Does the maturation of optogenetics enable new approaches to the treatment of Parkinson's Disease?

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Summary

Optogenetics has proven itself a powerful and versatile research tool, uniquely suited to studying neuronal circuits in intact tissue and *in vivo*. Today, our understanding of PD and its therapies relies on evidence gleaned using this technology. These insights have been applied to the iterative improvement of PD therapeutics.

The potential value of optogenetics as a therapeutic modality in its own right was anticipated from the outset: the same properties that make the technology a valuable laboratory tool make it promising for clinical use. Some have considered optogenetics an answer to the limitations of deep brain stimulation (DBS) and pharmacotherapy in PD.

Are optogenetic therapies realistic, and if so, why have we not seen them attempted? In this essay, I evaluate the present and future roles of optogenetics in PD as outlined in the visual abstract:

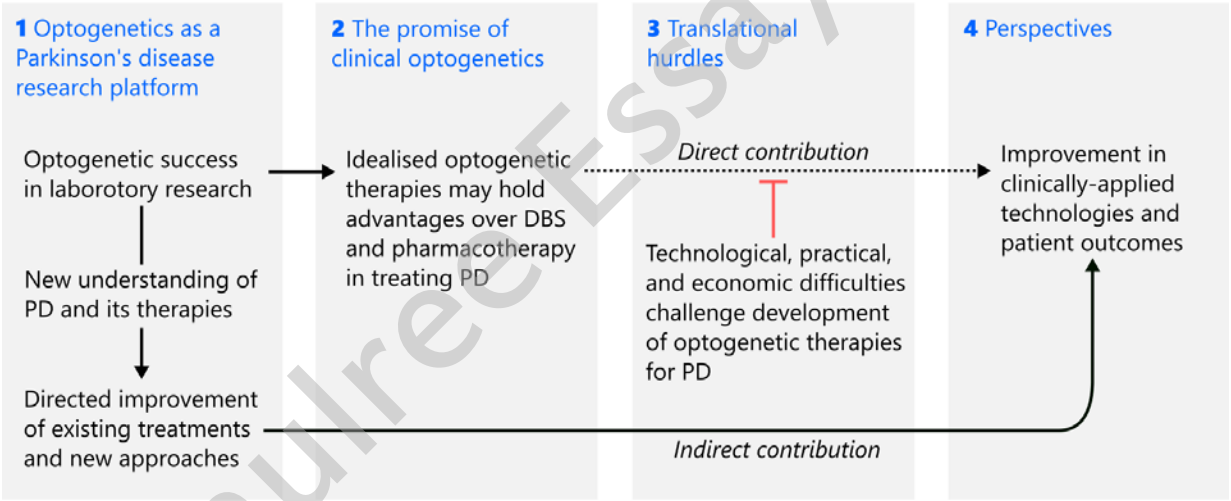

Figure 1 | Visual abstract. The optogenetic contribution to PD treatment is partly direct (above), if optogenetics can succeed as a therapeutic modality, and partly indirect (below) through the improvement and invention of other therapies.

1 Optogenetics in Parkinson's disease research

1.1 Optogenetics is a proven research toolkit possessing useful properties

The continual evolution of optogenetics since its inception at the turn of the century has produced a powerful and versatile toolkit of optics, opsins, and transgenic animals. It now affords an unprecedented level of control over target cell activity resulting from what is often a simple protocol (Figure 2).

Optogenetics uses opsins, light-responsive ion channels, as the interface between an illuminating device and cell activity. With suitable opsin expression control, a direct line of communication is established between illumination and target cells, permitting precise spatiotemporal control over cellular activity. This approach confers several advantages, summarised in Table 1 overleaf.

