SHiNE

SELECTIVE HARNESSING OF INTRINSIC NEUROPLASTICITY ENGINEERING

Source: DARPA | Artist-directed image with AI assistance

Selective Harnessing of Intrinsic Neuroplasticity Engineering (SHINE)

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Clarification

If there is any discrepancy between what is presented here and the SHINE Disruption Opportunity (DO) Solicitation, the DO Solicitation takes precedence.

- Proposals will only be evaluated in accordance with the instructions provided in the DO Solicitation. Review the DO Solicitation carefully prior to submitting your proposal.
- Examples in this briefing (e.g., technologies, use cases) are chosen for ease of illustration only and do not constitute endorsement of any particular approach.

Today rewiring the brain to restore function is invasive

Current state-of-the-art treatments for brain lesions, such as those associated with severe PTSD or epilepsy, rely on invasive surgical intervention to “rewire” connections

Surgery shows potential for treating post-traumatic stress disorder

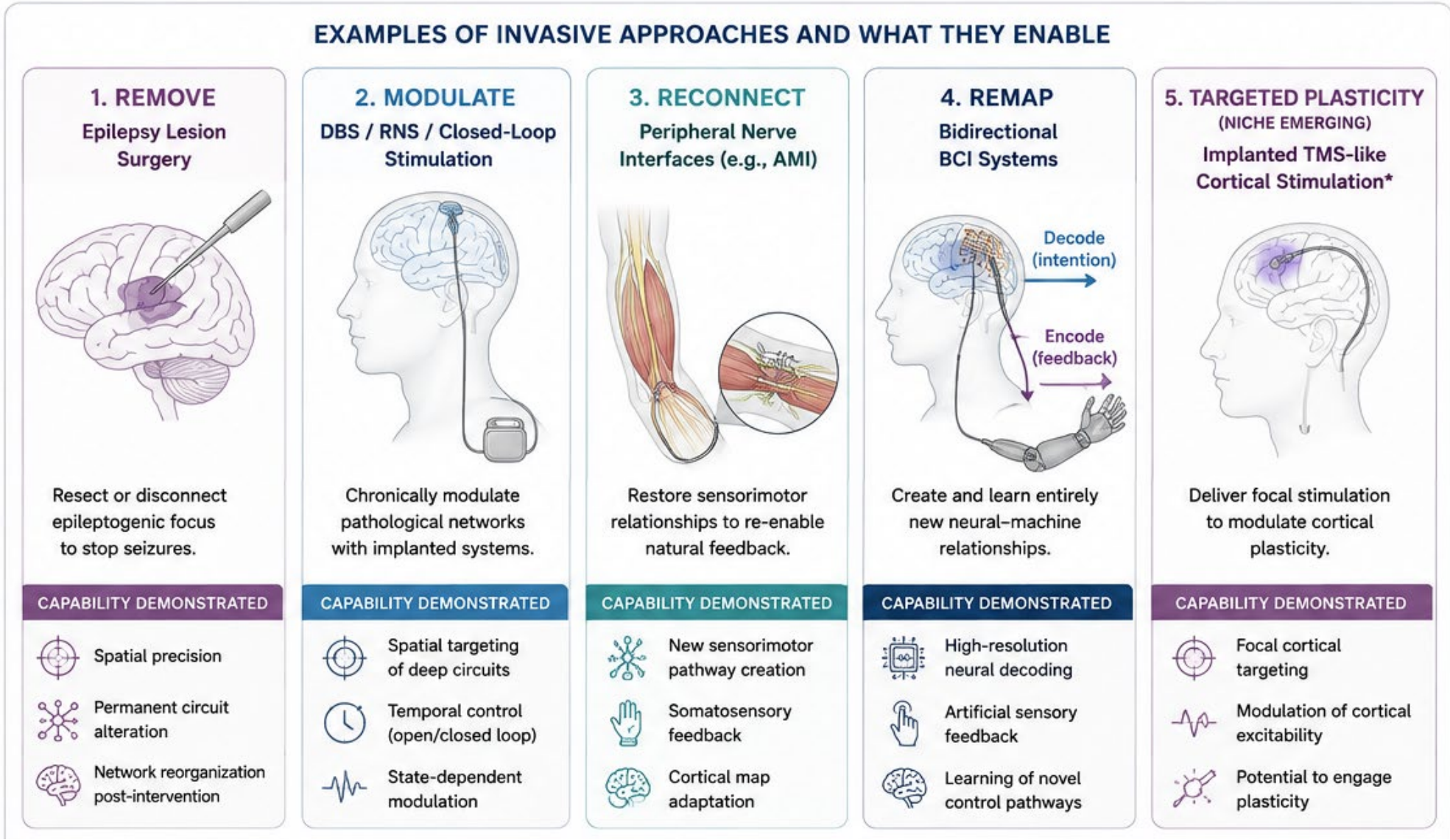
By Neurosurgery News and Brian • April 4, 2021

