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## Opportunity Cost

### Definition

The value that would have accrued to an agent had it pursued an alternative course of action during the time spent in a chosen activity.

### Cross-References

► Intracranial Self-Stimulation

## Optogenetics

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### Synonyms

Optical neural control; Photostimulation

### Definition

A neuromodulatory set of tools and techniques in neuroscience that involve the introduction of light-sensitive proteins, called opsins, into living cells and into the intact brain of freely moving animals to permit real-time control (both electrical and biochemical) of genetically defined populations of cells and neural circuits with both high spatial and temporal precision.

### Principles and Role in Psychopharmacology

#### Neuropsychiatric Illness as a Disease of Altered Brain Circuitry

A paradigm shift is occurring in how scientists and clinicians fundamentally think of neuropsychiatric diseases. Although psychopathology has long been thought to represent underlying neural chemical imbalances, it is becoming increasingly recognized that such an approach may not fully capture the complexity of neuropsychiatric illness. Indeed, pharmaceutical research and development based on this chemical imbalance approach has produced drugs that have proven frustrating in their lack of efficacy in a large portion of the patient population. Newer approaches that involve fundamental changes to how we view neuropsychiatric illness are required before great strides can be made.

The success of non-pharmacological approaches to the treatment of neurological and psychiatric illnesses suggests that altered brain circuitry may be the pathological driving force. For instance, electricity in the form of electroconvulsive shock therapy has been historically used to "jolt" the brain back into function and is the most effective treatment for depressions that are nonresponsive to drug therapy. More recently, deep brain stimulation (DBS) treatment has shown much promise for treating brain disorders. DBS involves the delivery of precise high-frequency electrical stimulation into affected brain areas for alleviation of patient symptoms. DBS of brain regions such as cortical area 25 and of the medial forebrain bundle has been successful at treating treatment-resistant depressions. Stimulation of the ventral striatum has been successful for the treatment of obsessive-compulsive disorder, and DBS of the nucleus accumbens has

proven useful in the treatment of drug addiction. As such, there is a growing awareness and agreement that certain brain disorders may be better conceptualized as diseases of chronic circuit-wide disruption. The exact mechanisms underlying the effectiveness of DBS, however, are currently unknown. Transformative leaps in our understanding of brain function have often been the direct result of the development of new tools for interrogating neural circuits. A new set of transformative tools has opened the doors to the study of how disrupted neural circuits ultimately lead to disease.

## Optogenetics as a Tool to Investigate Neural Circuit Function

The development of optogenetics has revolutionized the fields of behavioral and systems neuroscience with recent years witnessing an explosion of new scientific knowledge resulting directly from the use of this new technology. Optogenetics, in which genetically encoded, light-sensitive channels, pumps, and receptors are used to control the function of specific neurons, has enabled the dissection of the neural circuits mediating cognition and behavior with unprecedented temporal and spatial precision (Boyden et al. 2005). The brain is composed of tens of thousands of different kinds of neurons, each composed of a different combination of molecules that confers a distinct identity and function. These different cell types are tightly intermingled in a complex and heterogeneous neural thicket, which makes discerning their individual contributions to brain function a challenge. Traditional causal approaches to the study of neural circuits include lesion, electrical, and pharmacological approaches, which have been highly successful at advancing our understanding of brain function. For instance, lesions and electrical stimulation have enabled us to pinpoint precise brain regions mediating specific cognitive or behavioral functions, but have not enabled a more precise dissection of the underlying neural circuitry, as these approaches are usually not capable of targeting distinct cell types. Likewise, pharmacological approaches have been invaluable for probing the function of specific neurons defined by the receptors they express, but this approach lacks the temporal specificity required to obtain a full understanding of the millisecond-precision neural dynamics used by the brain.

The discovery and application of single-component microbial opsins was pivotal to the widespread adoption of optogenetics as an essential tool for probing neural function. As the expression of these opsins can be constrained to particular cell types, either defined by genetic identity or by topology, these tools have the potential to target neural circuits with unprecedented precision. Indeed, a central hope in the field is that these tools will eventually find clinical application without the side effects that often plague current therapeutic approaches as a result of this increased specificity. In addition, these tools are capable of influencing neural processing on a millisecond time scale; they speak the fast electrical language of the brain.