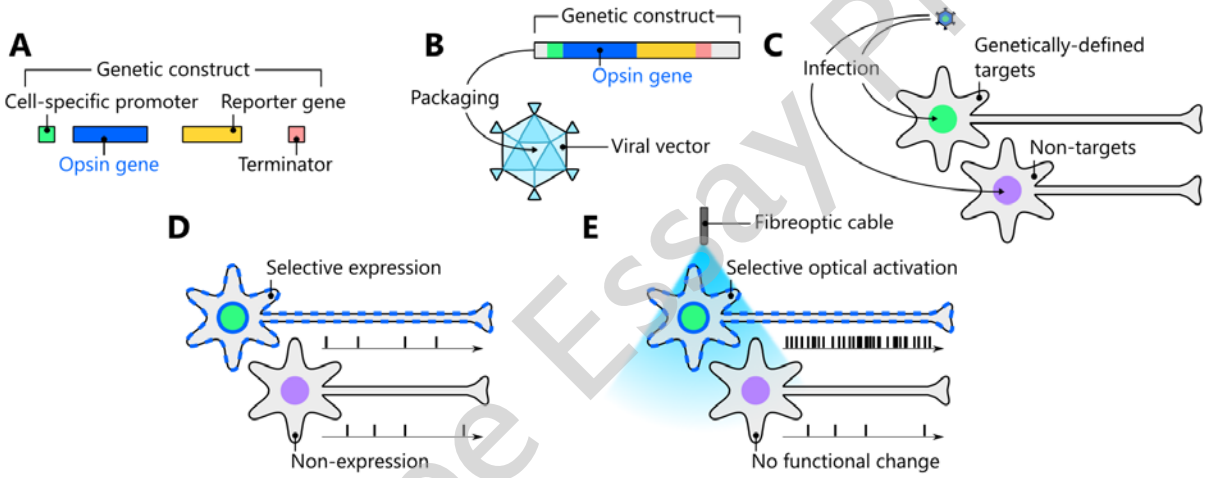

Figure 2 | An example optogenetic protocol. (A) The chosen opsin is incorporated into a genetic construct alongside a cell-specific promoter and packaged into a vector such as a virus (B). Cells are transfected at the site of application (C), but the construct is expressed only where the promoter is active (D). Illumination actuates the opsins expressed exclusively by the targets, resulting in selective activity enhancement (E). Most modern implementations are more complex but usually conserve these basic principles.

Genetic specificity	Selective opsin expression allows restriction of the target domain to a given cell type, even if diffusely distributed in heterogeneous tissue. Only cells that express opsins respond to light.
Anatomical specificity	Opsins are only activated on absorption of specific wavelengths, so controlling illumination determines which cells are affected.
Temporal precision	Ionotropic opsin kinetics range from the sub-millisecond scale to tens of minutes. Controlled illumination permits modulation of single action potentials (APs) and firing patterns that mimic endogenous activity. Metabotropic opsins also exist.
Reversibility	Changes in membrane electrophysiology following ionotropic opsin activation are rapidly and entirely reversed after illumination is ceased.
Electrical passivity	The passive electrical effects of inactive opsins are negligible, leaving cell function and health undisturbed. This compares favourably with pharmacological and lesional inactivation.
Bidirectionality	Illumination can couple to electrical excitation or inhibition with the use of different opsins.
Co-expression	Opsins with different properties and activation spectra may be coincident in the same tissue, taking independent input from a multicolour illuminator.
Single-component	Optical sensitivity can be conferred to target cells with a single genetic construct containing as little as an opsin gene and a promoter. Small constructs are eligible for viral delivery.
Model versatility	Optogenetics may be applied to cultured cells, intact tissue sections, and even freely-moving mammals for behavioural study.

Table 1 | Useful attributes of optogenetics with reference to Kim et al. (2017), Zhang et al. (2007), Deisseroth (2011) and Boyden et al. (2005)

In combination, these attributes suit the optogenetic toolkit to the interrogation of the meso-scale, circuit-level function of the brain: the gulf between cell biology and neuroanatomy. In the context of PD, investigation of the underlying aberrant circuitry is one way to better understand the disease and thus improve or invent therapies. I focus on this indirect role of optogenetics for the remainder of this section.