Jon T. Willie MD PhD after a laser ablation surgery to treat PTSD

Surgical procedures, while effective, carry significant risks, require long recovery times, and are not accessible to all patients

PTSD: Post-Traumatic Stress Disorder

Decoupling invasiveness from precision



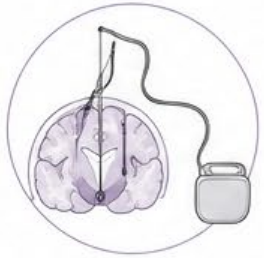
AMI: agonist-antagonist myoneural interface
BCI: brain-computer interface
DBS: deep brain stimulation
RNS: responsive neural stimulation
TMS: transcranial magnetic stimulation

Source: DARPA | Artist-directed image with AI assistance

From regional to circuit-level targeted interventions

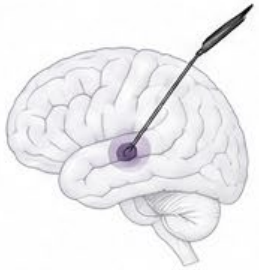
CURRENT INVASIVE METHODS

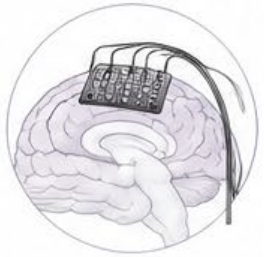
Highly precise, often single-site approaches



DBS / Stereotactic Stimulation

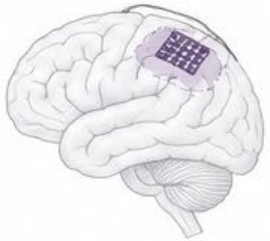
Millimeter precision targeting of a single nucleus or node.

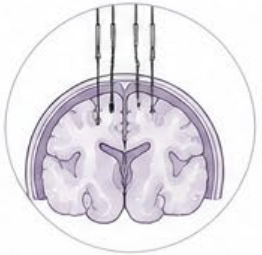




Cortical Stimulation

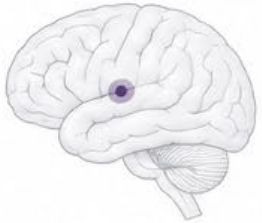
Precise targeting of a small cortical area or column.





Intracranial Sensing

Local recording and stimulation at high spatial resolution.



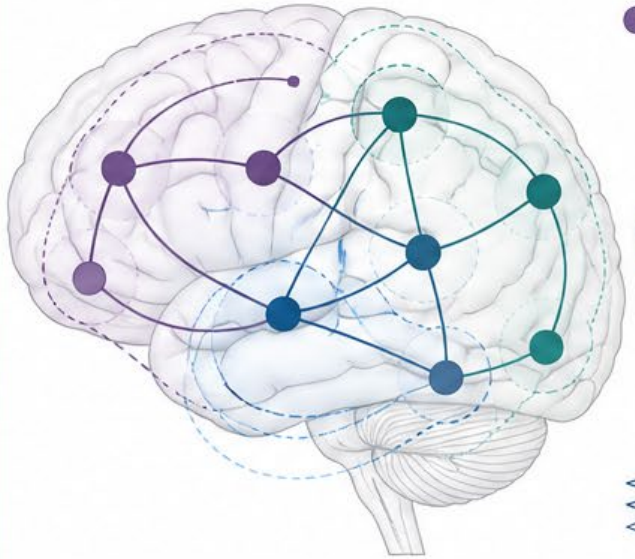
EXCEPTIONAL PRECISION.

