. & Vitale, F. Bio-inspired electronics: Soft, biohybrid, and 'living' neural interfaces. *Nat. Commun.* **16**, 1861 (2025).
44. Rivnay, J. *et al*. Integrating bioelectronics with cell-based synthetic biology. *Nat. Rev. Bioeng.* **3**, 317–332 (2025).
45. Zhang, H. *et al*. Dual-responsive biohybrid neutrobots for active target delivery. *Sci. Robot.* **6**, (2021).
46. Nagao, K. *et al*. Adeno-associated viruses escort nanomaterials to specific cells and tissues. *bioRxiv* (2025).
47. Yadav, S. *et al*. A nonsurgical brain implant enabled through a cell-electronics hybrid for focal neuromodulation. *Nat. Biotechnol.* 1–11 (2025).
48. Miyamichi, K. *et al*. Cortical representations of olfactory input by trans-synaptic tracing. *Nature* **472**, 191–196 (2011).
49. Jeon, S. *et al*. A magnetically powered stem cell-based microrobot for minimally invasive stem cell delivery via the intranasal pathway in a mouse brain. *Adv. Healthc. Mater.* **10**, e2100801 (2021).
50. Pardo, M. *et al*. Size-dependent intranasal administration of magnetoelectric nanoparticles for targeted brain localization. *Nanomedicine* **32**, 102337 (2021).
51. Wang, Z. *et al*. Acoustic Transparency Enabling Functional Ultrasound Imaging Through Mouse and Human Skulls. *bioRxiv* (2025).
52. Ou, Z. *et al*. Achieving optical transparency in live animals with absorbing molecules. *Science* **385**, eadm6869 (2024).
53. Lu, L., Xie, M., Yang, B., Zhao, W.-B. & Cao, J. Enhancing the safety of CAR-T cell therapy: Synthetic genetic switch for spatiotemporal control. *Sci. Adv.* **10**, eadj6251 (2024).
54. Lee, D.-M. *et al*. An on-demand bioresorbable neurostimulator. *Nat Commun* **14**, (2023).
55. Schmidt, F. *et al*. Noninvasive assessment of gut function using transcriptional recording sentinel

cells. *Science* **376**, eabm6038 (2022).

56. Jin, Z. *et al*. Ultrasonic reporters of calcium for deep tissue imaging of cellular signals. *bioRxiv* (2023).
57. Marichal, N. *et al*. Reprogramming astroglia into neurons with hallmarks of fast-spiking parvalbumin-positive interneurons by phospho-site-deficient Ascl1. *Sci. Adv.* **10**, eadl5935 (2024).
58. Stefanov, B.-A. & Fussenegger, M. Biomarker-driven feedback control of synthetic biology systems for next-generation personalized medicine. *Front. Bioeng. Biotechnol.* **10**, 986210 (2022).
59. Qu, J. *et al*. Multifunctional hydrogel electronics for closed-loop antiepileptic treatment. *Sci. Adv.* **10**, eadq9207 (2024).
60. Sinha, S. *et al*. Workforce planning in neurosurgery. *Br. J. Neurosurg.* **34**, 3–8 (2020).
61. Rosen, E. Operating Rooms Go Under the Knife. *The New York Times* (2021).
62. Childers, C. P. & Maggard-Gibbons, M. Understanding costs of care in the operating room. *JAMA Surg.* **153**, e176233 (2018).
63. Kountcheva, K. 'Huge and unjust disparities' across NHS neurology services. *Epilepsy Action* https://www.epilepsy.org.uk/news/huge-and-unjust-disparities-across-nhs-neurology-services (2024).
64. Wagle Shukla, A., Bange, M. & Muthuraman, M. Patient, target, device, and program selection for DBS in Parkinson's disease: advancing toward precision care. *NPJ Parkinsons Dis.* **11**, 195 (2025).
65. Bullard, A. J., Hutchison, B. C., Lee, J., Chestek, C. A. & Patil, P. G. Estimating risk for future intracranial, fully implanted, modular neuroprosthetic systems: A systematic review of hardware complications in clinical deep brain stimulation and experimental human intracortical arrays. *Neuromodulation* **23**, 411–426 (2020).
66. Atkinson-Clement, C., Junor, A. & Kaiser, M. Neuromodulation perception by the general public. *Sci. Rep.* **15**, 5584 (2025).
67. Figure 1 Created in BioRender.com