1.2 Optogenetic research clarifies the mechanistic basis of Parkinson's disease

Like other neuropsychiatric diseases, PD has a complex aetiology that confounds conventional investigation. Our understanding of PD circuitry stems largely from equivocal neuroanatomical and lesional evidence. From this, the existence of two competing basal ganglia (BG) pathways has long been implied to oppositely regulate internal globus pallidus (GPi) output. These are the inhibitory direct pathway (DP) and excitatory indirect pathway (IP) (Nelson & Kreitzer, 2014). BG cellular heterogeneity has historically prevented empirical confirmation of this "classical" model, shown Figure 3 (Levy et al., 1997). Consequently, the first causal evidence came only in 2010 from Kravitz et al., whose optogenetic manipulation of medium spiny neurones (MSNs) of both pathways proved their functional importance.

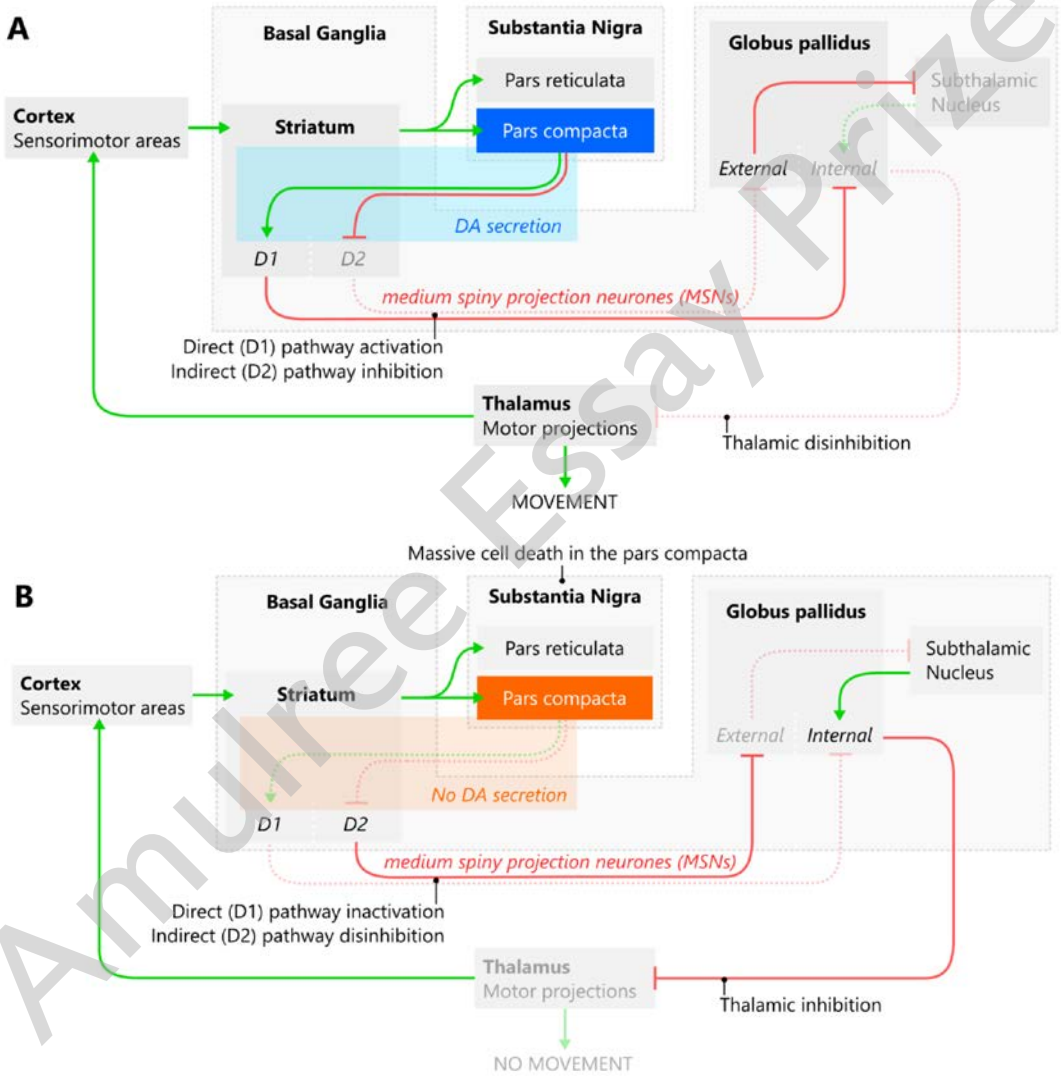

Figure 3 | The classical model (sometimes "rate model") of BG function during movement in the healthy (A) and the parkinsonian (B) brain. Volume secretions of dopamine, DA, are released from the substantia nigra pars compacta. DP MSN activation occurs via D1 receptors concurrent with IP MSN inhibition via D2 receptors. Consequent thalamic motor disinhibition permits movement in the healthy brain (A). Without this critical dopamine release in the parkinsonian circuit (B), IP activation prevails. The thalamus remains inhibited, manifesting the core PD symptoms: hypokinesia, bradykinesia, and tremors.

By using recombinant techniques to restrict channelrhodopsin 2 (ChR2) expression to MSNs alone, optogenetic control was achieved over each pathway in isolation (resembling Figure 2E). The results of coordination testing upon activating either pathway prompted revision of the classical model to reflect the finding that MSNs regulate patterns of locomotor initiation, but not coordination. Surprisingly, bilateral DP photoactivation was found to substantially ameliorate the movement deficits caused by 6-hydroxydopamine lesion of the dorsomedial striatum, an established model of PD (Mallet et al., 2006). This early study was a proof of concept for *in vivo* optogenetics and behavioural testing. Furthermore, the findings allude to a possible therapeutic role for the technology in PD.

However, due to contemporary optogenetic limitations, the team could not manipulate both pathways in the same animal. It was therefore impossible to comprehensively demonstrate the classical model's antagonistic regulation of GPi output. Furthermore, no enquiry was made of the steps between MSN activation and the downstream behavioural effects.