But often too narrow for distributed psychiatric circuits.

Need the ability to engage entire circuits—not just single points.

SHINE VISION

Selective priming of distributed circuits



Circuit-Level Selectivity

Engage networks of functionally connected regions.

Temporal Control

Prime circuits during behaviorally relevant or state-dependent windows.

Depth & Type Control

Target the right cell types and layers to shape the right plasticity mechanisms.

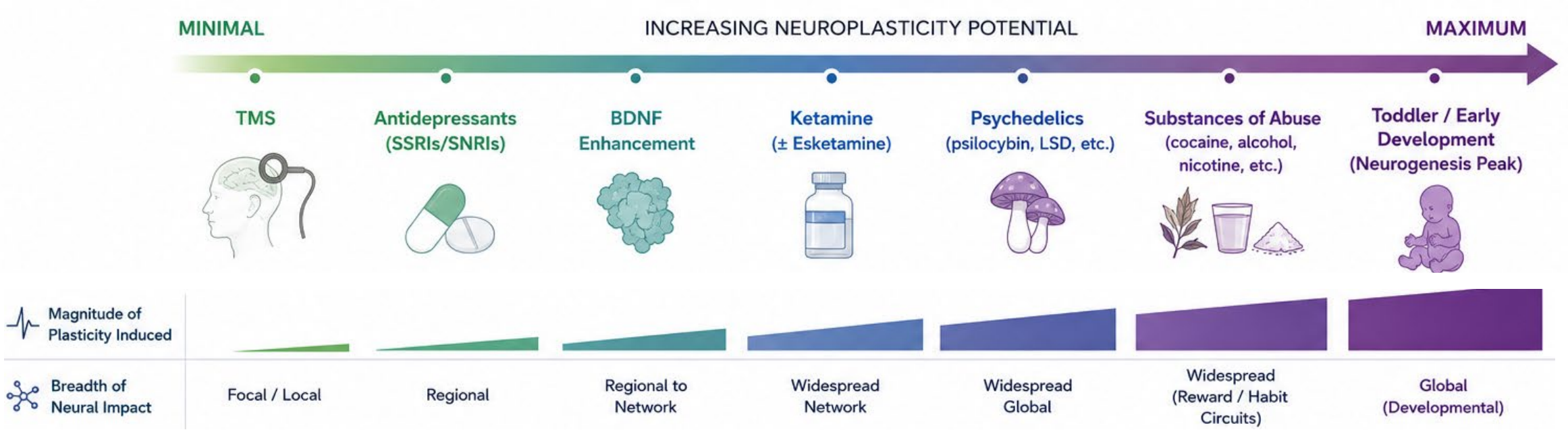
NUANCED. SCALABLE. PURPOSEFUL.

Enable the right circuits to change—when and how we intend.

DBS: deep brain stimulation

Source: DARPA | Artist-directed image with AI assistance

Learning from the spectrum of neuroplasticity



Sources:
Hensch, Takao K. Nature Reviews Neuroscience, November 2005
Nardou et al. Nature, June 2023
DARPA | Artist-directed image with AI assistance