Previous attempts to optically control neural activity had made some headway, but most of these technologies required the application of exogenous cofactors (chemical chromophores) that made routine use in mammalian systems difficult. The first successful use of optogenetics to control neural activity employed the single-component microbial opsin channelrhodopsin-2 (ChR2) (Boyden et al. 2005). This opsin, derived from the green alga *Chlamydomonas reinhardtii*, is a membrane-bound cation channel that can be expressed in genetically engineered neurons. Upon exposure to a short pulse of blue light, this channel opens, leading to the depolarization of the neuron and the generation of a single action potential. Initial experiments demonstrated the functional use of this channel to control neural activity in cultured hippocampal neurons; subsequent experiments have extended use to freely behaving vertebrate and invertebrate systems.

In the years since this first application, many new opsins – both naturally occurring and engineered – have been used to control neural activity in different and complimentary ways (Mattis et al. 2012). The inhibitory opsin shown

to be useful for in vivo applications was a halorhodopsin (NpHR) from the halobacteria *Natronomonas pharaonis*. This opsin, a chloride pump with peak photosensitivity at ~590 nm, hyperpolarizes and therefore silences neurons when they are exposed to yellow light. Other tools for inhibition of neural activity include the outward proton pumps Arch (from *Halorubrum sodomense*) and Mac (from *Leptosphaeria maculans*), now both optimized for use in mammalian systems (eArch3.0 and eMac3.0).

### Using Optogenetics in Preclinical Animal Models to Dissect the Neural Circuitry of Complex Behavioral States

Optogenetic tools have been widely used in both vertebrate and non-vertebrate systems. For the study of complex behavioral states relevant to human disease, rodents (mice and rats) have been the model organisms of choice. Indeed, optogenetics has been widely used in awake, freely moving rodents to study normal brain function and to understand how disrupted neural circuit activity drives altered behavioral states relevant to neurological conditions and psychiatric diseases (Tye and Deisseroth 2012; Nieh et al. 2013). The design and implementation of neural-optical interfaces optimized for the delivery of light to the intact brain has been instrumental in the ability to modulate circuit activity in awake, freely moving animals (Aravanis et al. 2007). Time-locked behavioral responses to neural circuit manipulation has allowed neuroscientists, for the first time, to ask causal questions linking altered circuit activity to a given behavioral state. For instance, studies examining normal brain function have investigated the neural circuitry underlying learning and memory, sleep-wake and arousal, locomotion, feeding behavior, motivation, stress, and social behavior, to name a few. These studies have provided great insight into the functional consequences of altered neural circuit activity in various neurological conditions, including Parkinson's disease and epilepsy. Additionally, optogenetic applications in rodents have been used to study core behavioral features that are observed across human neuropsychiatric diseases, such as depression, anxiety, fear, reward (natural and drug), and addiction.

### Combining Optogenetic Technology with Pharmacological Approaches

Opsin-based technology has excelled at manipulating neural activity through direct changes to ion conductance or through altering synaptic activity. The advantage of manipulating the electrical activity of the brain using optogenetics is the millisecond temporal specificity obtained, which permits time-locked behavioral responses to modulation of neural activity. However, neurological and psychiatric disorders can be conceptualized as diseases of chronic circuit dysfunction that develop over extended time scales. Long-term disruption of brain activity likely induces neural adaptive molecular changes that extend beyond immediate changes to membrane voltage to fundamentally alter the way circuits behave and function. These adaptive molecular changes can include altered intracellular signaling, protein-protein interactions, receptor expression, and neurotransmitter secretion, which ultimately involve changes at the gene transcription level. Indeed, there is a small but growing literature employing chronic optogenetic stimulation paradigms to induce sustained physiological and behavioral changes that persist well after cessation of optic stimulation (Sidor and McClung 2014). These will be essential in systematically investigating how chronic circuit disruption alters biochemical processes. In turn, delineating the biochemical changes that result from prolonged circuit disruption will be essential in understanding the molecular basis of brain disease. Technology that integrates optogenetics with molecular- and genetic-based approaches for circuit modulation will be crucial to investigating the neural adaptive changes that support abnormal physiology and behavior. Exciting new technologies and tools are emerging (discussed below) that combine the temporal and spatial precision of optogenetics with biochemical tools for user-defined manipulation of intracellular signaling pathways, receptor function, and gene expression (Stuber and Mason 2013).

