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Optogenetically inspired deep brain stimulation: linking basic with clinical research

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Summary

In the last decade, optogenetics has revolutionised the neurosciences. The technique, which allows for cell-type specific excitation and inhibition of neurons in the brain of freely moving rodents, has been used to tighten the links of causality between neural activity and behaviour. Optogenetics is also enabling an unprecedented characterisation of circuits and their dysfunction in a number of brain diseases, above all those conditions that are not caused by neurodegeneration. Notable progress has been made in addiction, depression and obsessive-compulsive disorders, as well as other anxiety disorders. By extension, the technique has also been used to propose blueprints for innovative rational treatment of these diseases. The goal is to design manipulations that disrupt pathological circuit function or restore normal activity. This can be achieved by targeting specific projections in order to apply specific stimulation protocols validated by *ex-vivo* analysis of the mechanisms underlying the dysfunction. In a number of cases, specific forms of pathological synaptic plasticity have been implicated. For example, addictive drugs via strong increase of dopamine trigger a myriad of alterations of glutamate and γ-aminobutyric acid transmission, also called drug-evoked synaptic plasticity. This opens the way to the design of optogenetic reversal protocols, which might restore normal transmission with the hope to abolish the pathological behaviour. Several proof of principle studies for this approach have recently been published. However, for many reasons, optogenetics will not be translatable to human applications in the near future. Here, we argue that an intermediate step is novel deep brain stimulation (DBS) protocols that emulate successful optogenetic approaches in animal models. We provide a roadmap for a translational path to rational, optogenetically inspired DBS protocols to refine existing approaches and expand to novel indications.

Key words: *optogenetics; addiction; neurology*

Brain diseases caused by circuit dysfunction

Brain diseases represent an enormous burden for society. The 2010 consensus document of the European Brain Council reveals that the most common condition is migraine, the most expensive one depression and the one where prevalence has increased most in recent years, dementia [1]. Despite massive efforts most diseases are today without cure because neither the aetiology nor the neural mechanisms that cause the symptoms are understood. One of the best-investigated diseases is acute stroke, where loss of neurons owing to ischaemia explains the paralysis because the pathology is localised to the brain region that normally controls the movement. The anatomical-clinical correlation can be confirmed with modern imaging techniques. This is not possible in schizophrenia, depression, anxiety disorders and addiction, where even latest generation imaging fails to visualise the disease in an individual patient. Therefore, many brain diseases cannot be explained by a loss of neural function mediated by cell death, and alternate explanations must be found. A leading hypothesis is that these behavioural diseases are explained by circuit malfunction [2, 3]. For example, in schizophrenia circuits of sensory perception would exhibit a pathological function such that the patient experiences hallucinations. In anxiety disorders, on the other hand, the function of fear circuits would be overactive and lead to generalisation whereby a normally harmless stimulus now triggers an intense fear response. These models are now supported by much experimental evidence (above all because of advances of optogenetics, see below). Mechanisms of pathophysiology are emerging where plasticity at specific synapses underlies altered circuit function to change sensory perception, emotions or decision making, eventually leading to behavioural symptoms. It is important to note that altered function can be either loss of normal function or gain of function. As in psychiatric disorders, the symptoms of many neurological disorders, such as Parkinson's disease, tremors, dystonia, chorea and Gilles de la Tourette syndrome, are associated with a network alteration related either to local circuit dysfunction or as a remote consequence of neuronal degeneration.

The synapse as a site of pathology

Much research tells us that circuits adapt their function with experience by changing the communication between

connected neurons. These interfaces are constituted by synapses, where for a brief period of time the electrically encoded information is transduced into a chemical signal. Synapses are capable of expressing a large variety of plasticity, which serves to adapt behaviour to external conditions. Such a learning process can malfunction and cause symptoms, which eventually define a disease. For example, excessively strong stimulation of the reward system by addictive drugs may compromise normal decisions to override the physiological prediction error signalling, triggering the induction of addiction. With cocaine, synapses of excitatory afferents into the dopamine neurons in the ventral tegmental area glutamate receptors redistribute hours after the first injection of the drug [4]. With repetitive exposure and after withdrawal from the drug, major synaptic changes are also observed in the nucleus accumbens, which integrates motivation, action outcome and valence. Specifically, the afferents from the orbitofrontal cortex are potentiated, which eventually leads to compulsive consumption of the drug. Thus a circuit model of addiction is emerging that causally links neural dysfunction to key symptoms of the disease (see table 1 for current state of the literature).

