

Neural Circuit Reprogramming: A New Paradigm for Treating Neuropsychiatric Disease?

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<http://dx.doi.org/10.1016/j.neuron.2014.08.022>

Theoretically, harnessing the brain's own endogenous plasticity mechanisms could serve to alter both internal states and external behavior in a therapeutic manner.

If I were to describe a future therapy for chronic, relapsing neuropsychiatric diseases where patients with anxiety, depression, or addiction could receive a painless treatment over a few days and emerge permanently cured without any undesirable side-effects, you might think this was science fiction. This scenario might seem fanciful in light of our current go-to strategies for treatment, which involve systemically administered drugs that bind to receptors throughout the brain and body. For the past few decades, progress in the medical treatment of neuropsychiatric disease states has been incremental. In our modern era, safety is a chief concern, so medicine typically follows science. There is good cause for caution, and scientific understanding should precede the medical treatment of brain disease. But how far must available treatments trail behind scientific insight?

The Path to Where We Are Now

In terms of first-line therapies, we are still making use of technologies and fundamental principles identified nearly a century ago, such as pharmacological agents. While new drugs are steadily being identified, the majority of these are variants of existing compounds. Other therapies, usually only used when patients are resistant to drug treatments, include electroconvulsive therapy (ECT) and deep-brain stimulation (DBS). ECT has been used to treat depressed patients for nearly 80 years. DBS has a slightly shorter history but has been used since the 1980s to treat tremors associated with Parkinson's disease (Brice and McLellan, 1980). More recently, DBS has been used to treat neuropsychiatric disorders such as depression (Mayberg et al., 2005). Despite evidence of superior effi-

cacy, ECT and DBS are not first-line treatments because of the risks and side-effects. ECT delivers electric shocks to induce seizures, and side-effects ranging from tissue and skeletal injuries to cardiovascular problems, as well as impairments in memory and cognition, have been reported. DBS requires an invasive surgery that inevitably incurs some damage to brain tissue.

In contrast to medicine, the progress in neuroscience research has been accelerating at an explosive pace in the past two decades. New technological developments have ushered in a new era for understanding the brain. While the 1990s introduced the power of multiphoton imaging along with glutamate uncaging, an approach that allows the activation of individual dendritic spines, this approach was largely reserved for the scientific elite—only those in the upper echelon of funding or those with access to premium facilities. By the turn of the millennium, an extraordinary level of spatial precision had been achieved with multiphoton imaging (Denk et al., 1990), a strong community had formed in elucidating the fundamental principles in synaptic plasticity (Malenka and Bear, 2004; Turriano, 2012), and the visualization of certain cell types using fluorescent proteins powerfully transformed our ability to observe a plethora of biological processes (Tsien, 1998).

In terms of manipulating the activity of neural circuit components to reveal causal relationships with behavior, optogenetic tools broke open the flood gates by making the ability to activate or inhibit specific cells and even populations of synapses with millisecond precision available to even the modestly funded researcher (Adamantidis et al., 2007; Boy-

den et al., 2005; Tye and Deisseroth, 2012). With the recent proliferation of studies demonstrating that acute modulation of synaptic transmission can produce acute changes in behavior, we are well positioned to combine this knowledge base with our understanding of synaptic plasticity. Given that we can alter transmission at specific synapses (Stuber et al., 2011; Tye et al., 2011), can we induce plasticity and therefore induce long-lasting changes in behavior? By establishing a new baseline level of synaptic transmission, we inevitably influence the downstream network.

Foundation for the Future

In terms of looking forward, toward a new era of therapy, neuroscience research has already begun a strong shift from general pharmacology to a circuit-based understanding of how the brain gives rise to behavior.

Hebbian plasticity mechanisms such as long-term potentiation (LTP) and long-term depression (LTD) have been identified as the cellular bases for learning and memory. Experiments demonstrating that ablating select neurons involved in the “memory engram” impaired memory formation and retrieval have also provided key insights toward how memories are stored in the brain (Han et al., 2009; Koya et al., 2009). Conversely, activating ensembles of neurons that encode an associative memory can elicit behaviors that suggest the animal is recalling that memory (Garner et al., 2012; Liu et al., 2012). However, these experiments have involved the modulation of ensembles of neurons, rather than populations of synapses. More recently the explicit induction of LTP and LTD has been shown to enable experimenters to “toggle” the

expression of a fear memory (Nabavi et al., 2014) or to reverse drug-induced behaviors (Pascoli et al., 2012); even further, it has shown that this could occur in an input-specific manner (Pascoli et al., 2014).

Homeostatic plasticity mechanisms are generally conceptualized to serve as a stabilizing force in a highly plastic system to keep synapses within a functional dynamic range and prevent the overexcitation (or inhibition) that could occur with Hebbian plasticity mechanisms (Turriano, 2012). In contrast to Hebbian plasticity, which typically underlies learning about discrete stimuli, contexts, or experiences and has relevance to disease states such as PTSD or drug abuse, homeostatic plasticity may be more relevant to chronic neuropsychiatric disease states that are independent of learning per se, such as anxiety or depression. Indeed, both pharmacologic and optogenetic-mediated sustained activation induced homeostatic plasticity that reduced depression-related behaviors in a mouse model (Friedman et al., 2014).