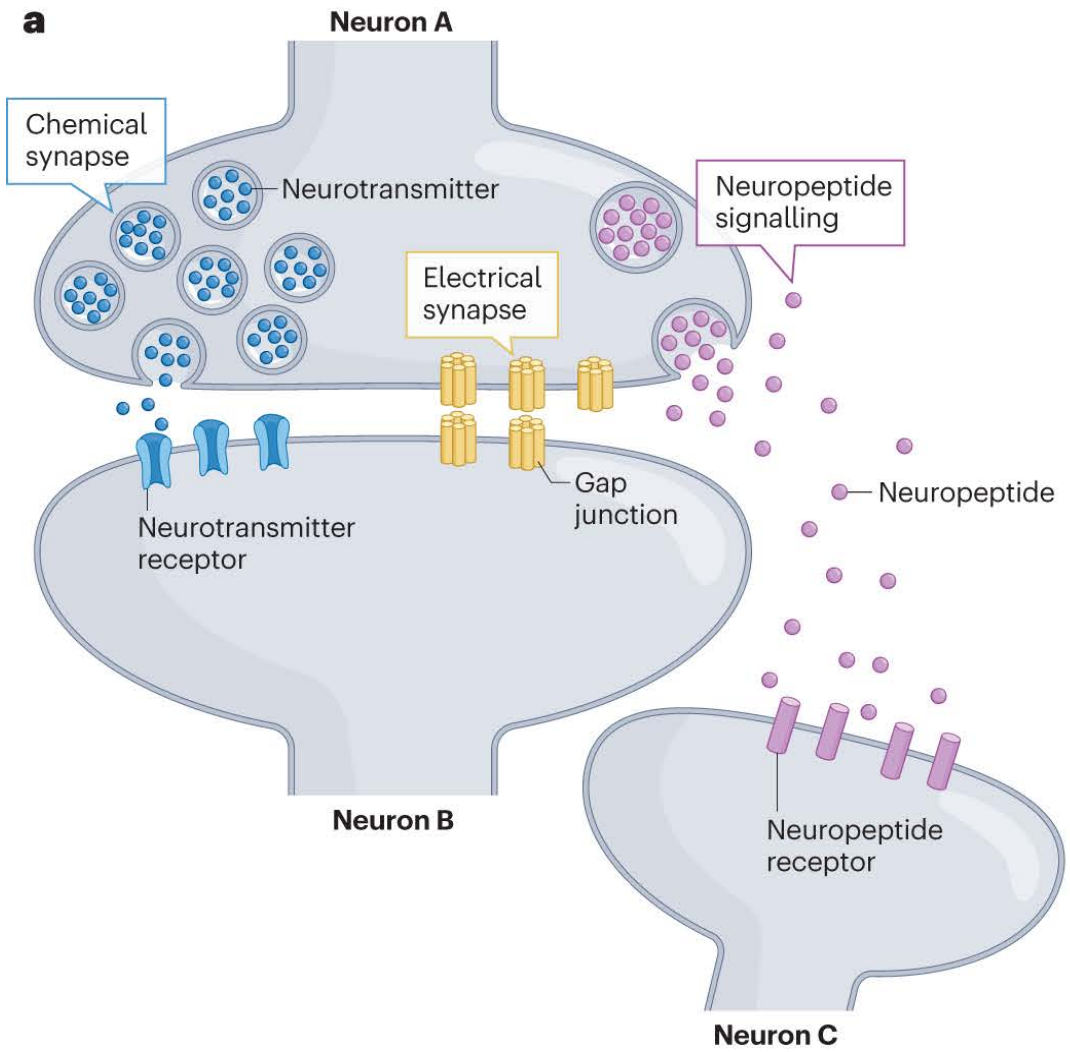
BDNF: brain-derived neurotrophic factor (BDNF)
LSD: Lysergic acid diethylamide
SNRIs: serotonin and norepinephrine reuptake inhibitors (SNRIs)
SSRIs: selective serotonin reuptake inhibitors
TMS: transcranial magnetic stimulation

