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Review article

The promise of low-tech intervention in a high-tech era: Remodeling pathological brain circuits using behavioral reverse engineering

Daniel B. Polley [a,b,*], Daniela Schiller [c,**]

[a] Eaton-Peabody Laboratories, Massachusetts Eye and Ear, Boston, MA, USA
[b] Department of Otolaryngology—Head and Neck Surgery, Harvard Medical School, Boston, MA, USA
[c] Department of Psychiatry, Nash Family Department of Neuroscience, and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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ABSTRACT

As an academic pursuit, neuroscience is enjoying a golden age. From a clinical perspective, our field is failing. Conventional 20th century drugs and devices are not well-matched to the heterogeneity, scale, and connectivity of neural circuits that produce aberrant mental states and behavior. Laboratory-based methods for editing neural genomes and sculpting activity patterns are exciting, but their applications for hundreds of millions of people with mental health disorders is uncertain. We argue that mechanisms for regulating adult brain plasticity and remodeling pathological activity are substantially pre-wired, and we suggest new minimally invasive strategies to harness and direct these endogenous systems. Drawing from studies across the neuroscience literature, we describe approaches that identify neural biomarkers more closely linked to upstream causes—rather than downstream consequences—of disordered behavioral states. We highlight the potential for innovation and discovery in reverse engineering approaches that refine bespoke behavioral "agonists" to drive upstream neural biomarkers in normative directions and reduce clinical symptoms for select classes of neuropsychiatric disorders.

1. Introduction

The neurotechnology boom of the early 21st century provided brain scientists with new tools to write the next chapter in our long quest to understand the neural determinants of behavior. Although neuroscience—in many respects—is enjoying a golden age, the near-term outlook for breakthroughs in the treatment of brain-based disorders does not look as rosy. Neurological disorders affect over one billion people worldwide (Organization, 2006), with a global financial burden across all mental health disorders projected to reach $16 Trillion by 2030 (Patel et al., 2018). Major pharmaceutical companies have shuttered central nervous system (CNS) programs on account of disappointing clinical trials and the lack of robust objective biomarkers. Neurologists and psychiatrists continue to prescribe drugs developed over fifty years ago despite knowing their limitations, because they have few alternatives. Clinicians are frustrated. Patients need help. Mental health care systems are stretched to their breaking point. The status quo is not good enough. Fresh ideas are needed.

The transformative potential for 21st century approaches to gene therapy, optogenetics, chemogenetics, and implantable devices for the treatment of neuropsychiatric disorders is undeniable. Many compelling reviews and forward-looking perspective articles have already been devoted to the topic of how high-tech neuroscience methodologies could flip the script on the treatment of brain-based disorders (Chow and Boyden, 2013; English and Roth, 2015; Rajasethupathy et al., 2016). Here, we offer a different point of view on the challenges facing the treatment of brain-based disorders, whether with conventional drugs and devices or through the clinical development of modern research-grade technologies.

Although we each work in different brain systems, we both have one foot in basic neuroscience research and the other in clinical neuroscience research. In our experience, the potential for these next-generation high-tech therapies can seem fairly abstract and remote for our clinical colleagues who are often more focused on solutions that can be implemented in the near-term. From our perspective, some of the most promising approaches to treat certain classes of brain-based disorders in the near future are low-tech, not high-tech. We have nothing against high-tech approaches. We both heavily rely on the latest advances in neuroscience methodologies in our own laboratories, and we forecast a critical role for these tools in the development of new therapies.

* Corresponding author at: Eaton-Peabody Laboratories, Massachusetts Eye and Ear, Boston, MA, USA.
** Corresponding author.
E-mail addresses: daniel_polley@meei.harvard.edu (D.B. Polley), daniela.schiller@mssm.edu (D. Schiller).

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However, a tool that has been effective for research will not necessarily fit treatment, and we do foresee some fundamental challenges to the translation of high-tech approaches into human therapies. Particularly in the context of the urgent and unmet needs for new interventions in the here and now, the translation of high-tech approaches from discovery to treatment, we argue, is missing exactly that—translation.

Neurobehavioral and neurogenetic interventions are not mutually exclusive or even antagonistic. To the contrary, we can anticipate how comparatively low-tech neurobehavioral approaches would be directly informed by laboratory discoveries driven by high-tech methods. Below, we describe how the bridge to translation and widespread clinical adoption for certain classes of neuropsychiatric disorders might be crossed by a marriage of low- and high-tech approaches. We offer a critique of the prevailing models for delivering neuropsychiatric therapies through drugs and devices, while acknowledging along the way that there are exceptions that work reasonably well. In addition to writing a critique, we also wanted to suggest what an alternative path forward might look like for minimal risk non-invasive therapies that could be developed for near-term implementation in select classes of disorders that have proven refractory to conventional modes of therapy. We wrote this review as a forward-looking perspective, not an exhaustive review of the literature, nor a data-based report.

We see untapped potential in non-invasive behavioral therapies that leverage the brain's endogenous plasticity to change itself. This, in and of itself, is not a new idea. Brain training software platforms, cognitive behavioral therapy, and the rapidly growing industry of digital therapeutics are all based on the idea that behavior can be used as a conduit to promote adaptive changes in brain function, which in turn can promote lasting, generalized, and clinically meaningful improvements in deleterious behaviors. This work provides a foundation for our proposal, but we contend that a few important new elements could dramatically improve the efficacy of neurobehavioral approaches. We argue that behavioral interventions would be more effective if they didn't target clinical symptoms or downstream biomarkers, but instead targeted physiological signatures of upstream brain activity processes (Fig. 1). Further, we argue that optimal behavioral interventions for overwriting aberrant neural processes could be categorically different for two individuals with the same diagnosis, and that there is value in data-driven, individualized processes for identifying optimal behaviors based on iterative, closed-loop measurements of brain and behavior. As a target for future research, we propose an approach to reverse engineer, from a well-defined neural target, an optimized behaviora 'behavioral agonist'—that will stimulate it. This approach requires re-classifying behaviors from their intuitive categories to their effect on a targeted physiological signature of aberrant activity. The landscape of re-drawn behavioral boundaries could appear quite different: a motor task could effectively engage a neural process normally studied in the context of emotion, and a sensory task could tap into a motor process.

As we discuss below, leveraging behavior to elicit and change targeted neural activity patterns warrants further consideration as a means of rehabilitating human brain disorders, whether on its own or in combination with assistive devices or pharmacological therapies. A clear advantage of delivering treatments in the form of behavioral agonists is that they are less invasive, less expensive, less risky, and could be more widely adopted by a diverse patient population than exogenous therapies based on drugs, devices, genetically encoded exogenous proteins etc. Another major advantage is that neural activity generated by behavior arguably flows through the dense, complex webs of interconnected neurons more naturally than the artificial neural activity generated by exogenous chemicals or electric fields. Behavior, in essence, is the product of neural circuit activity filtered through the structural, biophysical and synaptic properties of intervening motor neurons and muscles. While voluntary behaviors are traditionally (and correctly) conceptualized as the outcome of neural circuit activity, the process can also work when run in reverse: behavior can determine neural activity, just as neural activity determines behavior.