Three years later, Freeze and colleagues (2013) addressed these shortcomings with a protocol combining simultaneous control of both pathways, substantia nigra pars reticulata (SNr) electrophysiological recording[1], and analysis of unconstrained animal locomotion. It was thus possible to add the missing link of SNr activity to the causal chain posited by Kravitz et al. as well as to measure the contributions of each pathway to SNr activity. Intriguingly, both pathways were found to be selectively activating and inhibiting SNr neurones. By recording neural activity alongside movement, it was possible to identify SNr correlates to the point where local activity could be decoded to predict behaviour.

These studies exemplify the application of optogenetic specificity to dissecting functional neurocircuitry. Evidence collected in this manner contributes welcome detail to a continually evolving model of BG function (da Silva et al., 2018). Indeed, Figure 3 could not have been drawn without the optogenetic evidence presented here.

Other studies concentrate instead on BG dysfunction. Recent evidence from Kim et al. (2017) reveals that tremor, a hallmark PD symptom, may result from paradoxical rebound firing of thalamic neurones following periods of tonic BG inhibition. In their rodent PD model, photoinhibition of this rebound firing greatly relieved tremor and rigidity, and optogenetic reintroduction of rebound activity into the dopamine-normal brain reproduced these symptoms.

These findings benefit from the temporal fidelity of optogenetics in modulating native activity and contradict the notion that increased BG output causes tremor directly. Optogenetic research might also inform therapy: Kim et al. propose, for instance, that future neuromodulatory treatment should target rebound firing. This indirect role of optogenetics in improving treatment is the focus of the next section.

[1] The functionality of the rodent SNr is analogous to that of the primate GPi, reflecting differences between the pathway described by these studies and that shown in Figure 3. This illustrates the broader point that circuit-level findings in mice do not guarantee homologous circuits in humans.

1.3 Results from optogenetic studies inform the improvement of existing therapies

Although DBS is commonly employed in PD treatment, our knowledge of its mechanisms is lacking at a circuit level. As DBS nonselectively modulates local neuronal activity, it is difficult to tell which of its many resultant network effects is responsible for therapeutic outcomes, and which cause side-effects. Without this information, directed improvement of the ratio between these outcomes is impossible. Investigating the functional basis of DBS enables more informed and effective approaches to treatment, as per the scheme in Figure 4.