What is optogenetics?

This is a technique developed over the last decade whereby light is used to activate a light sensitive ion channel called channelrhodopsin that is genetically expressed in selected neurons (fig. 1). The channel occurs naturally in green algae, in which it activates flagellae for positioning to optimise photosynthesis [16]. The photosensitive molecule is retinal (also necessary for normal vision in the retina), which binds to the channel, which upon exposure to blue light lets ions flow through the membrane. In 2001 the gene of channelrhodposin was cloned, and a few years later researchers successfully expressed it in neurons to control their activity. Meanwhile this technique has been much refined

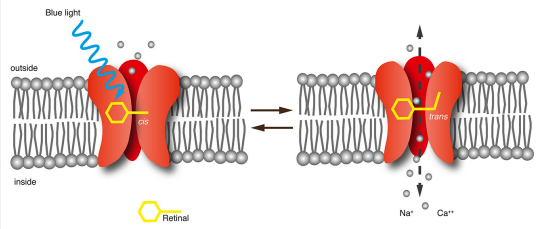

Figure 1

Principle of optogenetics. Channelrhodopsin is an ion channel that binds retinal. With blue light exposure the retinal conformation changes from *cis* to *trans*, which gates the ion conductance leading to depolarisation. When expressed in neurons this technique allows the activity to be controlled with high temporal resolution. Additional effectors also inhibit neurons (e.g. light-gated chloride conductance) or control G-protein signalling. (Modified from: Hegemann P, Nagel G. From channelrhodopsins to optogenetics. EMBO Mol Med. 2013;5:173–6. © 2013 EMBO Molecular Medicine, reprinted with permission).

Table 1: Drugs, circuits and addiction: a translational roadmap with a selection of the literature. Using addiction as an example, this table lists a number of steps (left column) that lead from the initial pharmacological effect of drugs on identified molecular targets to "drug evoked synaptic plasticity" that can be linked to drug adaptive behaviour. It then presents optogenetic treatment procedures to finish with their emulation using DBS. The right column lists key papers in support.

Convergence of addictive drugs onto mesolimbic dopamine system	Mechanistic classification [18]
Overriding of prediction error signalling triggering induction of addiction	Evidence for prediction error signalling in nonhuman primates [19] and rodents [20] Implication of prediction error signalling in addiction [21, 22]
Functional anatomy (selection)	Mesolimbic dopamine projection extends to NAc and prefrontal cortex [23] Accumbal D1R versus D2R dichotomy [24, 25] Inhibitory transmission from lateral habenula [26] Back-projection from the NAc onto VTA GABA neurons [27]
Observing neural activity during disease relevant behaviour	Behaviour of neurons in the VTA, prediction error signalling with much heterogeneity [28, 29]. Accumbal neurons during reward learning [30] Accumbal cholinergic interneurons pause their activity with salient stimuli [31]
Acute manipulation to connect to behaviour	Self-stimulation of VTA DA neurons reinforces behaviour [32, 33] Stimulation of VTA GABA neurons leads to aversion and disrupts reward consumption [34, 35]
Circuit manipulation as disease triggering event	Optogenetic self-stimulation leading to addiction-like behaviour [36] Hypoexcitability of prefrontal cortex as correlate of compulsion [37]
Neural trace of the disease (drug-evoked synaptic plasticity)	Drug-evoked plasticity in the VTA appears after the first injection [38, 39] Drug-evoked plasticity in the NAc is delayed [40, 41] Potentiation of GABA transmission disinhibits VTA dopamine neurons [42]
Molecular mechanism of disease relevant synaptic plasticity	GluA2-lacking AMPA receptors appear at many synapses [43] In the NAc initial depression in reversed into potentiation [44]
Reversal strategies	mGluR-LTD causes calcium permeable AMPA receptors to disappear [45] GluN3 containing NMDA receptors appear [46]
Proof of principle studies	Optogenetic "treatment" of – Behaviour sensitisation [47] – Cue associated relapse [7] – Incubation of craving [48] – Compulsive self-administration of cocaine despite punishment [36]
Translational circuit therapies	Optogenetically inspired DBS combines low frequency stimulation with D1R antagonist to abolish behavioural sensitisation [13] Use of mGluR1 positive allosteric modulators may enhance endogenous reversal [49, 50] Transcranial magnetic stimulation may inhibit hyperexcitability of prefrontal cortex [51]