OptoXRs are synthetic genetically encoded receptors that permit bidirectional control of intracellular G-protein-coupled signaling in vivo (Fig.1a). Briefly, these are a group of opsin/receptor chimeras between the light-sensitive protein, rhodopsin, and the β2-adrenergic receptor (for Gs control) or α1-adrenergic receptor (for Gq control). These receptors are engineered for insensitivity to endogenous chemical ligands in place of sensitivity to light. Transduction of OptoXRs in the nucleus accumbens of mice demonstrated their utility for altering biochemical cellular events at the precisely required time scales needed to support an operant conditioning behavioral task.

Optopharmacology involves the use of tools that fuse light-sensitive proteins to effector molecules for the control of channel and receptor function. These include caged ligands and chemical photoswitches (Fig. 1b). Briefly, caged ligands are released from a photosensitive protecting group in response to light where the uncaged ligand can now act on native channels and receptors. Chemical photoswitches undergo a conformational change upon illumination with light that permits binding of the ligand to its native receptor. The temporal specificity imparted through the use of light-sensitive ligands circumvents the disadvantages plagued by traditional pharmacological approaches. However, this approach still lacks the spatial precision for cell-specific targeting.

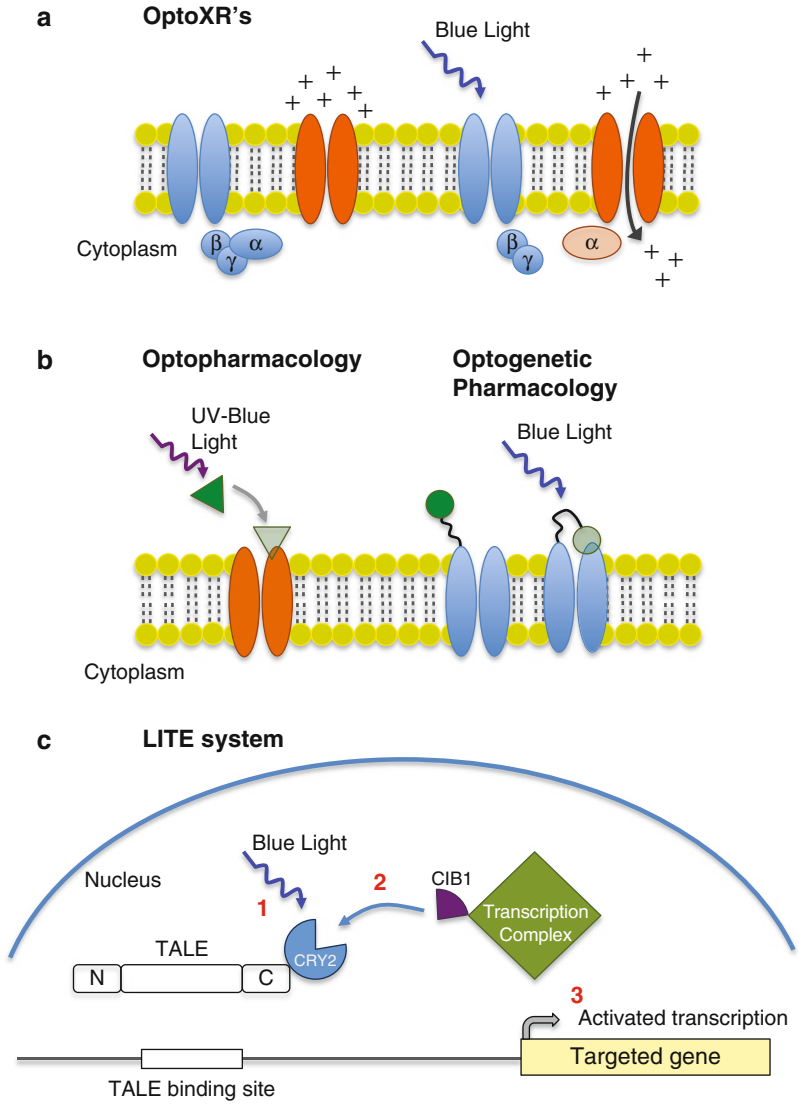
Optogenetic pharmacology represents an improvement on existing technologies that involves the use of designer ion channels and receptors that are made sensitive to synthetic light-activated ligands (photochromic ligands; Fig. 1b). Because these exogenous receptors are genetically engineered, any receptor subtype can be inserted into a neuronal population of interest. This is important since traditional optopharmacological approaches lacked the ability to specifically target native neurotransmitter receptor subtypes. Furthermore, the use of genetic technology permits insertion of designer channels and receptors into specified cell types. Optogenetic pharmacology, therefore, solves both the receptor subtype specificity issue and cell-targeting problems associated with conventional optopharmacology (Kramer et al. 2013).