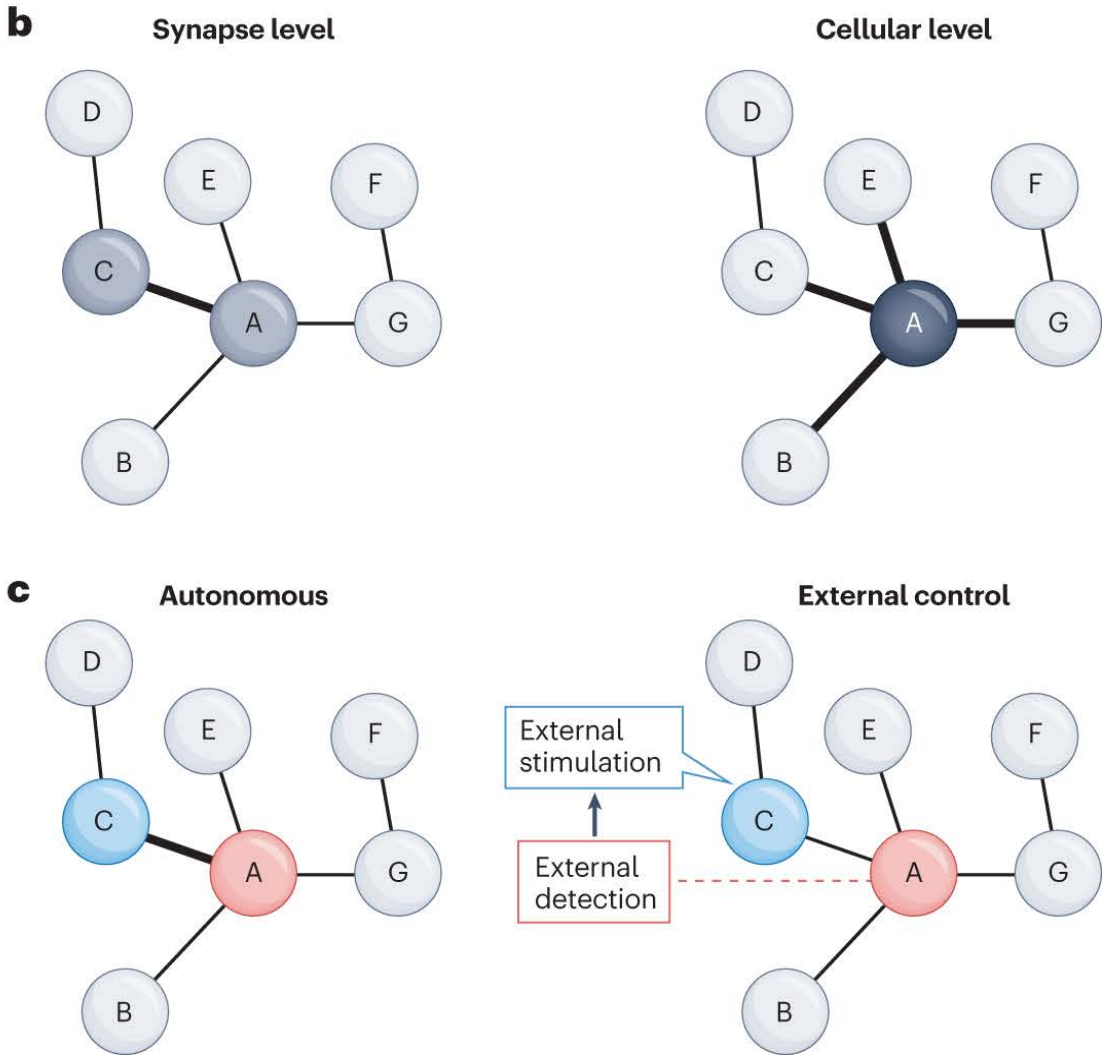
Spatially and temporally controlling a neuroplasticity for an engineered response

Can we control where and how this neuroplastic response occurs?

If so, we can start to control exactly what it accomplishes and achieve a much greater degree of synaptic rewiring than current methods allow.

Multileveled neuroplasticity approach tailored to the target





Source: Rabinowitch, Ithai. Nature, January 2024

The technical approach: dual-track framework

Common Goal: Determine if adaptive neuroplasticity can be induced with sufficient selectivity to preferentially modify intended neural substrates while limiting off-target remodeling

Track A: Accelerated Translation

Designed for mature interventions possessing a near-term, credible pathway toward human application. Focuses on clinically validated devices, physical modalities, or drug-device combinations.