2. Addressing brain pathologies at their native scale

There is a long-recognized mismatch between the lack of specificity of conventional brain therapies and the underlying scale and specificity of brain circuit organization. Conventional drug therapies often act on multiple organ systems, to say nothing of focal regions of pathology within the brain. But a challenge for conventional drugs and devices is more than just spatial precision—it is that electric fields and drugs do not reliably target particular cell types in the brain. Any introductory neuroscience textbook will explain that brain cells are divided into non-neuron and neuron types, with the latter further divided into excitatory and inhibitory neurons. But the biological ground truth is far more complex, where these coarse divisions are further divided into

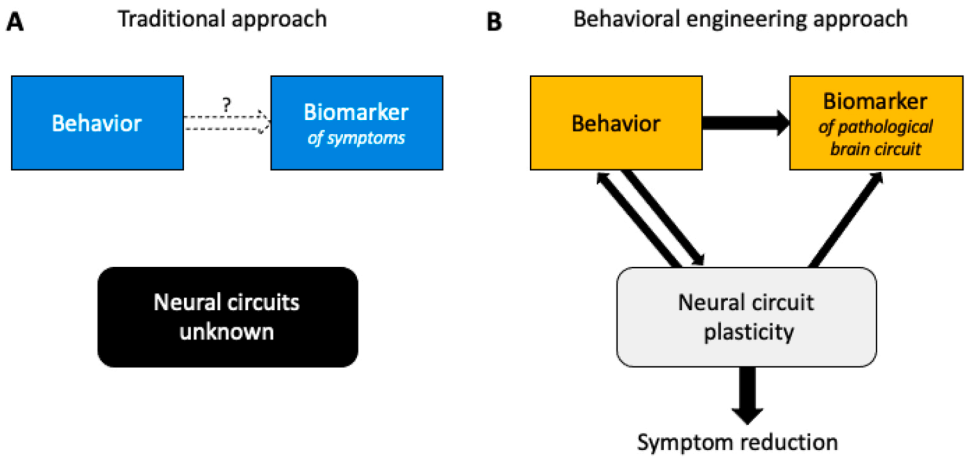

Fig. 1. Behavioral reverse engineering. (A) A traditional approach would identify a disease relevant behavior (e.g., working memory) and a neural correlate that appears different between healthy and patients (e.g., resting-state functional connectivity, or rsfMRI). A clinical study might then attempt to train patients on a working memory task in order to shift the biomarker into the healthy range. This approach is likely to fail because (i) there is no mechanistic connection between the behavior and the biomarker (unclear whether and how working memory would affect rsfMRI) and, (ii) even if it does, the circuit level mechanisms remain a black box, and it is unclear whether the behavior and the biomarker are linked to any disease relevant neural circuits, and if they are, whether they could induce plasticity for a long-term change that leads to symptom improvement. (B) A behavioral engineering approach would first identify a disease relevant underlying neural circuit defect, the corresponding behavior it produces, and a downstream biomarker to target. Behavioral training would then be used to coax the biomarker into a functional range. As behavioral a agonists are iteratively revealed, purified, and choreographed as treatments to be repeatedly performed, biomarkers could be sustained in the neurotypical state, supporting an improvement in clinical symptoms. The traditional approach (depicted in A) is less likely to produce clinical improvements because it is less constrained and could include a huge number of behaviors and biomarkers, most of which are likely mechanistically irrelevant. The behavioral reverse engineering approach, on the other hand, is anchored in putative disease relevant neural circuits, which are mechanistically related to both the behavior and the biomarker, and is thus hypothesis-driven and more constrained.

intermediate classes and subclasses that ultimately coalesce on a finite number of genetically defined neuron types. A recent taxonomy based on single-nucleus RNA sequencing from the human temporal lobe identified 45 transcriptionally distinct inhibitory neuron types and 24 excitatory neuron types (Hodge et al., 2019). These genetically defined clusters are not arbitrary markers, but instead very often identify neurons with distinct morphologies, biophysical properties, connectivity profiles, functional response types, and postsynaptic targets (Chen et al., 2019; Gouwens et al., 2020).

To pick one example out of many, indiscriminate stimulation and recordings of the lateral hypothalamus suggested a role in reward seeking behaviors, but the heterogeneity of hypothalamic cell types and projection targets obscured a clear understanding. Using optogenetics, researchers were able to dissect the functional connections between the lateral hypothalamus and ventral tegmental area to define unique contributions of feedforward and feedback neurons in reward seeking behaviors (Nieh et al., 2015). Among the feedforward hypothalamic neurons, it was the GABA neurons in particular that were implicated in compulsive maladaptive behaviors. Assuming that this discovery in mice (and many others like it) apply to human brains, it underscores the challenge faced by conventional drug-based approaches to treat reward-seeking compulsive behaviors. Even if a drug were engineered to act on GABAergic neurons, it would still run into the problem that GABAergic neurons themselves are heterogeneous, particularly when their function is considered from the perspective of the local circuits in which they operate. For example, GABA neurons that express the vasoactive intestinal peptide disinhibit excitatory neurons through inhibition of other local GABA interneurons, while activation of parvalbumin-expressing GABA neurons potently silences excitatory neuron spiking (Pfeffer et al., 2013; Pi et al., 2013). Even if a drug that selectively acted on GABA neurons were developed, it might still amount to pushing on the gas and brake pedals at the same time.

The 21st-century neurotechnology toolkit has allowed neuroscientists to illuminate the fabric of the brain (literally), and now that the complexity has been made clear, it raises reasonable concerns about the wisdom of regarding pharmacological and device-based interventions that act broadly across cell types and regions as the only clinical neurotherapeutic tools in our toolkit. These challenges are compounded when one considers the tremendous heterogeneity in individual genomes, developmental histories, and patterns of structural and functional brain connectivity. Twentieth century traditions for drug development can synthesize compounds with affinity for particular receptor subunits, but receptor subunit composition does not provide a map for navigating the territory of brain circuit connectivity. Electrically stimulating the brain offers some advantages over drugs with spatially focused electric fields, but the more common types of non-invasive clinical neurostimulation devices (e.g., tDCS, rTMS, TMS etc.) may only be able to offer—at best—regionally specific activation that recruits neuronal and non-neuronal cells of all possible types.

As an example, *MECP2* mutations cause Rett syndrome, which can be modeled in female mice lacking one *Mecp2* allele. *MECP2* expression abnormalities are mosaic and the challenge of targeting just the subset of MeCP2 protein-deficient neurons with pharmacological or gene therapies is further compounded because excessive MeCP2 expression in neurons with the normal allele can also produce neurological abnormalities (Sandweiss et al., 2020). Deep brain stimulation via implanted electrodes can mitigate some of the memory deficits observed in mouse models of Rett syndrome, but the procedure is invasive and difficult to implement and translate, particularly in the context of an early postnatal sensitive period (Hao et al., 2015). Turning to a "low-tech" behavioral solution, researchers recently discovered that engaging young pre-symptomatic Rett mice in the types of motor coordination and behavioral memory tasks that they would otherwise struggle to perform in later life "inoculated" them from the functional deficits observed in their naive or late-trained counterparts (Achilly et al., 2021). It is easy and tempting to doubt the potency of behavioral interventions because they are non-invasive. But this example and many others described below demonstrate that they can produce marked, specific, and sustained effects on brain function and behavior. and can inspire further research to isolate and amplify the most efficacious "ingredients" of the behavioral training as well as detailed neurobiological research to determine how the benefits are mechanistically implemented (Fig. 2).