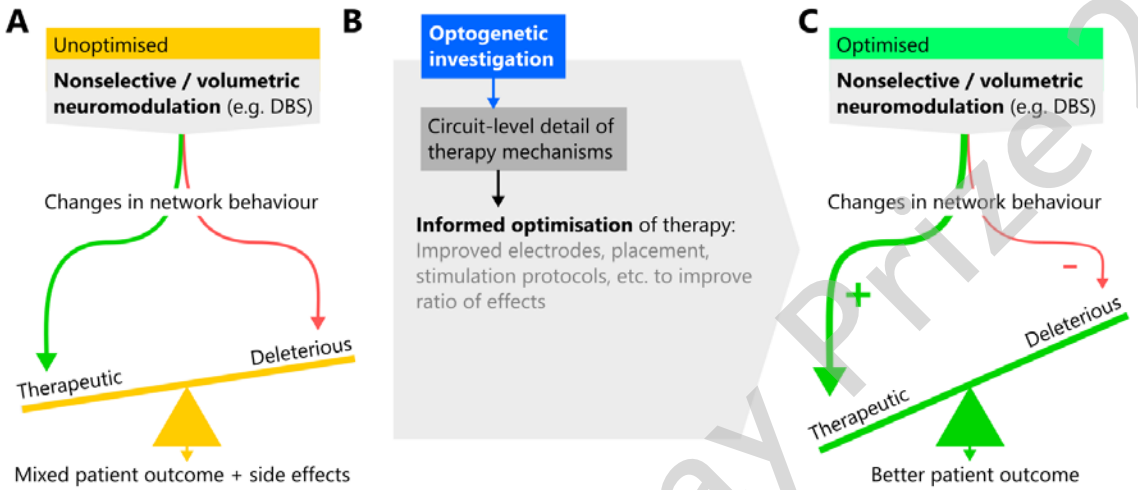

Figure 4 | A role for optogenetics in the improvement of DBS. Optogenetic insights on neuromodulatory network effects (B) can be used to drive a transition from an unoptimized treatment protocol that is mainly the product of trial-and-error (A) to one that is developed with consideration of circuit-level mechanisms (C). These optimised protocols could deliver better patient outcomes with fewer side-effects.

The basis for DBS high-frequency stimulation of the subthalamic nucleus (HFS-STN) is one such mystery whose network effects may resemble Figure 4A (Liu et al., 2008). The classical model (Figure 3) predicts that HFS functions in the broader network by inhibiting the predominantly excitatory STN through depolarisation block. Gradinaru et al. (2009) individually photoinhibited different STN circuit elements in hemiparkinsonian mice to identify which network responses correlated with prokinesis. Global photoinhibition of STN cells resulted in no detectable improvement, but selective inhibition of afferent fibres broadly restored pre-lesion behaviour.

Investigation of the sources of STN afferents revealed layer V neurones in M1 neocortex as both potent modulators of STN activity and as antidromically activated by HFS-STN. Selective optogenetic HFS of this population alone resulted in restoration of pre-lesion behaviour. Narrowing this down to M1-STN projections, rather than axons to other destinations, only became possible after the advent of projection targeting in a later paper supporting this model (Sanders & Jaeger, 2016). These findings are in line with previous evidence for abnormally strong M1-STN connections in PD that transmit pathological oscillatory activity (Degos et al., 2008). It is possible that the disruption of the M1-STN connection is a key mechanism responsible for the therapeutic effects of HFS-STN. This finding implies a way in which the therapy can be improved: if M1-STN afferents, not local STN cell bodies, are targeted directly by future protocols with optimised electrode placement, it may be possible to yield better outcomes than those achievable with generalised HFS-STN. This scheme of targeted improvement follows that of Figure 4.

1.4 Evaluating the significance of optogenetic research of PD and its therapies

Animal behavioural studies are central to the study of neuropsychiatric illnesses like PD. They are expedited by the optogenetic ability to induce gain and loss of function quickly and selectively: there is no need for wash-out of drugs, and multiple trials can be performed in each animal. In addition, as has been described, any conclusions are made more definitive by the ability to selectively control neuronal pathways, and the causal relationships between network elements are more readily described than with fMRI or electrophysiology. The lasting impact of the studies presented here, many still recent, remains to be seen.