- ✓ May leverage approaches with existing human safety data
- ✓ Evaluated in clinical populations or translationally relevant animal models

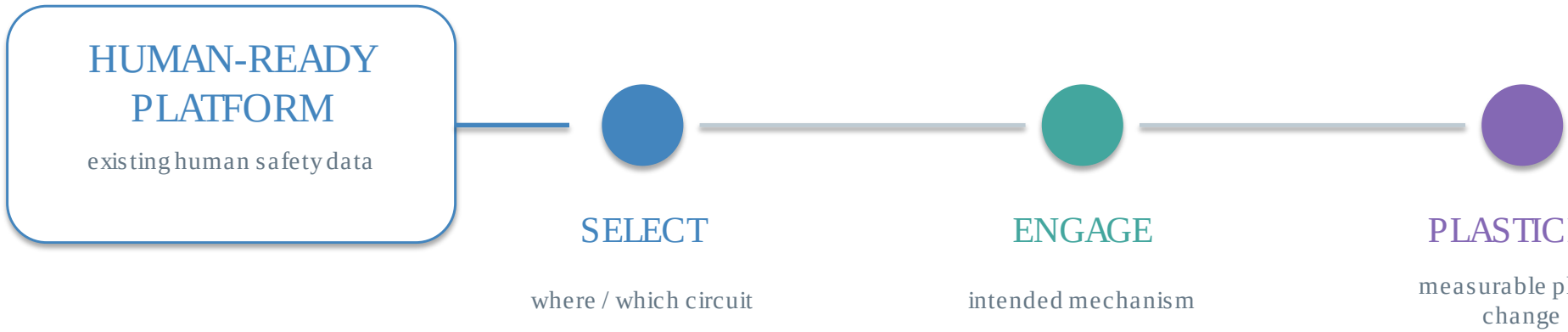
Track B: Foundational Technology Development

Designed for novel biological mechanisms establishing a de novo, targeted pathway toward network precision. Focuses on engineered biologics, programmable biomaterials, or cellular-scale platforms.

- ✓ Must leverage fundamentally novel approaches
- ✓ Evaluated in advanced in vitro architectures or early-stage preclinical animal models

*Each proposal must address either Track A or Track B. Proposers wishing to propose to both Tracks must do so in separate, independent submissions.

Track A: accelerated translation



TRACK A MAY CULMINATE IN:

