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Optogenetic dissection of neural circuitry: from synaptic causalities to blue prints for novel treatments of behavioral diseases

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Optogenetics has enabled the characterization of the neural circuits involved in brain diseases, such as addiction, depression or obsessive compulsive disorders. Recently, the technique has also been used to propose blueprints for novel treatments aiming at restoring circuit function through the reversal of specific forms of synaptic plasticity. Since optogenetic manipulations cannot be immediately translated to human use, we argue that an intermediate strategy could consist of emulating optogenetic protocols with deep brain stimulation (DBS). This translational path to rational, optogenetically inspired DBS protocols starts by refining existing approaches and carries the hope to expand to novel indications.

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Disorders caused by neuronal circuit dysfunction

Diseases of the brain represent a tremendous personal and financial burden to society [1]. Some conditions are defined by the death of neurons such as stroke, Parkinson's disease, or Alzheimers disease. In contrast, a large number of disorders are characterized by dysfunction of neuronal circuits: a functional ensemble of neurons connected via synapses [2]. Neuronal circuit dysfunction is characteristic of depression, obsessive-compulsive disorder, schizophrenia and addiction, for example. Since no neurons are lost, no macroscopic structural alteration occurs, which precludes the diagnosis with classical imaging methods. Pre-clinical models are therefore particularly useful because they allow invasive functional investigation of the disease pathology with cellular resolution. To this end, the advent of optogenetics has allowed for the dissection of underlying neural circuits and their alterations in mouse models of brain diseases. Combining cell type-specific viral expression of the light-sensitive effectors with stereotactic region targeting and precise focus of optic fibers, optogenetic manipulations allow for the control of defined neurons *in vivo*. In this review, we focus on addiction as a case study in the synaptic and circuit basis of disease and discuss how optogenetic manipulations of neuronal circuitry can inspire novel treatments for this disorder.

The synapse as site of pathology in addiction

A leading hypothesis posits that addictive drugs hijack the mesocortico-limbic dopamine (DA) system [3]. This starts with a strong increase of extracellular DA levels, an acute effect shared by all drugs tested to date [4,5]. This is followed by activation of intracellular pathways [6] leading to a long lasting remodeling of synaptic transmission that outlasts the presence of the drug in the brain, even in the case of a single exposure [7]. With repeated drug consumption, drug-evoked synaptic plasticity can persist for weeks and months. Even if consumption is ceased, synaptic transmission remains altered and contributes to craving and relapse, two defining symptoms of addiction. We will briefly review some of the key features of drug-evoked synaptic plasticity to develop the rationale for reversal strategies.

After a single exposure to an addictive drug, glutamatergic afferents from the laterodorsal tegmentum onto DA neurons of the VTA that project to the NAc are strengthened for approximately seven days [8–10]. This potentiation is expressed by the redistribution of both AMPA and NMDA receptors. GluA2-containing AMPARs present in naïve animals are exchanged for GluA2-lacking AMPARs [11], while NMDARs switch from a GluN1/GluN2A heteromeric to a GluN1/GluN2B/GluN3A heterotrimeric subunit composition [12]. Consequently, AMPARs can flux calcium, whereas NMDAR are calcium impermeable after drug exposure. Because of the inward rectification of GluA2-lacking AMPARs, synaptic calcium influx is favored by hyperpolarization of the membrane, which is in stark contrast to the situation before drug exposure, where calcium enters the cell through NMDAR only if they are depolarized. As a consequence, the rules for the

induction of activity dependent plasticity at this synapse are inverted; pairing glutamate release with postsynaptic depolarization no longer elicits long-term potentiation (LTP), which can be rescued if the postsynaptic neuron is hyperpolarized instead [13].

All addictive drugs tested till date potentiate synaptic transmission at excitatory afferents onto VTA DA neurons, including nicotine, morphine, cocaine, amphetamines, benzodiazepines and ethanol [9,14,15]. Even strong, selective optogenetic stimulation of VTA DA neurons evokes an identical plasticity [16], further demonstrating that addictive drugs converge on the activation of VTA DA neurons. The return to baseline transmission following this potentiation relies on the activation of metabotropic glutamate type 1 receptors (mGluR1), which require strong excitatory inputs for activation, owing to their perisynaptic location [11,17]. In the slice preparation, this is best achieved with a short train of action potentials (5–10 stimuli at 10–15 Hz). This depotentiation is protein synthesis dependent, most probably relying on local de novo synthesis of GluA2 subunits from prefabricated mRNA, and their subsequent assembly into functional AMPARs and exchange for GluA2-lacking receptors [18].