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; D1R = dopamine type-1 receptor; D2R = dopamine type-2 receptor; DA = dopamine; GABA = γ-aminobutyric acid; GluA2 = subunit of AMPA receptor; GluN3 = NMDA receptor subunit; LTD = long-term depression; mGluR = metabotropic glutamate receptor; NAc = nucleus accumbens; NMDA = N-methyl-D-aspartate; VTA = ventral tegmental area

by expressing mutated versions of channelrhodopsin with different ion selectivity (e.g. chloride instead of sodium conductance leads to inhibition). Most importantly, using selective recombination genetics in combination with stereotaxic injections of the vectors, the expression of channelrhodopsin can be limited to certain cell types in specific part of the brain (e.g. cholinergic neurons in the dorsal striatum [17]). Transfecting channelrhodopsin in living rodents (using certain viruses as vectors) therefore allows the interrogation of circuits while the animal is awake and freely moving.

Optogenetics to define novel therapeutic approaches

In line with a circuit model of behavioural diseases, a technique is needed that modulates neural activity and synaptic transmission in identified circuit nodes. Optogenetics has been shown to do just this in animal models. In this approach, stimulation of identified neurons becomes possible through light stimulation of an ion channel called channelrhodopsin (see previous section and fig. 1). Over the last decade [5] the technique has been used for both the characterisation of disease-relevant circuits and to establish novel treatment protocols. Optogenetic manipulations have proved efficient in animal models of disease.

Therapeutic optogenetics protocols rely on the ability of the methods to evoke synaptic plasticity *in vivo*. For example, an intermittent train of high-frequency stimulation applied in a waking mouse can potentiate synapses, while low-frequency protocols (e.g. 1 Hz for 10 minutes) depress transmission. Several groups have now provided proof of principle that this approach can also be used to restore normal transmission in pathology, for example in addiction [6]. Resetting of the excitatory afferents from the cortex to the striatum that have been potentiated by cocaine erases simple drug-adaptive behaviour [7].

Impossible translation of optogenetics for human use

Translation into humans of optogenetic manipulations is not possible in the near future [8]. The delivery of the effectors and their stable expression over long periods of time cannot be achieved with the currently available tools. Moreover, the techniques used to achieve cell-type specificity in rodents rely on the use of transgenic animals, which will of course remain impossible in humans. Design of the devices for light stimulation, on the other hand, while currently not in existence, seems feasible. Taken together, optogenetics will remain an experimental technique for at least another decade, which underlines the need for intermediate solutions.