3. Identifying brain disorders most in need of alternative approaches

It is important to acknowledge that conventional drugs and devices can be successful in treating certain classes of neuropsychiatric disorders, even though they act on genetically heterogeneous cell types distributed over multiple brain regions. The drugs that are effective in reducing clinical symptoms are valuable both as therapeutic tools and for the perspective they provide into the neural mechanisms underlying neuropsychiatric disease states. The bulk of intellectual and financial capital for CNS disorders remains focused on improving pharmaceutical therapies for neurodegenerative disorders, mood disorders, brain tumors, and epilepsy. For example, L-dopa was first introduced as a treatment in Parkinson's disease over sixty years ago and is still widely prescribed today because it forestalls the progression of motor symptoms by several years. More recently, the glutamate N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine was repurposed as a rapidly acting antidepressant for treatment-resistant depression, shifting attention to glutamate-signaling modulators as novel therapeutic agents for depressive disorders (Murrough et al., 2017). Although the clinical outcomes with drug-based treatments generally leave much to be desired, they remain the most widely useful tool in the current clinical toolkit for treating brain-based disorders.

On the other hand, many neuropsychiatric conditions have proven more refractory to treatment with drugs or devices. This could just be a matter of not yet having identified the right molecule or correct setting on the neurostimulation device, but it might also indicate a need to consider different treatment modalities. Our own clinical research has underscored the need to develop better therapeutic options for persons who feel overwhelmed by the sensory world. Here, we refer to a cluster of relatively common complaints in which persons cannot habituate to background stimuli, are tormented by irrepressible phantom percepts or traumatic memories, and they find moderately intense stimuli to be intolerable and distressing. Colloquially, this condition is called sensory overload, and it is a common feature in normal age-related decline in addition to neuropsychiatric conditions including autism spectrum disorder, post-traumatic stress disorder, fibromyalgia, schizophrenia, traumatic brain injury, sensorineural hearing loss, attention deficit hyperactivity disorder, and migraine.

These symptoms are often particularly acute in the auditory modality. For a combat veteran with post-traumatic stress disorder, the sound of neighborhood fireworks can elicit acute distress and the resurgence of traumatic memories. Persons on the autism or mild brain injury spectrums very often exhibit hypersensitivity or hyperreactivity to moderately intense sounds. For each of the disorders above, the constant hum of an overhead fluorescent light, a classroom air conditioning unit, or the babble of background conversations in a restaurant are invasive and cannot be segregated from foreground sounds, producing fatigue, distraction, irritability and social isolation. For each of the disorders above, there are no reliable biomarkers for sensory overload symptoms, nor widely effective treatments. Sensory overload is by no means the only condition that raises questions about the prevailing model for treating neuropsychiatric disorders, but we use it as an example that we will come back to throughout our paper as a condition that deserves consideration from new perspectives.