A common limitation of this research lies in its reliance on animal models. Although BG structure and connectivity are relatively conserved among vertebrates, species-specific variations must be considered. For example, some striatal neural populations present in primates are absent in rodents (Petryszyn et al., 2017). Additionally, involvement of other loci in PD (locus coeruleus degeneration, for instance) has not been widely investigated using optogenetics. Experimental models that ignore these additional loci present a reductionist view of the disease.

Furthermore, optogenetic studies have not begun to address the panoply of affective and cognitive symptoms of PD. Although these contribute enormously to patient morbidity, they are difficult to assess in animal models. The resultant deficiency in our mechanistic understanding of the nonmotor symptoms of PD makes targeting them difficult. For example, dementia and cognitive decline in many patients is associated with forebrain cholinergic denervation. Although this is an important prognostic indicator, our understanding of the topic remains scant. A future direction for optogenetic PD research would pursue these additional, extra-dopaminergic facets of the disease process to enable more sophisticated treatment that directly addresses nonmotor morbidity.

At the time of writing, the indirect benefits discussed in this section remain the only way in which optogenetic technology has contributed to the treatment of PD. This does not herald radically different approaches to treatment but does enable iteration of existing methods, as I have described with DBS. Optogenetics can equally be applied to developing putative therapies by investigating stem cell functional integration or even drug discovery (Steinbeck et al., 2015; Zhang & Cohen, 2017). Many of these research thrusts will not ultimately reach clinic, but propositions are necessary to move beyond antiparkinsonian drugs and DBS.

In addition to the roles that optogenetics has had in improving and understanding PD treatment, its potential as a novel therapeutic modality was recognised concurrent with its development. The notion of an optogenetic treatment for PD is therefore one that features in the speculative concluding paragraphs of several papers. Today, with a successful research history and recent technological advances, its promise is greater than ever.

2 The promise of clinical optogenetics

2.1 Idealised optogenetics compare favourably with existing therapies

The same properties that make optogenetics a valuable investigative tool (summarised Table 1) make it a tantalising prospect for therapeutic use. As was soon recognised by researchers, its capabilities could be applied to counteract pathological activity in human parkinsonian circuitry. However, a nascent optogenetic therapy would need to show clear advantages against established therapies in order to succeed.

I evaluate clinical optogenetics in this section with attention to the most common pharmaceutical and surgical approaches (L-DOPA monotherapy and DBS respectively) with the acknowledgement that less common or supplementary treatment types exist. In such a comparison, an idealised optogenetic therapy (IOT) can be predicted to outperform these existing approaches in many important parameters.

Properties	**L-DOPA**	**DBS**	**Optogenetics**
Installation and invasiveness	None, taken orally	Surgical, stereotaxic implantation	Gene therapy + Stereotaxic implantation
Spatial precision	All dopamine-sensitive cells within the brain	Volume around electrode, variable	Illuminated volume around fibre tip, variable
Cell-type specificity	Limited[2]	None	Arbitrary[3]
Temporal precision	Low (minutes)	High (sub-millisecond)	High (sub-millisecond)
Duration of effects	Hours	Up to hours	Up to hours
Tissue excitation	No	Yes	Yes
Tissue inhibition	No	Yes, via excitation	Yes
Metabotropic	Yes	No	Yes

Table 2 | Comparing the properties of existing PD treatments against an IOT reveals multiple ways in which the latter might excel, thus justifying some of the excitement surrounding clinical optogenetics (Aravanis et al., 2007; Deisseroth, 2011).

[2] Conventional drugs target all cells with complementary receptors.

[3] Selective expression cannot be practicably achieved using viral transfection in all cell types, owing to weak expression or the size of some cell-specific promoters. This problem is tractable in transgenic animals, and additional solutions for humans are explored in section 3.2.

All existing PD treatments operate by modulating neurological function but do so indiscriminately in one of two ways (summarised Figure 5):

1. The activity of L-DOPA is restricted to the brain through peripheral DOPA decarboxylase inhibitors, preventing peripheral dopamine generation. However, the central effects on dopamine-responsive neurones are nonselective. This precipitates nausea, impulse control disorders, and cognitive disturbances through collateral effects on other dopaminergic pathways (Connolly & Lang, 2014).