While the molecular mechanisms underlying this early form of drug-evoked synaptic plasticity are well established, much less is known about the behavioral consequences. Using positive allosteric modulators of mGluR1 it is possible to rapidly reverse drug-evoked synaptic plasticity in the VTA [19]. However, reversing plasticity in the VTA does not affect reinforcement, or early adaptive behaviors such as locomotor sensitization or conditioned place preference [20]. Altered synaptic transmission in the VTA may therefore represent a metaplasticity enabling changes in target region of the projection, which then would be more causally implicated in drug-adaptive behaviors [21]. In line with this idea, genetic ablation of GluN1 selectively in midbrain DA neurons precludes cocaine-evoked plasticity not only in the VTA, but also in the NAc [19]. The same study also showed that rapid reversal of the cocaine-evoked plasticity in the VTA prevents synaptic changes in the NAc even after repeated injections.

VTA DA neurons target the NAc, which is composed of medium sized spiny neurons (MSNs, 95% of all neurons), which fall into two classes based on their expression of either D1 or D2 dopamine receptor [22,23]. MSNs receive excitatory inputs from limbic and cortical areas that form synapses onto the dendritic spines, which are also targeted by ascending DA afferents. The characteristic synaptic arrangement with glutamatergic synapses on the head of the spine and DA terminals at the spine neck underlines the modulatory role of DA onto glutamate transmission [24]. At excitatory afferents onto D1-MSNs, drug-evoked synaptic potentiation is observed typically after multiple exposures ([25] but in some cases one injection is sufficient provided the withdrawal period is long enough, [26]) and persists after weeks of withdrawal. For example, in the case of 10 days of cocaine self-administration followed by a month of withdrawal, the ratio of the amplitude of AMPAR-EPSCs to NMDAR-EPSCs is higher than in naïve mice and the current–voltage curve of the AMPAR-EPSC shows inward rectification [27,28]. Interestingly, the two changes are carried by specific inputs, increased AMPA/NMDA ratio is a feature of afferents from the ventral hippocampus, while rectification appears selectively at the medial prefrontal cortex (mPFC) inputs [28]. At this mPFC input, unsilencing of synapses containing only NMDARs by insertion of GluA2-lacking AMPAR may contribute to the increase in rectification [29,30].

Synaptic potentiation at accumbal synapses can be reversed using appropriate stimulation protocols, previously established to induce long-term depression (LTD; [31,32]). For example, stimulation frequencies between 10 and 15 Hz induces mGluR-LTD which, among other effects removes GluA2-lacking AMPARs, while 1 Hz stimulation can induce a form of LTD that is NMDA-dependent [33]. For mGluR-LTD, it is crucial that these protocols selectively activate glutamatergic inputs because D1Rs inhibit the signaling required for mGluR-LTD [34,35].

Using pharmacological tools [36,27,37] and optogenetic reversal protocols [26], cocaine-evoked synaptic plasticity in the NAc has been implicated in drug-adaptive behavior. Behavioral sensitization and cue-associated seeking for example have been attributed to the mPFC input, whereas strengthening of excitatory inputs from the ventral subiculum of the hippocampus (vHipp) may mediate the motivation for cocaine-seeking [26,28,38]. Plasticity at the BLA to NAc input, on the other hand, correlates with the increase of seeking over withdrawal time, a phenomenon termed incubation of craving [29].