4. Opportunities and challenges with high-tech brain therapies

Whereas targeting specific nodes of interconnected brain circuits is

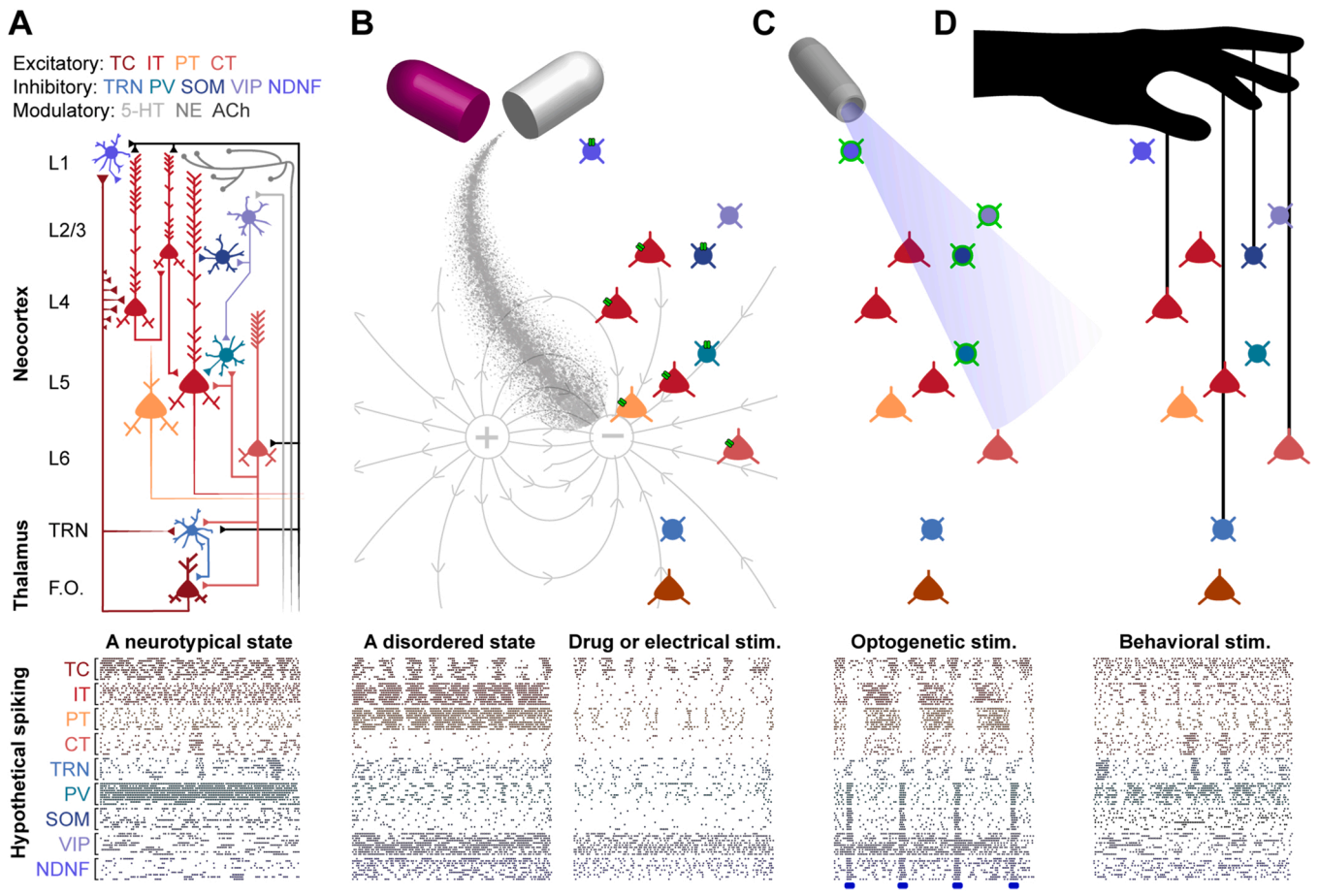

Fig. 2. Addressing neural circuit pathophysiologies at their native scale. (A) Top: Cartoon illustrates a "simplified" canonical neural circuit linking the thalamus and cortex involving just four types of excitatory neurons, five types of inhibitory neurons, and three sources of long-range neuromodulatory input.This canonical circuit illustrates the cell-type specific connections found throughout the brain as well as the varied types of neural connection motifs (e.g. feedback, disinhibitory, recurrent etc.). L = Layer. F.O. = first-order thalamic nucleus. Cell types are defined either by their anatomical connectivity or their transcriptional profile. Excitatory: TC = thalamocortical, IT = intratelencephalic, PT = pyramidal tract-like, CT = corticothalamic. Inhibitory: TRN = thalamic reticular nucleus, PV = parvalbumin, SOM = somatostatin, VIP = vasoactive intestinal peptide, NDNF = neuron-derived neurotrophic factor. Modulatory: 5-HT = serotonin, NE = norepinephrine, ACh = acetylcholine. *Bottom:* Hypothetical rastergrams depict the decorrelated spiking activity among ensembles of ten simultaneously recorded single thalamocortical neurons of each class listed above in a neurotypical thalamocortical circuit. (B) Rastergram at left depicts a commonly occurring thalamocortical circuitopathy typified by hyperactive excitatory neurons, hypoactive inhibitory neurons, and bursting patterns of thalamic input. Drugs or externally applied electrical fields can change the overall activity levels within this hypothetical hyperactive circuit, but act non-selectively on cell types to produce non-specific and unnatural effects on activity within the circuit. (C) Unlike conventional drugs or devices, high-tech future therapies for hyperactivity disorders could target genetically identified cell types to, for example, express channelrhodopsin. However, even high-tech therapies may not restore natural activity patterns within the example hyperactive circuit, at least not with the approaches available for use in humans. In this hypothetical example, pulses of light (shown at bottom) produce synchronized spiking across transduced inhibitory cell types and post-inhibitory rebound spiking in excitatory cell types, thereby switching one disordered state for another. (D) During natural behaviors, activity flows through genetically addressed nodes of neural connections to produce varied forms of activity motifs across the hypothetical thalamocortical circuit. Even in a disordered hyperactive state, certain behaviors could temporarily change circuit activity into a more normative state. If these behavioral agonists could be identified, controlled, repeated and "locked in" via recruitment of neuromodulatory centers or other mechanisms for enhancing long-term reorganization, it could provide a means for remodeling disordered circuit activity.

not possible with conventional drug- and device-based approaches, the contemporary neurotechnology toolkit provides the means to steer light- or drug-sensitive exogenous proteins into genetically targeted cell types. This feature has been used to great advantage for causal hypothesis testing in laboratory studies but has also prompted interest and discussion about potential therapeutic uses in human neuropsychiatric disorders (Chow and Boyden, 2013; English and Roth, 2015; Rajasethupathy et al., 2016). In laboratory studies, genetic targeting of neuron types is often achieved via genetically modified animals. There is good reason to believe that genetic engineering could be improved to the point where viruses or other gene editing agents could modify targeted cell types in the nervous system (i.e., without the need for transgenic humans) (Graybuck et al., 2021; Vormstein-Schneider et al., 2020). It is also reasonable to speculate that delivering some gene therapies or light-sensitive proteins might be performed without intracranial surgery (Chen et al., 2020; Gao et al., 2018; Gong et al., 2020).

For forms of sensory and movement disorders that arise from single gene mutations, the potential for gene therapies based on a single injection of gene editing agents into the (relatively) accessible regions of the peripheral nervous system is real and near. But this does not apply to the vast majority of neuropsychiatric conditions that affect our population. Most disorders arise from dysfunction across hundreds of genes that produce complex pathophysiology across widespread brain systems. Introducing gene editing agents into the human brain to make neurons sensitive to light or designer drugs may prove technically possible but developing them to the point where they could restore more normative brain activity patterns in persons with neuropsychiatric disorder warrants additional critical consideration.

From our perspective, stimulating or silencing genetically targeted cell types has a critical role to play in the development of future therapies, but less as a means of therapy in and of itself. Chemogenetics and conventional approaches to optogenetic stimulation can activate or silence the native microcircuitry of the brain during behavior but would not be able to produce natural spatiotemporal patterns of activity in those circuits, at least not with the relatively non-invasive methods that would be applicable in the human brain. One could envision that introducing widespread, temporally synchronous activation could prove useful as a means of disrupting sub-clinical patterns of activity preceding seizures, migraine, or panic attacks. However, if the goal of next-generation brain stimulation strategies is to supplant pathological activity patterns with neurotypical spatiotemporal activity patterns, we would suggest that such an approach would just replace one form of abnormal activity with another (Fig. 2C).

Even if the pathophysiology underlying our most pressing neuropsychiatric disorders could be reversed by replacing a defective gene or simultaneously activating thousands of genetically photosensitized neurons, where would that leave us in terms of solving the societal problem? In the United States and other industrialized nations, persons with chronic mental illness are often under-insured or are among the tens of millions without access to care. What is the basis for thinking that a garden variety patient with a debilitating mood disorder will check into their local health care provider for implantation of biocompatible meshes or injection of genetically encoded activity switches into their brain? Or that mounting optic fibers, light sources, and power supplies to the skull will become routine outpatient procedures that would be widely accepted by persons with mental health disorders?

Financing high-tech invasive therapies is also a concern. The bill for the latest one-time gene therapy procedure for inherited retinal disease comes to $850,000 per patient. Of course, medical costs would come down to an extent as the procedures become more commonplace, but these are still complex, invasive procedures with uncertain feasibility for common mental health conditions. For a fraction of the very sickest, most refractory cases who are fortunate enough to have the financial resources to defray the costs of the procedure, invasive therapies might be an effective tool of last resort (Crowell et al., 2015). The financial, legal and ethical considerations for delivering high-tech therapies into the brains of persons with mental health disorders in the *near*-term future represents a massive challenge for any health care delivery system. Given that there is an urgent unmet need for many brain-based disorders and given the significant challenges that will be faced both in terms of technological development and access to care, we see a strong motivation to consider alternative models for minimally invasive relatively low-cost brain-based therapies that could be more readily implemented on a short time horizon.

5. Right behind our noses

The clinical targets and modes of application for these relatively low-tech neuroscience approaches vary widely, but they are collectively based on the notion that the most effective tool for reprogramming pathological brain circuits is right under (or, more accurately, behind) our noses. The endogenous systems that regulate brain plasticity are an exploitable tool for reprogramming pathological neural circuits. The brain's endogenous systems possess a connectivity logic that has been sculpted over millions of years of evolution to address the appropriate nodes within neural circuits to impart lasting changes that support learning, memory, and adaptive behavior. In this way, the brain's systems for self-regulation and plasticity may already possess the cell type-specific actions that elude exogenous therapies. From our perspective and others working in this field, the best device to generate natural activity patterns within the intricate webs of neural circuits and sculpt long-lasting change in those circuits is… the brain itself.

We are well aware that leveraging behavior to reverse the neural underpinnings of declining mental health and cognition has a long history. Cognitive behavioral therapy and related forms of psychological talk therapies aim to amplify, attenuate, and redirect specific behaviors and underlying cognitive processes to decrease maladaptive behaviors. Additionally, computerized 'brain training' games first came to the fore 25 years ago as a means of reversing low-level auditory processing deficits in children with specific language impairment (Merzenich et al., 1996; Tallal et al., 1996). Nowadays, companies offer a variety of brain training games or cognitive exercises as means of reversing or forestalling deleterious behaviors and cognitive processes associated with attention deficits, aging, and a wide spectrum of neuropsychiatric disorders.

Here, we are focused on something different. We see value in approaches that build on these platforms but focuses the intervention on neural processing abnormalities, rather than downstream behavioral outcomes. We propose that concurrent (or near-concurrent) measurements of brain function and behavior could be used to more efficiently identify behavioral agonists that act on candidate biomarkers. As we describe below, select classes of brain-based disorders might be addressed through a three-step process that involves: 1) isolating a physiological signature of the pathological brain state (rather than a biological marker of symptoms); 2) identifying a behavioral agonist that temporarily shifts this physiological signature into a more normative direction; 3) deploying this neurobehavioral treatment over time to determine if it mitigates clinical symptoms and disease burden (Fig. 1B).