HUMAN STUDY

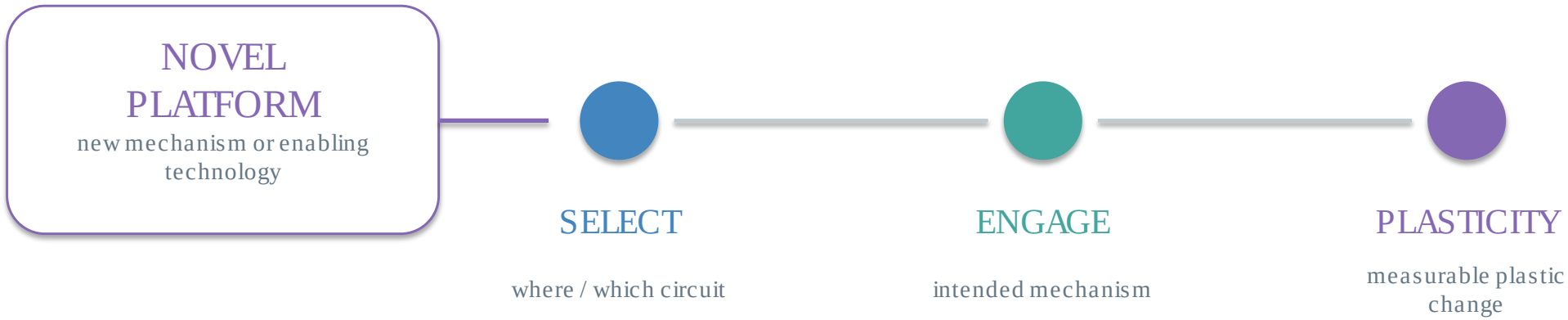
Demonstration in human participants

ADVANCED PRECLINICAL → HUMAN

Advanced animal demonstration + IRB submission by program end

IRB: institutional review board

Track B: foundational technology development

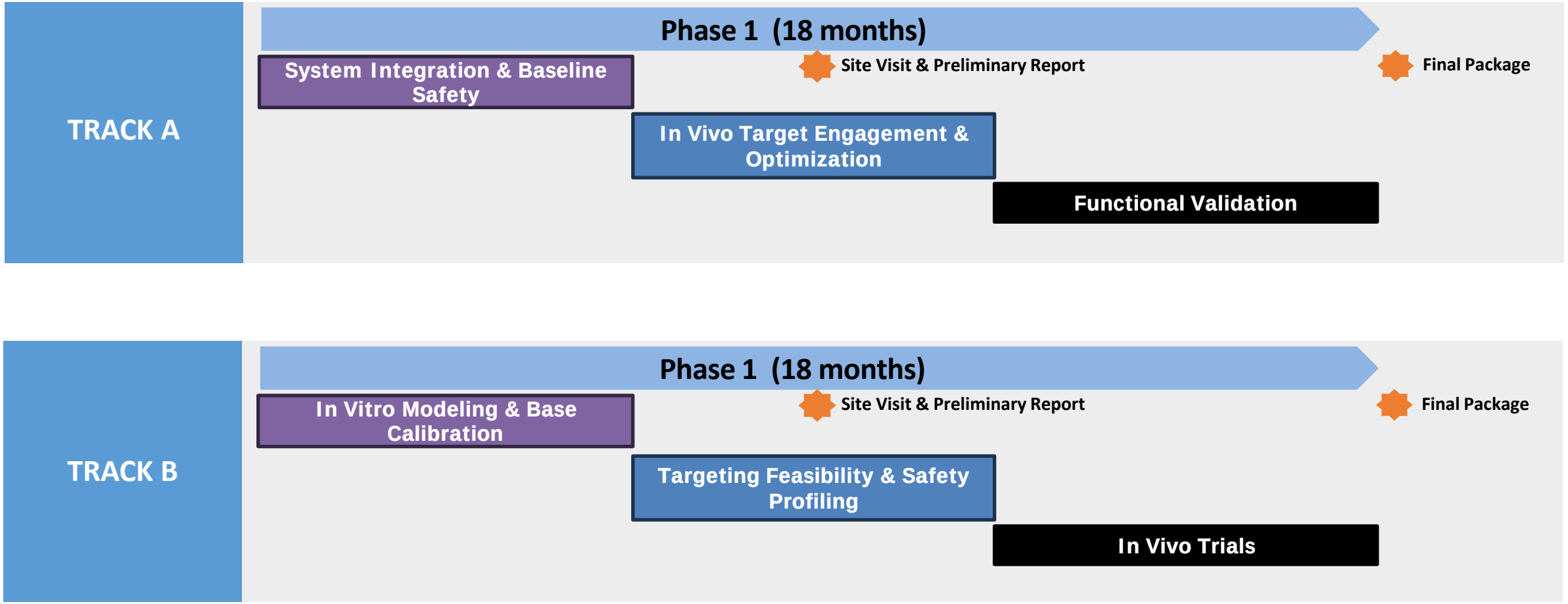


TRACK B CULMINATES IN:

IN VIVO MATURATION

Proof-of-concept selective neuroplasticity + clear pathway to advanced animal validation