The Road Forward

Based on these exciting studies that have used optogenetic tools to induce Hebbian or homeostatic forms of plasticity in vivo to alter subsequent behavior, we can now ask the question of whether an acutely induced manipulation of synaptic strength could produce long-lasting—or even permanent—changes in behavior. While these studies have broken new ground, we have much work to do in terms of laying down a solid foundation for a new paradigm for therapy. New questions can now be asked and answered:

What are the best parameters for inducing a change to a stable “new baseline”? There are many populations of synapses to probe, and many types of plasticity that can occur, so answering this question will require the systematic investigation of various circuit connections, behavioral readouts, plasticity induction protocols, and time points for testing. In essence, painstaking optimization is required to identify the briefest treatment period and the longest, most robust, and most stable therapeutic effect. Importantly, different circuits may have unique optimal parameters.

What does plasticity at a given population of synapses do to the rest of the circuit? While there have been major advances in terms of high-density recordings in animal models along with a new focus on “big data” sets, achieving a complete answer in a noninvasive manner in the human brain is not yet possible, though efforts toward this goal have been made. Much work remains to be done in terms of the ultrastructural characterization of all the neurons in the brain. Even if the entirety of anatomical connections were known, the functional relevance in terms of behavior represents an even more formidable task given the vast parameter space. For now, we can build upon acute manipulations of synaptic transmission and observe how changes in synaptic transmission or the strength of certain synapses impacts activity in a subset of neurons in the associated circuit, and even this represents a great challenge that will involve the efforts of many research groups.

How could plasticity at specific populations of synapses be induced safely and noninvasively in humans? This is the most important, yet most challenging, question to answer. The first step is to capitalize on powerful, but invasive, manipulations in animals to establish a comprehensive characterization of various targets, and the relative potency and specific behavioral and cognitive changes that occur when plasticity is induced at a given neural circuit locus. Once ideal targets have been identified, translation to humans could occur using a hybrid of stimulus presentations and cognitive behavioral therapy, and noninvasive manipulation of neural activity at specific sites could be used to achieve site-specific plasticity. While many of these tools are still in development and/or require further optimization, transcranial magnetic stimulation (TMS) as a technique for noninvasive, transient manipulation of neural activity shows promise in inducing plasticity and changing subsequent behavior (Gorelick et al., 2014). However, these approaches do not allow for the cell-type- and projection-specific precision of optogenetic manipulations. While the toolbox of opsin variants is growing, and the use of red-shifted opsins could indeed sidestep the necessity for implanting an optical fiber

into brain tissue, the greater concern with respect to safety is the expression strategy. Most viruses show some toxicity after long periods of expression, and to warrant use in humans, nontoxic expression must be demonstrated on the order of at least ten years or so. Thus, the winning strategy for translation to humans remains to be determined, and improvements in the penetration and specificity of tools such as TMS and the development of nontoxic viral vectors will both take time to develop and test. Other solutions will probably surface in the coming decade, but admittedly, this represents the greatest challenge in a shift toward circuit-based therapeutics.

And then there are other questions. *In the case that science and technology triumph, what are the ethical considerations for neural circuit reprogramming? What else needs to happen to make this a reality?* In addition to the scientific, technological, and optimization challenges discussed above, there is the issue of inertia. Drugs have had a very long history of medical use. For ailments of the body, they will probably remain the first-line therapy for the foreseeable future. Ailments of the brain represent an entirely different beast, and first-line treatments may very well change as we embark on this “golden era” in neuroscience research.

Translation or Reverse Translation?

Perhaps the concept of neural circuit reprogramming as a more effective strategy for mental health treatment is not so unbelievable, or even so new, after all. Another perspective could be that this is a reverse translational concept, confirming theories that plasticity is the mechanism mediating the therapeutic effect of antidepressant treatments, from drugs to ECT. Whether you believe that neural circuit reprogramming as a strategy for therapy represents a major paradigm shift or an improvement on a crude but effective approach, a shift toward circuit-based diagnostics and treatments has the potential to transform the quality of mental health treatment.

ACKNOWLEDGMENTS

I thank S. Allsop, A. Burgos-Robles, and C. Eckhardt for comments and discussion. K.M.T. acknowledges funding from the Whitehall Foundation, Klingenstein Foundation, NARSAD Young Investigator Award, Alfred P. Sloan Foundation,

RF1-AG047661-01 (NIH), Whitehead Career Development Chair, JPB Foundation, PIIF Funding, PNDRF Funding, R01-MH102441-01 (NIMH), and NIH Director's New Investigator Award DP2-DK-102256-01 (NIDDK).

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