6. Behavioral reverse engineering

Behavioral reverse engineering, as we define it here, works by measuring activity in a targeted brain circuit (in animals) or a more macroscopic measure of distributed network activity (in humans) while the subject engages in a wide range of behaviors. The key idea is during or immediately after an overt behavior, imagined behavior, or sensory stimulation regime, a neural target will temporarily shift in the desired direction. Then, through reverse correlation or other machine learning-assisted online analysis methods, the behavior that produced the targeted neural change can be iteratively purified into a behavioral agonist capable of efficiently and reliably shifting the neural target towards an identified neurotypical endpoint. With repeated performance, augmented (perhaps) with pharmaceutical or device-based methods to ensure that the recruited networks are in an optimal state for long-term reorganization, it would be possible to impart a long-lasting change in a well-selected neural target with consequent improvements in mental health and behavior. Because the behavioral agonist is identified and tailored on an individual basis, such an approach may prove more tolerant to the biological and psychological heterogeneity that can often be a point of failure for conventional prescriptive models of brain-based therapies. Providing a rich virtual (or real) sensorium to promote a wide variety of motor activities, social interactions, emotional states etc., increases the probability of identifying behavioral sequences strongly associated with neuromodulatory surges or targeted changes in the neural marker of pathological activity. Effective behavioral sequences can be identified, refined, and replicated by the experimenter or future neurotherapist to coalesce around a distilled repertoire that promotes reliable activation of neuromodulatory signatures or pathological brain targets.

We refer to this process as "reverse engineering" because we are proposing that coupling behaviors with closed-loop neural feedback can isolate behavioral elements associated with targeted biomarker changes. This is consistent with the usage of reverse engineering in that we are proposing an inductive process to first reveal behavioral agonists that elicit targeted neural changes, and then to assemble those components for a combined behavioral therapy that may be able to shift brain function towards more sustained neurotypical endpoint. By contrast, in cognitive behavioral therapy or computerized brain training exercises, the exercises maybe broken down into parts, but the basic formulation of the therapy (e.g., the programming of the game or the approach of the

talk therapy) is known *ex ante* and is not discovered through observation.

To this last point, there is a temptation to think that we know what behaviors are best suited to engage a pathological brain network. But consider how often our research communities have ascribed a singular function to a brain region or cell type by aptly observing its involvement in a narrow behavioral protocol but then stopping short of testing a wider range of behaviors to determine what it is *not* involved in. For example, it was widely agreed that midbrain dopamine neurons specifically encoded reward prediction error, until a wider set of test conditions revealed that they also encode aversive reinforcement, sensory inputs and movement-related variables (Engelhard et al., 2019; Matsumoto et al., 2016). Visual cortex neurons were described as low-level visual feature encoders, until they were studied in the context of richer behaviors and were found to encode movement-related inputs as well as the timing of reinforcement outcomes (Ramesh et al., 2018; Shuler and Bear, 2006). CA1 hippocampal neurons were thought to embody an egocentric mental map of space until an expanded testing repertoire revealed selective encoding of sensory sequences, allocentric locations of social conspecifics, or the faces of famous actresses (Aronov et al., 2017; Eichenbaum et al., 1987; Omer et al., 2018; Quiroga et al., 2005; Schiller et al., 2015). Confirmation bias entrenches our tendencies to make narrow assignments of behaviors onto neurons, because the range of behaviors to which a neuron contributes can never be broader than the range of behaviors that are tested. For the purposes of this article, it is unimportant whether a cell type, circuit, or network is necessary or sufficient for a behavior; here, we are more interested in the behavioral determinants of neural activity than the neural determinants of behavior.

7. Getting down to brass tacks

We propose that a future behavioral reverse engineering approach would include three key steps: (i) identify a biomarker of an upstream pathological state (rather than symptoms) against which the efficacy of behavior would be measured; (ii) purify and repeat behaviors until identifying the optimal behavior; (iii) deploy the combined behavior and examine the disease state: have symptoms subsided? if not, repeat the process and search for another behavior; if yes, move on to implementation and further mechanistic investigation.

7.1. Identify a biomarker

A joint FDA-NIH panel defined a biomarker as "*A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions*" (FDA-NIH Biomarker Working Group, 2016). By their definition, a biomarker could be a protein measured in blood, a structural feature from a radiological scan, or even the subjective self-report of pain, depression, fatigue, or other internal states. Here, we refer to a much narrower definition of biomarker as a "macroscopic" physiological or low-level involuntary behavioral readout of a targeted brain circuit that can be measured with conventional non-invasive methods either during behavior, or in close temporal proximity to behavior. Technological and financial barriers will likely prevent us from ever monitoring the flow of activity through genetically targeted brain circuits in the human brain, in the way we can in laboratory animals. This is where animal research and computational models of neural ensemble dynamics have a critical role to play, because they can provide the Rosetta stone for translating ground truth measurements of neural circuits to macroscopic signatures that can be rapidly and non-invasively measured in the offices of the neurotherapists of the future (see (Krol et al., 2018) for an elaboration of this argument in the context of neurodevelopmental disorders).

For example, although dysfunction in key sub-types of cortical GABA neurons cannot be resolved by non-invasive brain measurements systems, their involvement in particular frequency bands of rhythmic brain activity can be proven with causal hypothesis testing in animals, which can then establish a trustworthy surrogate for use in future patients (Cardin et al., 2009; Sohal et al., 2009; Veit et al., 2017). Likewise, if the targeted recruitment of specific neuromodulatory cell types that regulate brain plasticity cannot be directly visualized with non-invasive imaging, their connection with iso-luminous pupil dilations can be proven in animals to provide a surrogate biomarker for use in humans (Cazettes et al., 2021; Joshi et al., 2016; Larsen and Waters, 2018; Reimer et al., 2016). Neural circuit functions and dysfunctions that can be demonstrated in animal models to produce surrogate biomarkers at the level of event-related potentials, a specific resting state network, oculomotor signatures, involuntary facial expressions, oscillatory activity, or sensory-evoked abnormalities are all fair game for reverse-engineered behavioral therapies, as we describe below.

An optimal biomarker might be defined both by its logical connection to a core underlying neurobiological defect, but also by being sufficiently far "upstream" of the neural circuits that drive the deleterious behaviors. To that last point, electromyogenic recordings are a valid biomarker of Parkinson's, essential tremor, and other neurodegenerative disease processes, but would clearly make a poor choice as a biomarker to feed into the behavioral reverse engineering process because it is too far downstream of the proximal neural changes that produce the disordered condition.

Returning to our example of auditory overload, animal research has identified a core neurobiological defect that plausibly underlies the perceptual disruption observed in humans. Advancing age and progressive sensorineural degeneration in the inner ear causes the balance of excitation and inhibition to tip towards hyperexcitability throughout auditory processing centers of the brain. In acute brain slice preparations, neural hypersensitivity and disinhibition can be observed directly through measurement of inhibitory and excitatory synaptic conductances (Caspary et al., 2008; Caspary and Llano, 2017; Middleton et al., 2011; Yang et al., 2011). In intact animal preparations, the pathophysiology often manifests as increased spontaneous spike rates of excitatory neurons, depressed sound-evoked responses of inhibitory neurons, and optogenetically identified reductions in feedforward inhibition (Ouda et al., 2015; Parthasarathy et al., 2019; Resnik and Polley, 2021, 2017). None of these neurobiological markers of dysfunction can be resolved in human subjects. However, neural recordings in animal models can also link these finer grain abnormalities to more macroscopic markers of aberrant physiological processing that can be measured in human subjects. For example, local field potential recordings in animal models of auditory hypersensitivity consistently show abnormally strong neural responses to moderate intensity sounds, which can also be reliably measured in human participants with EEG or fMRI recordings (Auerbach et al., 2014; Gu et al., 2012, 2010; Koops and van Dijk, 2021). This link—to a core neural circuit defect underlying a disordered perceptual state and the type of measurement that could be performed in human subjects—provides a reliable physiological signature to be targeted with the behavioral reverse engineering approach described below.