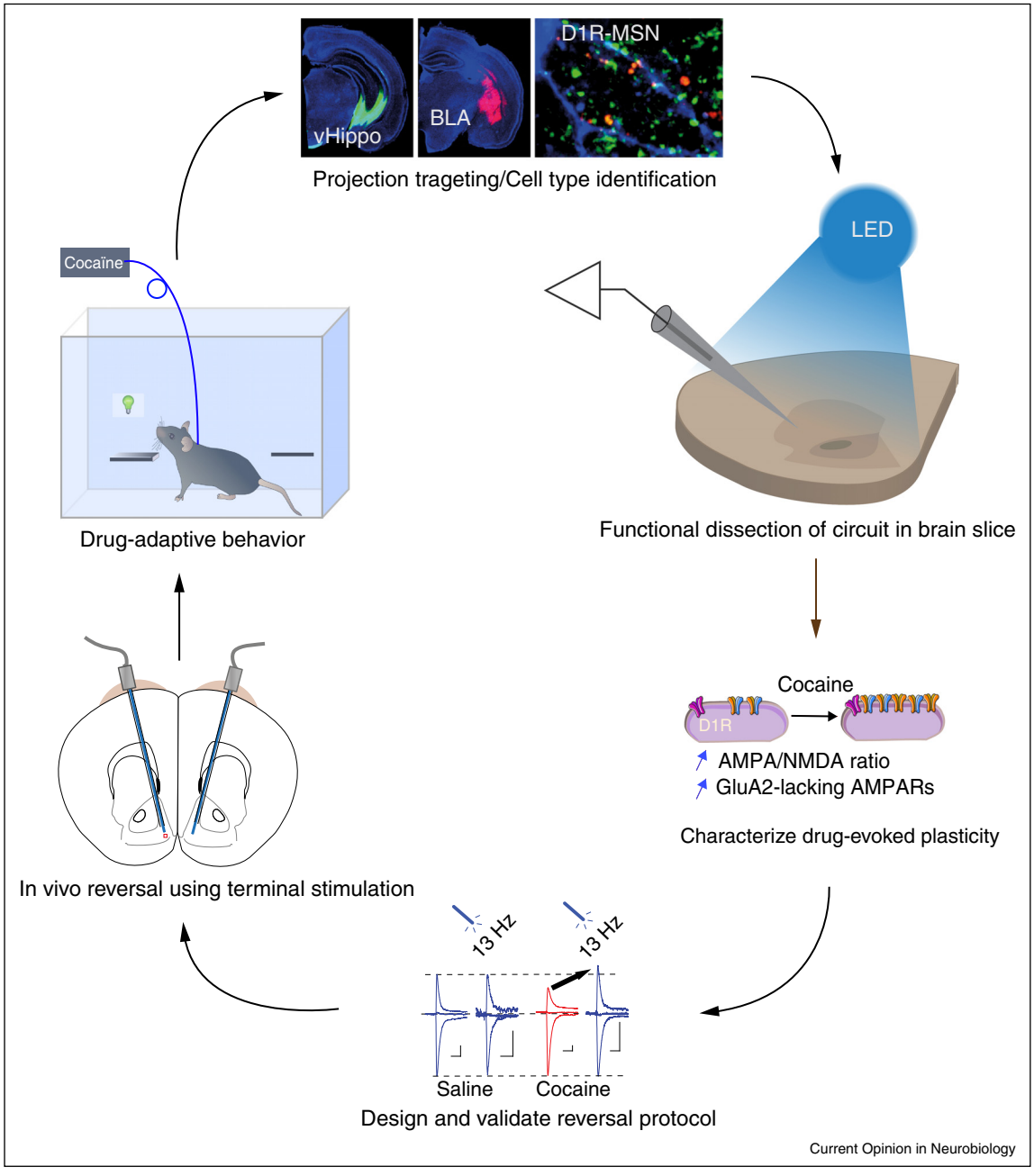
Drug-evoked plasticity also affects the output of the NAc, specifically a population of D1R-MSNs neurons which project preferentially onto the VTA GABA neurons [39]. Following cocaine exposure, these D1-MSNs express a pre-synaptic form of synaptic potentiation, leading to the disinhibition of VTA DA neurons, which may thus contribute to their enhanced excitation. When this plasticity is reversed, locomotor sensitization is abolished.