Deep brain stimulation to restore normal circuit function

The circuit hypothesis of behavioural diseases requires manipulations that modulate synaptic function to restore normal circuit function. This is inherently difficult when using a classical pharmacology approach with small molecules. Systemic application will target the entire brain, which may not only cause side effects but actually occlude the therapeutic effect. A recently developed experimental approach to narrow down the neurons targeted by pharmacological intervention uses artificial ligands of a designer receptor that is coupled to G proteins [9, 10]. When expressed in selected neurons, the ligand then can excite or inhibit the cells. However, for many reasons this approach will remain off limits for human application in the near future. This is where deep brain stimulation (DBS) comes in: the only currently approved treatment that allows for selective circuit modulation (fig. 2). More than 100 000 patients have been treated worldwide, mostly for Parkinson's disease [11]. While the precise mechanism of action is still being investigated, there is good evidence that DBS in Parkinson's disease works because a hyperactive indirect striatal output pathway can be inhibited. The symptoms of Parkinson's disease are thus due to a circuit malfunction in the absence of dopamine and DBS corrects this rather than restoring dopamine levels. Clearly, there are major limitations to our understanding of what DBS is doing. When targeting the subthalamic nucleus, the high frequency stimulation that is therapeutically efficacious cannot be followed by neurons and the electrical field stimulation will affect not only neurons of all different types in the target nucleus, but also many passing fibres. It is conceivable that DBS prevents abnormal neuronal discharges within a specific network associated with a given symptom [12].

Optogenetics may, therefore, be used as blueprints for novel DBS protocols that may eventually be applicable in humans. The major challenge consists of emulating the specificity of the optogenetic intervention. Even with the most refined electrodes, attempts to modulate selectively neurons belonging to one, but not the neighbouring, circuit are futile, because all excitable structures within the field generated by the DBS electrode will change their activity. Over the last 5 years many studies have been published that confirmed the link of causality between neuronal activity and behaviour with unprecedented precision.

To overcome the nonspecific activation of all neural elements, the major limitation of DBS, it may be necessary to combine DBS with pharmacology to refine its effects. For example, in the striatum where excitatory transmission has

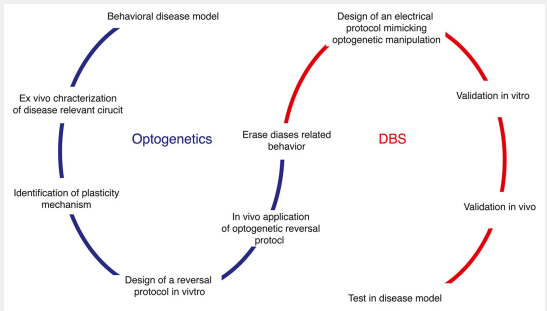

Figure 2

Blueprint of translation of optogenetic approaches into novel protocols of deep brain stimulation (DBS). Research starts in animal models of the disease and with identification of the relevant circuits. A crucial step is the *in vitro* emulation of the successful optogenetic protocol with DBS, still in animal models. Once validated *in vivo*, protocols can be designed for human applications.

gone awry in addiction, combining DBS with antagonists of dopamine receptors may allow selective manipulation of glutamate transmission. A recent study demonstrated that this refines DBS, mimicking optogenetic "treatment" of addiction in a simple rodent model [13]. In this study cocaine-evoked potentiation in the nucleus accumbens was reversed with low frequency electrical stimulation in combination with a blocker of the D1 type of the dopamine receptors. This triggered a robust form of synaptic depression that reversed the cocaine-evoked potentiation and the behavioural adaptation. Adding the dopamine type-1 receptor antagonist proved necessary, because the electrical stimulation also drives the release of other transmitters including dopamine that preclude the expression of the reversed potentiation.

The perspective of novel indications

Following this logic, it may be possible to propose novel DBS protocols, carefully choosing the stimulation site and with a clear goal as to which circuit alteration needs to be restored. Indications that come to mind are obsessive-compulsive disorder, depression and, as already discussed, addiction [14, 15]. There is no doubt that DBS will evolve over the next decade and not only provide relief for the persons who have the misfortune to suffer from these brain diseases that are currently without cure, but also provide insight into the underlying mechanisms.