7.2. Reverse engineer behavior

With a disease-relevant biomarker identified, the next challenge would be reverse engineering a behavior capable of shifting the biomarker of abnormal brain function towards a desired state. Isolating a behavioral agonist that recruits the targeted biomarker and moving it towards a more normative operating point may prove to be quite challenging, particularly when a behavior capable of modulating the neural measurement is unknown or untranslatable from animal models. This process could involve cycling through different behaviors while monitoring the biomarker, until identifying behavioral elements that reliably modify the neural measure in the targeted direction.

In some cases, the logic for pursuing a behavioral reverse engineering approach is straightforward. Take for example, the case of

reconsolidation, which refers to the process by which memories return to a labile state when reactivated and need to be restored (restabilized/reconsolidated) (Dudai, 2004). Hundreds of animal studies have identified the cellular and molecular processes involved in reconsolidation (Haubrich et al., 2020; Nader and Hardt, 2009). Most compounds that are used to target reconsolidation in animals are toxic for humans, and circuit-level manipulations are impossible to translate. A behavioral reverse engineering approach can be utilized in combination with drugs (Brunet et al., 2018; Kindt et al., 2009) and devices (Borgomaneri et al., 2020; Mungee et al., 2014) that are safe to use in humans, with a behavioral agonist—in this case, memory reactivation. Specifically, memory reactivation might open a reconsolidation window during which the drugs or devices will be administered. Alternatively, a purely behavioral approach could replace the drugs and devices, with behavioral agonists timed to the reconsolidation window, such as various learning tasks that interact with the neural resources of reconsolidation (Agren, 2014; Gale et al., 2020; Lee, 2009; Monfils et al., 2009; Mungee et al., 2014; Schiller et al., 2010).

Human imagination is another putative agonist, even if it does not involve an externalized behavior. Motor imagery, for example, has been shown to activate motor circuits in place of real movement, and it is possible to augment motor imagery-induced neural activation by pairing it with reward (Bhattacharjee et al., 2020; Savaki and Raos, 2019). The pairing with reward synchronizes imagery-activated motor circuits with reward-activated circuits, suggesting a biomarker for an imagery-based behavioral task that could influence motor action and choice (Mendelsohn et al., 2014). As another example, imagery of aversive conditioned stimuli (i.e., imagined extinction) achieves the same levels of threat memory attenuation as exposure to real conditioned stimuli during extinction learning. Imagined extinction appears to work by activating real extinction neural circuits (Reddan et al., 2018). This demonstrates that a physiological or fMRI signal could serve as surrogates for imagery-related circuit activation during various behavioral tasks that are highly relevant for clinical applications, such as imagined extinction during reconsolidation (Agren et al., 2017; Vermes et al., 2020), and pharmacological reconsolidation disruption of imagined events (Soeter and Kindt, 2012).

Isolating a promising behavioral agonist may not even require overt behavior. Aversive conditioned stimuli, for example, have a unique signature in the visual cortex. It is possible to induce such representations using proxy (ambiguous, non-threatening) stimuli, and whenever these representations are observed in the visual cortex—using real time fMRI and machine learning decoding methods—pair these representation with reward, a process that reduces the threat arousal response to the conditioned stimuli (Koizumi et al., 2017). Directly targeting the neural correlates of behavior suggests a method and a biomarker to reduce anxiety and phobia without actually exposing the patients to their anxiety triggers, circumventing one of the major causes of patient attrition (Taschereau-Dumouchel et al., 2018).

How might the reverse engineering process work for our example condition of sensory overload, in which persons may experience hypersensitivity to sound, perceive continuous phantom sounds, experience acute anxiety or distress triggered by sounds, or increased distractibility from background sounds? As described above, animal models for this condition suggest a core neural circuit defect in auditory processing centers of the brain in which sensitivity to inhibitory synaptic input is reduced, while sensitivity to excitatory synaptic input is enhanced, producing net neuronal hyperexcitability. The goal for a reverse engineering session would be to monitor an electrophysiological, autonomic, or involuntary behavioral proxy for sound-evoked hyperexcitability while identifying sensory, motor, or cognitive features that could temporarily shift these biomarkers towards a more normative level. For example, tactile stimulation transiently suppresses activity at multiple stages of the central auditory pathway and, when presented in close temporal proximity to auditory stimulation, can promote synaptic depression and reduce neural hyperactivity related to tinnitus (Wu et al., 2015). Alternatively, motor-corollary discharge preceding bouts of locomotion or orofacial movements also suppress sound-evoked activity throughout the central auditory pathway (Schneider and Mooney, 2018). One could imagine that these types of sensory- or movement-based features could be manipulated either concurrently or in close temporal proximity to physiological monitoring and tailored for individual subjects to optimize the conditions that temporarily shift the biomarker signal towards its normative state.

7.3. Deploy behavior

With a promising biomarker and behavioral agonist identified, the next step would be to repeatedly administer this therapy under the strictures of clinical research studies. This approach could be pursued as a pure behavioral intervention or could be amplified through concurrent drug- or device-assisted behavioral stimulation to shift the brain into a more permissive state for modulation and enduring plasticity. The desirable outcomes are improved prognosis and possibly even prevention with a sort of behavioral inoculation. For example, attentional threat avoidance—the tendency to shift attention away from negative stimuli—has been linked with the severity of PTSD symptoms (Bar-Haim et al., 2010) and is predictive of PTSD symptoms following combat exposure (Wald et al., 2011). It is possible that attention bias modification training (Wald et al., 2017), that also modifies the underlying biomarker, could be used as a preventative measure to reduce the risk of developing PTSD.

Returning to our example, auditory overload subjects who perceive continuous phantom sounds, are hypersensitive to sound, or struggle to suppress the sound of distracting noise sources, behavioral agonists identified from the reverse engineering stage could be packaged into a format that could be repeatedly delivered without concurrent brain measurements. To this end, randomized control trials have confirmed that extended periods of chronic bi-modal audio-tactile stimulation can promote clinically significant reductions in self-reported tinnitus severity as compared to control groups (Conlon et al., 2020; Marks et al., 2018).

As another example, older adults who struggle to follow conversations in background noise do not show generalized speech intelligibility improvements when they are trained to recognize sentences in increasing levels of background noise, because this type of behavioral intervention targets the downstream symptom, not the underlying neural process. A different outcome is observed when subjects are instead trained on different types of audiomotor exercises developed from prior studies of cortical plasticity processes in animal models (Whitton et al., 2014). Using a randomized double-blind placebo-controlled task design, it was reported that elderly hearing-impaired subjects that trained on placebo speech memory tasks only improved at the task they are trained on, whereas training on auditory computer games that use synthetic sounds to emphasize distractor suppression, multi-modal stimulation, and sensory prediction error imparted clinically significant, generalized improvements for processing speech in multi-talker background noise (Whitton et al., 2017).