Optogenetic restoration of synaptic transmission and circuit function

Beyond strengthening the links of causality between drug-evoked synaptic plasticity and drug adaptive behavior, reversing drug-evoked synaptic plasticity could also have therapeutic potential. Would it be possible to

develop manipulations of synaptic function to permanently restore normal transmission and thus abolish addictive behavior? Specific 'circuit-breaking' interventions are inherently difficult to achieve using classical small molecule pharmacology. Since systemic administration affects the entire brain non-specifically, side effects are probable and the therapeutic effect may be obscured. In pre-clinical models, circuit-specific manipulations can be achieved using optogenetics: by applying specific stimulation protocols in awake mice, synapses can be potentiated or

Figure 1



Establishing links of causality between drug-evoked synaptic plasticity and drug-adaptive behavior. Top panel: anatomical identification of the relevant circuits. Two AAV2 virus expressing eGFP and mCherry were injected into the BLA and ventral Hippocampus, respectively. The imaged from the NAc then shows a MSN filled with biocytin after streptavidin staining (blue). The next step consists of characterizing the connections in acute slices after targeting specific projections with ChR2 assessing synaptic strength. In slices, parameters such as AMPA/NMDA ratio and rectification are used to explore the expression mechanisms of drug-evoked synaptic plasticity. Base on these findings a reversal protocol is established and validated in slices obtained ex vivo after drug exposure. This protocol is the implement *in vivo* typically by performing terminal stimulation in freely moving animals with the goal to test for the impact on drug-adaptive behavior.

depressed. Several groups have now provided proof of principle that this approach can also be used to restore normal transmission in situations of pathology. For example, reversing potentiated auditory inputs to the lateral amygdala with an *in vivo* LTD protocol reduced conditioned fear responding in a model of post-traumatic stress disorder [40]. Optogenetically driving cortico-striatal projections suppresses pathological grooming in a model of obsessive compulsive disorder [41], whereas activation of cortico-striatal projections at frequencies known to induce an LTD cause pathological grooming in wild-type mice [42]. In models of addiction, applying LTD protocols at excitatory synapses in the nucleus accumbens reverses cocaine-evoked potentiation of excitatory transmission and addiction-related behavior, as discussed above [26,28–30]. Applying LTD protocols at inputs from the basolateral amygdala or ventral hippocampus reduced responding for cocaine after withdrawal from self-administration (Figures 1 and 2).

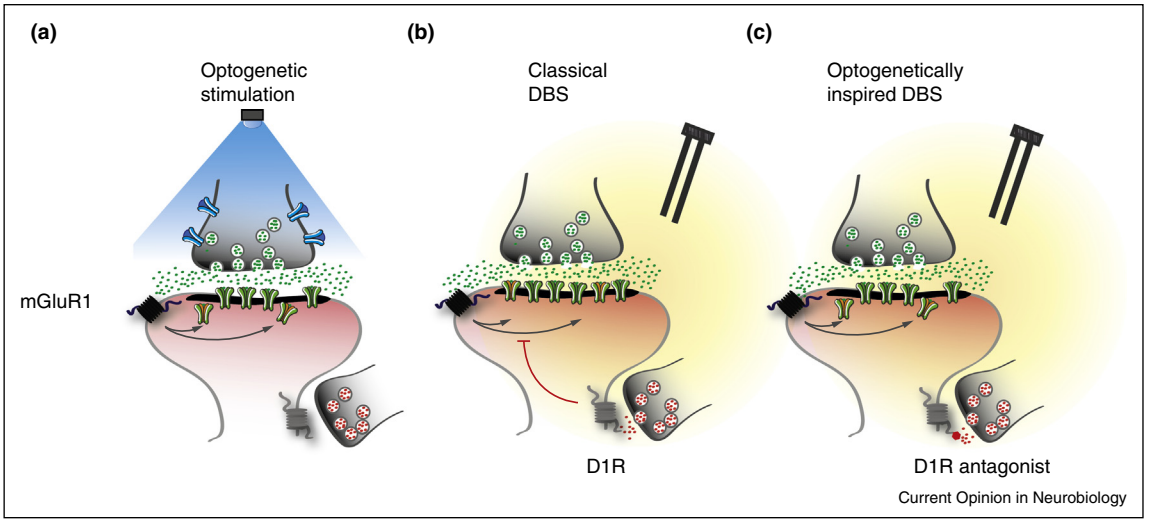
Despite the powerful, specific control of neuronal circuits that is possible with optogenetics, translation of this therapy into humans is not possible, at least for the near future [2]. The delivery and safety of viral effectors and their stable expression over long periods of time has yet to be realized, and light-delivery systems would have to be optimized [43]. Moreover, the techniques commonly used to achieve cell type specificity in rodents involve the use of transgenic animals; achieving similar levels of specificity in humans remains a significant challenge. However, we may be able to capitalize on optogenetic insight to inspire novel protocols for deep brain stimulation (DBS), to achieve a similar synaptic reversal in pathological conditions.