The *L*ight-*I*nducible *T*ranscriptional *E*ffectors (LITEs) system uses a two-component modular design that enables the optical control of gene transcription in select cell types with the temporal precision of optogenetics (Fig. 1c; Konermann et al. 2013). Here, the naturally light-sensitive protein, cryptochrome-2 (CRY2) protein, is fused to a transcription-activator-like effectors (TALE) DNA-binding domain (1st component) that can be custom engineered to bind any DNA sequence of interest. Illumination with blue light induces a conformational change in CRY2 that recruits a customizable effector (2nd component) to the gene target for activation or repression of transcription. Additional light-switchable transgene expression systems are currently in development (Wang et al. 2012), meaning there is great potential for using these tools to investigate how altered gene function in specific populations of neurons affects normal and diseased brain states.

## Summary

### Optogenetics for Targeted Drug Discovery

The future of optogenetics in the context of drug discovery starts with the exploration and identification of distinct gene regulation patterns that occur in response to cell-type-specific optogenetic manipulation of neural circuits that drive pathological behavioral states. Combining optogenetics with deep-sequencing approaches, such as high-throughput RNA sequencing technology (RNA-seq), will prove instrumental in profiling the cell-type-specific transcriptional changes that occur in response to neural circuit modulation (Stuber and Mason 2013). RNA-seq is a whole transcriptome analysis technique that can sequence the entire transcriptome from single cells of a specific cell type or from whole brain regions for the non-biased identification of candidate genes (transcriptome is the functional "readout" of the genome that includes all classes of coding and noncoding RNA molecules found in a single cell or in a collection of cells).




**Optogenetics, Fig. 1** (**a**). OptoXRs are a component of the optogenetic toolbox that permit bidirectional and temporally precise control of intracellular G-protein-coupled signaling in genetically defined cell populations. These are a group of opsin/receptor chimeras between the light-sensitive protein, rhodopsin, and the β2-adrenergic receptor (for Gs control) or α1-adrenergic receptor (for Gq control). (**b**). An example of a photoactivatable ligand (*left*) that permits binding of the ligand to its native receptor upon illumination with UV light. Such optopharmacology tools represent an improvement on traditional agonist/antagonist pharmacological approaches by increasing the temporal precision of receptor control. However, the ability to target specific receptor cell types is not possible. Compare this with optogenetic pharmacology (*right*) that uses genetically engineered, or designer, receptors and ion channels, which are light sensitive, to control specific receptors and cell types with the temporal and spatial precision imparted by optogenetics. (**c**). Newer technologies, such as the *L*ight-*I*nducible *T*ranscriptional *E*ffectors (LITEs) system, can turn gene transcription on and off in specific cell types through use of the natural light-sensitive protein, cytochrome 2 (*CRY2*). In this system, CRY2 is bound to a transcription-activator-like effector (*TALE*) DNA-binding domain that is engineered to bind specific DNA sequences. *Blue light* induces a conformation change in CRY2 (step 1) that enables the protein to fuse to a transcription complex (step 2) which then activates transcription (step 3) (Figure C adapted from: Konermann et al. (2013))

Once candidate genes are identified, their role in mediating a particular behavioral state will need to be systematically analyzed and validated. Through a reverse engineering approach, it may be possible to use the findings from these optogenetic-transcriptome approaches to design drugs that target specific populations of neurons based on their unique gene regulation profile. Ultimately, the ability to deliver such drugs to the brain in a cell- or circuit-specific manner will depend on emerging technologies for targeted small molecule delivery. The continued development and refinement of transformative tools will depend on a multidisciplinary approach that combines efforts across the fields of neuroscience, pharmacology, engineering, and related disciplines to inform the development of improved and novel pharmacotherapies for neurological and psychiatric diseases.

## Cross-References

- ▶ Animal Models for Psychiatric States
- ▶ Anxiety: Animal Models
- ▶ Depression: Animal Models
- ▶ Electrochemical Techniques
- ▶ Genetically Modified Animals

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# Orexigenic

## Definition

Systems or endogenous factors that provoke and/or sustain eating events.

## Cross-References

- ▶ Appetite Stimulants

# Organic Brain Syndromes

## Definition

Organic brain syndrome is a largely obsolete term that refers to mental dysfunction resulting from a physical, as opposed to primary psychiatric, disorder. Examples of diseases causing organic