Failures to see clinical benefits are not necessarily failures of the overall approach. For example, if the biomarker were shifted in the desired direction during the application of the behavioral agonist but reverted back to its baseline state in other contexts, it might suggest that additional components of the behavioral stimulation are needed to engage the long-term plasticity processes of the brain, and “lock in” the transient circuit modification observed during behavioral stimulation. Another possibility is that the biomarker could be persistently modified in the right direction, but there was no change in the presentation of clinical symptoms. This outcome would suggest that the selected biomarker might be too far downstream; it may be correlated with disease symptoms, but not causally related to the originating circuit-level mechanism. In these cases, revisiting each of the previous steps would be required. In the section below, we provide a few concrete

examples that highlight important aspects of the neurobehavioral reverse engineering methodology or conceptual approach.

8. A review of behavioral reverse engineering successes and pitfalls

As we have described above, there may be untapped clinical potential for remodeling pathological brain circuits by developing an approach for engaging the brain's endogenous pathways for plasticity and self-regulation while forcing a neural biomarker into a targeted functional state. There are three key considerations at play: the degree of plasticity in the targeted neural biomarker, whether the biomarker can be shifted towards a neurotypical target state through the behavioral intervention, and how well these two events can be synchronized. Below, we review recent studies that have contended with one or more of these factors and discuss how the findings may guide a path forward with behavioral reverse engineering approach that we have described.

8.1. Applications in which the targeted neural biomarker is amenable to measurement and manipulation but is not inherently plastic, limiting the potential for sustained change outside of the behavioral intervention

In sensory and motor brain regions, producing targeted activity patterns that course through genetically defined brain circuits can be relatively easy to accomplish neural activity can be sculpted in both space and time with properly designed sensory stimuli or movements. The fundamental challenge for scaling sensory- or motor-based stimulation regimes up to human therapies is less about moving the biomarker towards the desired endpoint, but more about how to make it stick once it is there. In adult brains, passive, meaningless stimuli generally have only transient effects on cortical circuits. Imparting more permanent changes in adult cortical circuits is accomplished by the additional involvement of neuromodulatory brain centers that remove the brakes limiting adult plasticity, allowing for longer-lasting remodeling of brain circuits and perception (Bakin and Weinberger, 1996; Bao et al., 2001; Bavelier et al., 2010; Froemke et al., 2013; Marlin et al., 2015; Martins and Froemke, 2015; Reed et al., 2011).

Here, the reverse engineering process described above could play a pivotal role. Once the targeted activity patterns in sensory and motor areas are produced through sensory stimulation and movement, it would be up to behavioral reverse engineering to identify the cognitive or environmental agonists agonists that produce reliably timed neuromodulatory surges, as indexed through concurrent brain imaging or other autonomic proxies such as phasic changes in pupil diameter. Alternatively, the neuromodulatory levels associated with heightened plasticity could be elevated artificially while the corrective sensory stimulus or motor sequence is produced. This could be accomplished with relatively coarse temporal resolution using pharmacological approaches (Gervain et al., 2013; Rokem and Silver, 2013, but see Chung et al., 2017), or with more precise temporal synchronization using peripheral nerve stimulation (Naufel et al., 2020).

As another example, associative synaptic strengthening of the connections between neurons (i.e., Hebbian plasticity) is sufficient to produce aversive associative learning under laboratory conditions based on strong and iterative conditioning protocols. Under moderate training conditions, however, Hebbian mechanisms alone are necessary but not sufficient to produce aversive associative memory formation through neural plasticity in the lateral amygdala—the activation of beta-adrenergic receptors is an additional requirement (Johansen et al., 2014). Such cooperation between neuromodulatory and Hebbian mechanisms indicates that even highly plastic learning systems may not always reside in a permissive state. Behavioral reverse engineering would have to be attuned to both the neural circuit activation and its neuromodulatory permissive state. In a clinical setting, for example, the behavioral task could be performed under conditions of high or low arousal, depending on the desired direction of modulation.

8.2. Applications in which the targeted neural process is inherently plastic but a targeted neural biomarker is challenging to measure or manipulate during controlled behavioral interventions

Consider the case of memory circuits of simple associative learning, which could be tagged and manipulated to selectively engage the memory engram (Josselyn et al., 2015). For example, long after an aversive context conditioning, the reactivation of this remote memory—defined as recall-induced activation of neurons in the dentate gyrus—was required to induce memory attenuation via extinction. The more neurons were reactivated, the stronger was the remote memory attenuation through extinction (Khalaf et al., 2018). This finding suggests that, in a clinical setting, recall-induced engagement of traumatic memory circuits may be a prerequisite for effective behavioral therapy. Memory destabilization may also be constrained or facilitated by neuromodulatory activity (Wideman et al., 2018), further pointing to important behavioral task elements.

In the human brain, it is yet unclear whether a certain memory engram has been reactivated and mobilized into a labile state during recall (Cassini et al., 2017; Vaverková et al., 2020). There are behavioral parameters that have been shown to destabilize memory, such as the presence of a prediction error—when cue-induced expectations are violated—signaling a need to update the memory representation. Such parameters could guide the search for the right behavioral task for memory reactivation (Díaz-Mataix et al., 2013; Kida, 2019; Sevenster et al., 2014). In the clinic, prediction error could be systematically manipulated, for example, by using different lengths of reminder duration (Hu et al., 2018). Behavioral parameters of the retrieval cue should be accompanied by biomarker measurement, such as event-related potentials (Campos-Arteaga et al., 2020; Mueller et al., 2014; Mueller and Pizzagalli, 2015) or fMRI signals of resting-state functional connectivity (Hermans et al., 2017), which may capture a downstream surrogate of the cellular and molecular mechanisms of memory consolidation, destabilization, and attenuation.

Following the previous example, let's consider the case of traumatic memories, which are strong, persistent, and intrusive. Let's assume we have the right manipulation to return these memories into a labile state using reactivation methods. How could we now coax a change or an update in these modification-resistant memories? Research suggests drugs (Brunet et al., 2018; Kindt et al., 2009) or devices (Borgomaneri et al., 2020; Sandrini et al., 2015) that interfere with the restabilization (reconsolidation) of the memory could serve this purpose. Alternatively, (or in conjunction with drugs and devices), a behavioral agonist following memory destabilization may be effective in inducing a permanent change through updating of the original memory (Cassini et al., 2017; Lee et al., 2017).

Behavioral stimulation of emotional memory could also take the form of a behavioral interference process that in and of itself is irrelevant to emotional processes. For example, the method of eye movement desensitization and reprocessing (EMDR) has gained traction in recent years as a possible treatment for maladaptive aversive memories and psychological stress relief. During an EMDR session, the aversive memory is triggered while the therapist directs the patient's eye movements rhythmically from side to side or uses other bilateral stimulations like hand movements (Novo Navarro et al., 2018). Research on the neural mechanisms of EMDR is still in its infancy, but the outcomes are intriguing. Preliminary evidence for the underlying mechanisms suggests long-range synchronization among brain regions, including interhemispheric communication between the right and left hemispheres, and region-to-region connectivity within and between the attention and default mode networks (Calancie et al., 2018). It is also possible that EMDR causes transient suppression of amygdala activity (de Voogd et al., 2018), in which case it may serve as a behavioral antagonist for undesired biomarker activation. Essentially, in the context of attenuating traumatic memories, any behavior that competes with the resources of memory restabilization, or capitalizes on

reconsolidation mechanisms for enduring change, will be a viable candidate for behavioral reverse engineering.