Proof of principle: using DBS to restore circuit dysfunction

DBS is the only FDA approved treatment that allows for direct circuit modulation in humans. It involves surgically implanting electrodes into specific nuclei in the brain, and passing current continuously through these electrodes at high frequencies. Originally used in cases of Parkinson's disease, the indications for DBS have expanded to include a variety of neurological and psychiatric disorders, including depression, tremor and obsessive-compulsive disorder [44].

The precise mechanisms of action of DBS remain elusive. It is inherently non-specific, as electrical field stimulation affects all cell types in a heterogenous nucleus, and may also modulate activity of afferent and efferent projections as well as fibers of passage [45,46]. Computational models and evidence from *in vivo* recordings suggest that DBS can have both excitatory and inhibitory effects on neuronal activity, depending on stimulation geometry and composition of the brain nucleus [47]. Despite these limitations, it may be possible to design a novel DBS protocol that would emulate optogenetic reversal strategies. To propose such a novel protocol, one would need to refine the technique to manipulate neural activity and synaptic transmission at identified circuit nodes. This is challenging because of the heterogeneity of neurons in the brain and the fact that functional circuits are anatomically intertwined. One possible approach may therefore

Figure 2



Schematics of approach for optogenetically inspired DBS (oiDBS). **(a)** Optogenetic stimulation is limited to excitatory afferents because ChR2 is only expressed in these neurons (blue). This stimulates the mGluR1, which triggers the removal of glutamate receptors (green) previously inserted by the exposure to cocaine. **(b)** Classical DBS is inefficient because the electrical stimulation also evokes release of dopamine (red), which through the D1R inhibits the signaling of mGluR1s. **(c)** Optogenetically inspired DBS associates electrical stimulation with a D1R antagonist (e.g. ecopipam, red diamonds) thus blocking the D1R signaling and restoring the ability to depotentiate the synapse.

be to combine DBS with specific pharmacology to refine its effects.

In the field of addiction, DBS has been used in a few instances to reduce symptoms of craving in severely treatment-refractive patients [48,49]. However, the effects are variable and transient. While pre-clinical studies have implicated altered activity in areas projecting to the NAc (such as the mPFC) in the effects of DBS [50], the mechanisms underlying the therapeutic effects are not well understood. In recent proof of principle study, a novel DBS protocol was developed to reverse cocaine-evoked plasticity in the NAc and consequently reduce addiction-related behavior, through a defined mechanism of action [51]. By building on insight from optogenetic reversal strategies of cocaine-evoked plasticity in the NAc (see above), a stimulation frequency of 12 Hz stimulation for 10 min was used to induce a long-term depression (LTD) of excitatory synapses in this structure. As with optogenetics, this protocol aimed at inducing mGluR-LTD. Stimulation alone had no effect on cocaine-evoked plasticity or drug-adaptive behavior; however, it is also known that signaling through dopamine D1 receptors can oppose mGluR-evoked depression of excitatory synapses [35,52]. We therefore hypothesized that non-specific DBS stimulation may not only cause glutamate release (to activate mGluRs), but could also release dopamine, which would signal through D1 receptors on MSNs. DBS may therefore activate two opposing signaling cascades. In agreement with this hypothesis, electrical stimulation in the presence of a D1-antagonist unmasked mGluR-LTD. With this optogenetically inspired DBS protocol, cocaine-evoked plasticity in the NAc was reversed and cocaine-adaptive behavior abolished. Importantly, the effects of this optogenetically inspired DBS protocol persisted for several days, and the pharmacological adjuvant is approved for multiple indications [53,54]. Such proof-of-principle based on optogenetic manipulations and circuit dissection can lead to novel blue prints for DBS protocols applicable to human patients.

Conclusions and perspective

With a rational approach as described above, it may be possible to propose novel DBS protocols by carefully choosing the stimulation site and with a clear goal as to which synaptic alterations need to be normalized. Potential indications include obsessive-compulsive disorder, depression and, as discussed, addiction. There is no doubt that DBS will evolve and will not only provide long-lasting relief from symptoms of psychiatric disorders, but will also provide insight into their underlying mechanisms, which will facilitate the development and optimization of future circuit-based treatment strategies.

Conflict of interest statement

Nothing declared.

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