2. In contrast, the effects of DBS are spatially restricted to the volume surrounding the implantation site. This invariably contains therapeutic targets in addition to unrelated cell bodies and fibres of passage which are equally affected, often antidromically, resulting in unwanted effects as visualised in Figure 4 and 5 (Zhang et al., 2007). This collateral neuromodulation is also thought to result in lost efficacy through cancellation of opposing pathways. DBS protocols emphasise electrode positioning to optimise results, whereas the specificity afforded by optogenetics relieves this requirement.

In this domain, IOTs surpass existing treatments by exclusively modulating targets defined by the intersection of their phenotype *and* anatomical location (Figure 5A).

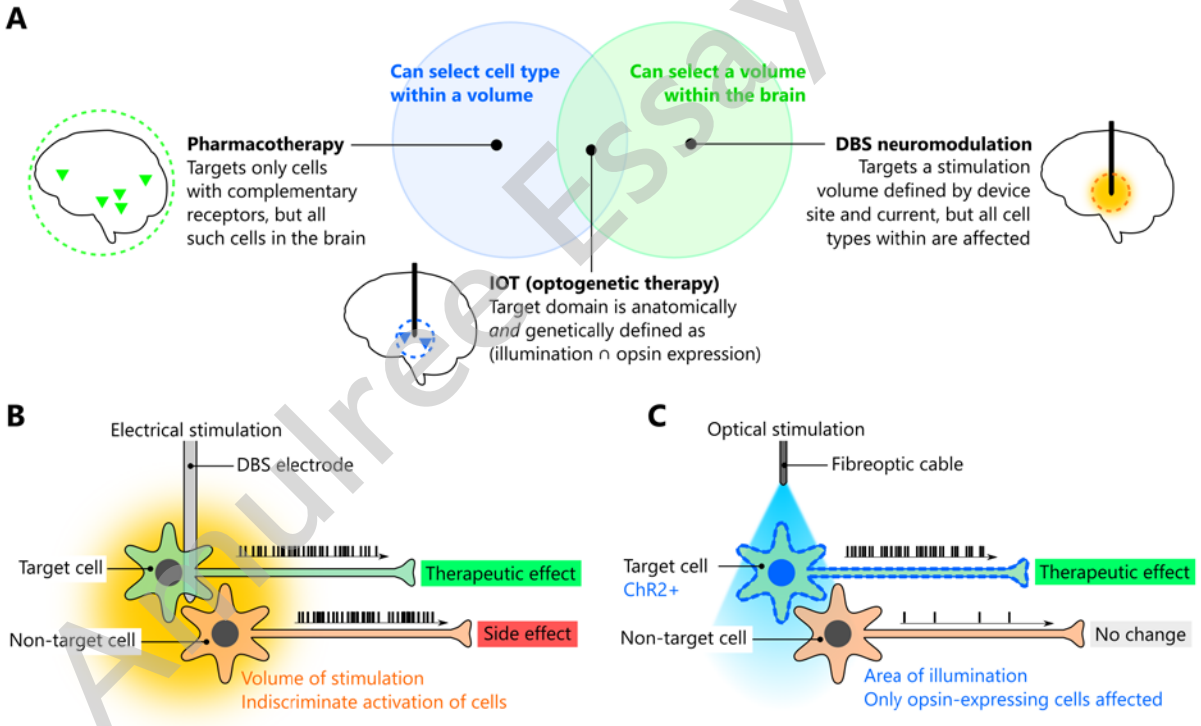

Figure 5 | Comparing the precision of pharmacotherapy, DBS and IOT. (A) variations in target domain: the IOT domain is defined by both anatomy and target phenotype, thus sharing desirable properties of both DBS and pharmacotherapy. (B) DBS indiscriminately activates all cells within a volume, resulting in side-effects or lost efficacy. (C) Optogenetic stimulation using ChR2 restricts neuromodulation to a genetically-defined target population and thus may reduce adverse effects.