8.3. Choreographing controlled behaviors with targeted changes in neural biomarkers: the case of brain training games versus digital therapeutics

Leveraging behavior to reverse the neural underpinnings of declining mental health and cognition has been with us—occasionally for the better, sometimes for the worse—for quite some time. Computerized "brain training" games first came to the fore 25 years ago as a means of reversing low-level auditory processing deficits in children with specific language impairment (Merzenich et al., 1996; Tallal et al., 1996), but has since grown into an unwieldy commercial and academic industry that promotes behavioral training exercises as means of reversing or forestalling deleterious behaviors and cognitive processes associated with aging and a wide spectrum of neuropsychiatric disorders. Within this vast literature are a few success stories that underscore the tremendous potential of these relatively low-tech behavioral interventions.

A key distinction between the most successful efforts and all the rest is whether the behavioral intervention targets a dysfunctional neural circuit or surrogate neural biomarker, or instead targets the behavior without considering the underlying neural process. While there is a certain surface logic for training people with poor working memory on working memory tasks, it does little to address the underlying core defect. The behavioral deficiencies targeted by most forms of brain training are the downstream consequences of distributed upstream neurological failures, and it is therefore totally unsurprising that training on the downstream process can narrowly improve performance on the training set without imparting a more generalized transfer of benefits to unpracticed stimuli or behavioral contexts.

The success stories of brain training may not have always tuned their behavioral intervention through concurrent neural measurements, but they have been validated through well-designed experiments and emphasize training targets that promote a broad transfer of learning to untrained clinical outcome measures. They are also nearly always based on neurophysiological studies in animals and humans, and - most importantly—they have typically focused on a neural process that serves as a root directory for a wide range of downstream cognitive processes, not on the clinical symptom itself. As one example, EndeavorRX is the first FDA-approved computerized training product, which can be prescribed for poor attentional control in children with attention deficit hyperactivity disorder. The core architecture of the computerized training exercises target distractor suppression processes that were directly linked to a human EEG biomarker (frontal theta power) and underlying single neuron processes in animal models from prior studies (Anguera et al., 2013; Mishra et al., 2014).

The vast wilderness of brain training is likely splitting into a large cohort of computer exercises that are diverting but offer little in the way of lasting changes in brain function, and a smaller cadre of prescription digital therapeutics that must pass stringent regulatory requirements after validation through randomized control trials. This latter class holds the most potential for neurobehavioral therapies, particularly when their claims of clinical efficacy can be supported with adequately powered placebo controlled double-blind study designs (Green et al., 2019), and when the rich behavioral milieu of virtual computerized platforms can be combined with real-time measurements of carefully selected neural biomarkers.

9. Concluding remarks

Twenty-first century neuroscience research is confronted with an old, stubbornly unresolved, challenge: treating mental disorders of the brain. Modern neuroscientific research tools have revealed the intricate richness of brain circuits composed of multitudes of genetically distinct nerve cells. Traditional approaches, although the best we currently have, are fundamentally limited by (i) their scale—targeting vast regions composed of multitudes of underlying neuron types, and (ii) their specificity—manipulating genetically heterogenous neurons that performs distinct roles within local and distributed neural circuits.

Nowadays, discussions about next-generation brain therapies are often focused on the translation of the same tools that fueled the rapid pace of laboratory behavioral neuroscience research. It is easy to be optimistic and envision a point on the horizon where the development and translation of these tools for use in humans will converge with the standard of care for neuropsychiatric disorders. Precisely here, in the transition from discovery to treatment, lies the focus of this review article. We also look forward to what high-tech treatments for brain-based disorders may one day look like, but here we wish to draw attention to relatively low-tech, less invasive, less costly, less risky, and less widely appreciated approaches that have tremendous potential for the near-term reduction of the burden that mental health disorders impose on individual lives, families, and societies.

We have argued that behavior can be considered as both a product and a source of neural activity, and have drawn attention to studies that have leveraged behavior to ameliorate neurological and psychiatric conditions ranging from traumatic memory to tinnitus. Even though the neural activity patterns produced through controlled behaviors are less precise than what can be accomplished with high-tech methods, the activity would likely flow through more natural circuits of interconnected cell types with more normative spatiotemporal patterns. We suggested that by studying carefully selected neural biomarkers in close temporal proximity with behavioral stimulation, it maybe be possible to reveal agonists that could then be iteratively (and individually) distilled and refined to form the basis of a behavioral therapy. Behavioral agonists could target an abnormal neural biomarker with the intent of shifting it towards a neurotypical endpoint or could target endogenous neuromodulatory systems that regulate braking mechanisms on adult brain plasticity.

The detailed analysis of functional brain circuits at their native scale provides the blueprint that would guide the selection of behavioral agonists for these circuits or their surrogate biomarkers. As with the serendipitous psychiatric drug discovery that dominated the previous century, forms of cognitive-behavioral therapy largely emerged independent of neural mechanistic insight. We have argued here that both the identification of non-invasive neural biomarkers as well as behavioral agonists in humans should be anchored in an understanding of circuit-level mechanisms and their related macroscopic physiological signatures from animal studies. In human subjects, biomarkers could be derived directly from neural activity (e.g., an event-related potential), an indirect physiological measure (e.g., a resting state fMRI network or pupil dilations), or even an objective low-level computational (Niv, 2021) or behavioral readout (e.g., micro facial expression, saccadic eye movements). Whereas the conventional usage of "biomarker" amounts to any measurable signal that can be correlated with any aspect of the disease process, we emphasized the selection of biomarkers that can be measured during behavior, or in close temporal proximity to behavior.

Although measurements of human brain activity are notoriously noisy and require extensive trial averaging with traditional analysis approaches, significant progress has been made in recent years with machine-learning assisted real-time decoding of brain states based on EEG (Abiri et al., 2019; Geirnaert et al., 2021), fMRI (Sorger and Goebel, 2020; Watanabe et al., 2017), and movement videography (Sehara et al., 2021). Given the pace and astonishing progress made in human health applications of machine learning, the development of algorithms to monitor real-time biomarker dynamics and compute behavioral features closely associated with changes in those markers towards neurotypical endpoints, appears to us as a plausible and worthy area for future research.

Identifying biomarkers that can be linked to circuitopathies underlying core neural defects is key, and this process will be greatly facilitated by animal studies that relate neurobiological measurements to the

type of signals that can be measured in human subjects and—conversely—a willingness among clinical researchers to think creatively about the selection of new measurement targets based on publications in animal models. Developing new approaches for treating brain-based disorders demands a call for action: we must create channels for ongoing and smooth communication across levels of investigation. There has to be an iterative exchange of information between circuit-level basic neuroscientists, system-level cognitive neuroscientists, and clinical psychiatrists. Multidisciplinary and integrative research programs should be created with the explicit goal of identifying functional neural circuits that are relevant for psychiatric disease, behavioral reverse engineering of those circuits, designing behavioral stimulation methods with their appropriate mechanistic-level biomarkers, and their implementation in clinical populations.

The behavioral reverse engineering approach described here will not be a solution that fits all brain disorders. For behavioral reverse engineering to be successful, a certain set of conditions need to be established: (i) the subject's physical wellness and neurological health be sufficiently intact, such that the subjects understand instructions, produce behaviors, and generate the targeted neural biomarker; (ii) there is a good enough understanding of neural circuits and macroscopic pathophysiological signatures; (iii) there are candidate central nervous system disorders for which behavioral stimulation is relevant. Here, we emphasized certain classes of perceptual disorders and mood disorders as reasonable ongoing and future targets for this approach. When the conditions above are not met, exogenous tools that act directly on the brain may be the better option. But within this sweet spot, it may be the right time to invest more effort into low-tech, more cost-effective, minimally invasive, neuroscience-based approaches that rely on behavior as an agonist to stimulate the brain's endogenous systems for change, repair, and healing.

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