SHINE schedule



SHINE milestones

Month	Milestone	Required Demonstration
3	Experimental Baseline & Validation Protocol	Finalize experimental design; identify intended neural target(s) and predefined nontarget control(s); establish quantitative validation strategy, success criteria, and comparator(s); obtain regulatory approvals as appropriate; complete baseline characterization.
6	Selective Substrate Localization	Complete initial testing and deliver a quantitative dataset and analysis evaluating the localization, confinement, or activation of the intervention within predefined neural substrates relative to appropriate controls.
9	Localized Target Engagement Verification	Perform target engagement assays, deliver the associated dataset analyzing and quantifying biological mechanism activation within targeted substrates using molecular, physiological, imaging, or functional biomarkers. Progress towards the final metrics must be quantifiably demonstrated with statistically significant changes found in target engagement.
12	Circuit-Selective Neuroplasticity Demonstration	Complete comparative evaluations of the neuroplastic response within predefined target substrates relative to nontarget substrates and submit a Preliminary Report along with the comparative experimental dataset.
18	Intervention Prototype Finalization	Deliver the fully integrated, validated intervention prototype (comprising physical hardware, biological constructs, or therapeutic delivery platforms) along with the execution of complete end-to-end intervention prototype validation testing across the full chain of evidence (selectivity, target engagement, and neuroplasticity). Delivery should include 1. The prototype assembly (or certified laboratory configuration specifications), 2. A final prototype technical data package detailing the system's performance metrics, and 3. An end-to-end validation report demonstrating the prototype's capability to meet program goals of either A) clinical trial readiness or B) animal testing capability.

SHINE metrics and impact

Metric	SHINE Target	Track A – Specific	Track B – Specific
Intervention Selectivity	3:1 Ratio (Target vs. Off-Target)	In vivo: ≥ 80% targeted delivery, ≤ 10% off-target dispersion	In vitro / preclinical: ≥ 90% spatial containment
Biological Target Engagement	≥ 2-fold increase (≤ 20% off-target variance)	Statistically significant change on mechanistic and clinical biomarkers, $p \leq 0.01$	Statistically significant change on mechanistic pathway or region markers, $p \leq 0.01$
Quantifiable change in Neuroplasticity	Demonstrate effects of neuroplasticity with effect size > 0.6	Plasticity consistently persists with quantitative proof in vivo	Proof-of-concept: Acute plasticity (≥ 72 hours)
Transition Readiness	N ≥ 3 cohorts / comparators	Therapeutic Index ≥ 5, roadmap to clinical use	In vivo maturation plan

SHINE will transition brain rewiring from a broad 'floodlight' into a precise 'spotlight,' enabling future non-invasive, circuit-selective therapies to cure severe trauma, addiction, and brain injury without off-target cognitive side effects

Human and Animal Subject Research

Proposals could potentially include animal use research and/or human subject research. Proposers that anticipate involving animals or humans in the proposed research must comply with the approval procedures detailed at https://www.darpa.mil/policies/human-animal-research to include providing the information specified therein as required for proposal submission.

Human subject research (HSR) and animal subject research (ASR): review of the protocol

All DARPA animal and human use protocols must go through two reviews in series (not parallel)

1st review

Local Level (IACUC / IRB Review)

2nd review

DoW Level (Secondary Review)

Approval for the DoW step alone can take 2-3 months

Proposals should plan for approval timelines in their proposed strategies.

DoW-level approval is needed before any funds can be used for HSR or ASR, such as towards the purchase and care of animals. Purchase of supplies and equipment is allowed prior to DoW-level approval.

IACUC: Institutional Animal Care and Use Committee
IRB: institutional review board

ACURO review

Required Submission Docs from Performer

- ✓ IACUC approved protocol
- ✓ Evidence of IACUC approval
- ✓ ACURO appendix
  - Available on ACURO's website

Approval Process

- ✓ ACURO reviews docs
- ✓ May ask PI for clarifications
- ✓ Sends to DoW vet for final review and approval

Approval can take 2-3 months

ACURO approval is needed before any funds can used for the purchase and care of animals. Purchase of supplies and equipment is allowed prior to ACURO approval.

ACURO: Animal Care and Use Review Office within the Defense Health Agency
IACUC: Institutional Animal Care and Use Committee

SHINE reminders

- FAQ will be posted on the SHINE webpage
- PM is not available for individual meetings related to SHINE proposal content for fairness to all proposers
- No abstract requirement
- **Proposal Due Date: October 2026***
- **Work expected to start January 2027***

***Please check the webpage and solicitation for updates. If there is any discrepancy between what is presented here and the SHINE Disruption Opportunity (DO) Solicitation, the DO Solicitation takes precedence.

www.darpa.mil