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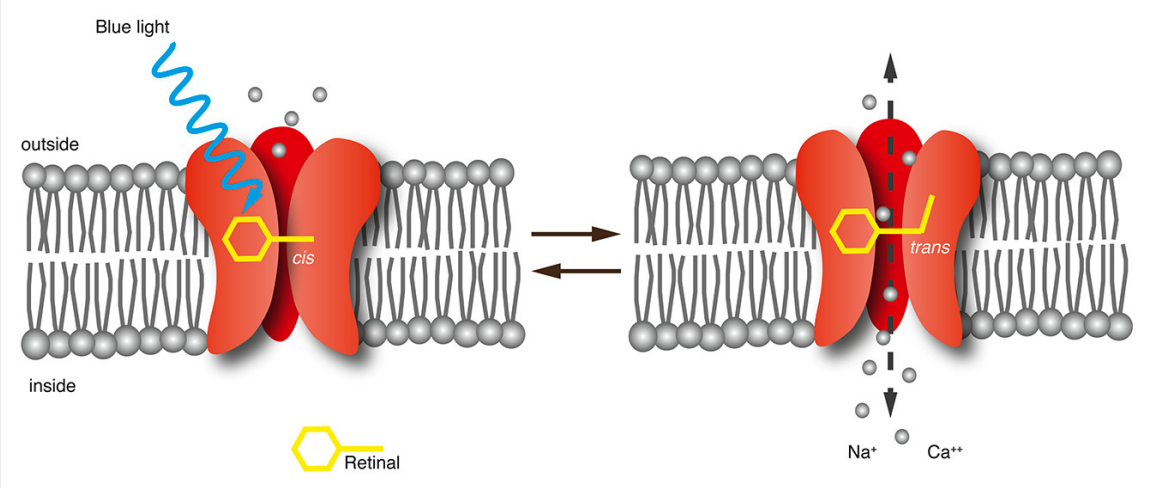
Figures (large format)



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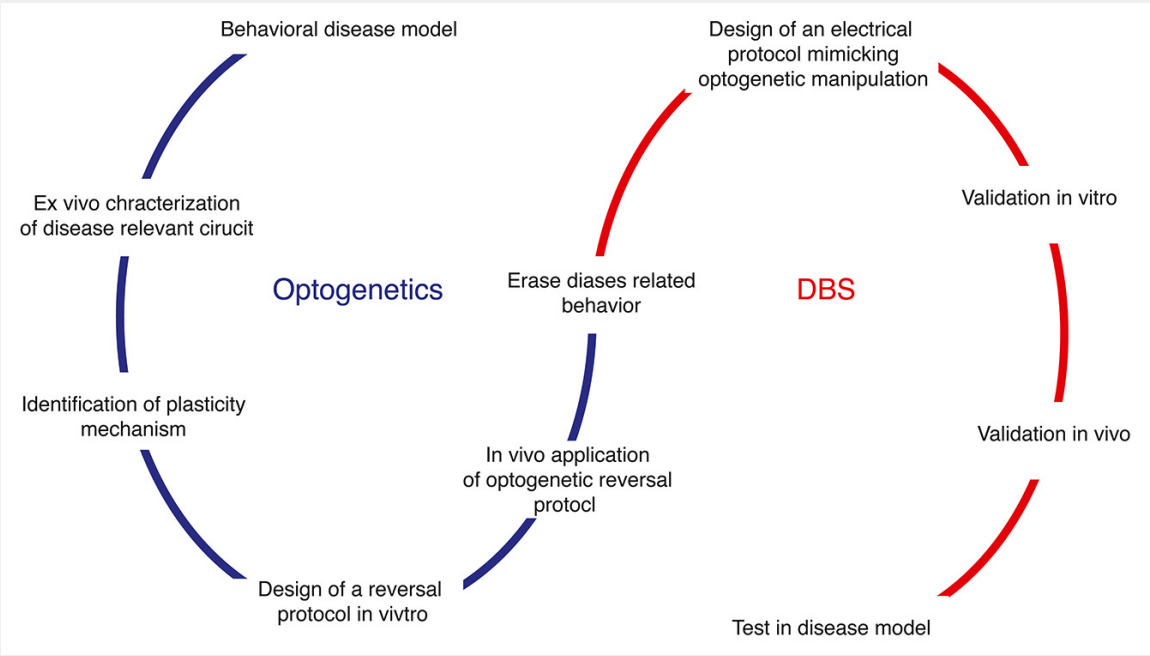

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