Progressive resistance and dyskinesia curtail L-DOPA treatment in 90% of patients, often necessitating DBS intervention (Connolly & Lang, 2014). This phenomenon is partially attributable to the pulsatile L-DOPA concentrations achieved in the brain by intermittent oral delivery. Whilst this is mitigated by controlled dosing and release, evidence from nonhuman primate (NHP) studies suggests that continuous intravenous administration diminishes dyskinesia further (Bibbiani et al., 2005). Unfortunately, this is not practicable in humans without sacrificing the convenience of non-invasive oral drugs. Although oral formulations simplify treatment, they cannot meet acute demands for symptomatic relief due to slow absorption and activation pharmacokinetics. These examples are illustrative of the drawbacks of low temporal resolution in pharmaceutical treatment.

In contrast, DBS achieves fine temporal control at the cost of invasive neurosurgery. Millisecond resolution is necessary to immediately counteract aberrant network activity. Closed-loop DBS delivers such responses autonomously, using electrophysiological recording to inform stimulation patterns. Regardless, DBS performance also declines over time. This results partially from gliotic encapsulation of the implant - scarring that is electrically insulating but optically transparent (Polikov et al., 2005). In theory, an IOT could match the advantageous temporal resolution of DBS whilst also continuing unimpeded if encapsulation occurs.

Another temporal parameter to consider is duration of effect. Typical L-DOPA formulations relieve symptoms over hours, requiring only infrequent dosing (Connolly & Lang, 2014). The effects of DBS coincide with stimulation only: they are current-locked. This is recapitulated for most optogenetic implementations in model animals. However, newer DBS protocols such as coordinated reset are beginning to produce lasting, non-current-locked symptomatic relief in nonhuman primates. Wang and colleagues (2016) attribute these lasting effects to disruption of pathological synchronisation in the BG, a mechanism also purported to explain HFS-STN.

IOTs could extend this approach by selectively disrupting pathological networks. Recent results from Mastro and colleagues (2017) demonstrate that selective optogenetic neuromodulation of the external globus pallidus (GPe) results in prokinetic effects lasting up to four hours in parkinsonian mice. Such therapeutic longevity rivals even pharmaceutical methods. DBS stimulation of the same site, however, evoked only current-locked prokinesis. The paper identifies transient dissociation of the activities of interspersed cell populations as the likely origin of this difference. Within the heterogeneous GPe, DBS cannot discriminatively modulate these cell types, but optogenetics can. Achieving persistent therapeutic effects from transient manipulations will also lower power consumption and cytotoxic effects by permitting lower duty cycles when compared to existing light-locked optogenetic protocols.

2.2 Situating optogenetic therapies among their competitors

I have presented an IOT that combines pharmaceutical pathway-specificity with DBS spatiotemporal precision and, moreover, exceeds both in cell type specificity. When considering this idealised comparison, early excitement for optogenetic therapies seems justifiable. However, it is likely that any real-world optogenetic therapy (OT) would fall short of expectations. It is not known, for example, how OTs would compare to other therapies in the long term: they may suffer from unreliability ("off-time") and declining efficacy ("wearing off") over time like L-DOPA, or cause inflammatory responses like DBS.

Although there are well-defined disease pathways in PD that could be OT-targeted, predictions must be tempered with the idea that PD is more complicated than any single group of cells.

OT modulation of unitary cell populations cannot universally ameliorate symptoms, as even murine studies show. For example, the lasting therapeutic effects from Mastro et al. (2017) leave postural and gait symptoms unresolved; the responsible circuitry is untouched by the hyperspecific modulation in their protocol design. The translational implication here is that OTs are unlikely to address the full spectrum of symptoms in PD patients. Hence, OTs would likely be supplemented by pharmaceutical approaches that confer broader symptomatic relief. Several additional problems stand between optogenetics and clinical trials. I will now explore these further, providing reasons why clinical optogenetics is far from a reality.

3 Translational hurdles

3.1 Defining the problem space

Despite the many advantages presented in Section 2, OTs remain remote due to several biological, technological, and practical limitations. For some of these problems, potential solutions are emerging whilst others remain uninvestigated. Critically examining the optogenetic approach shown earlier for clinical practicality reveals several such challenges. Each of these is made more delicate by the necessarily higher standards of safety and efficacy for clinical technologies:

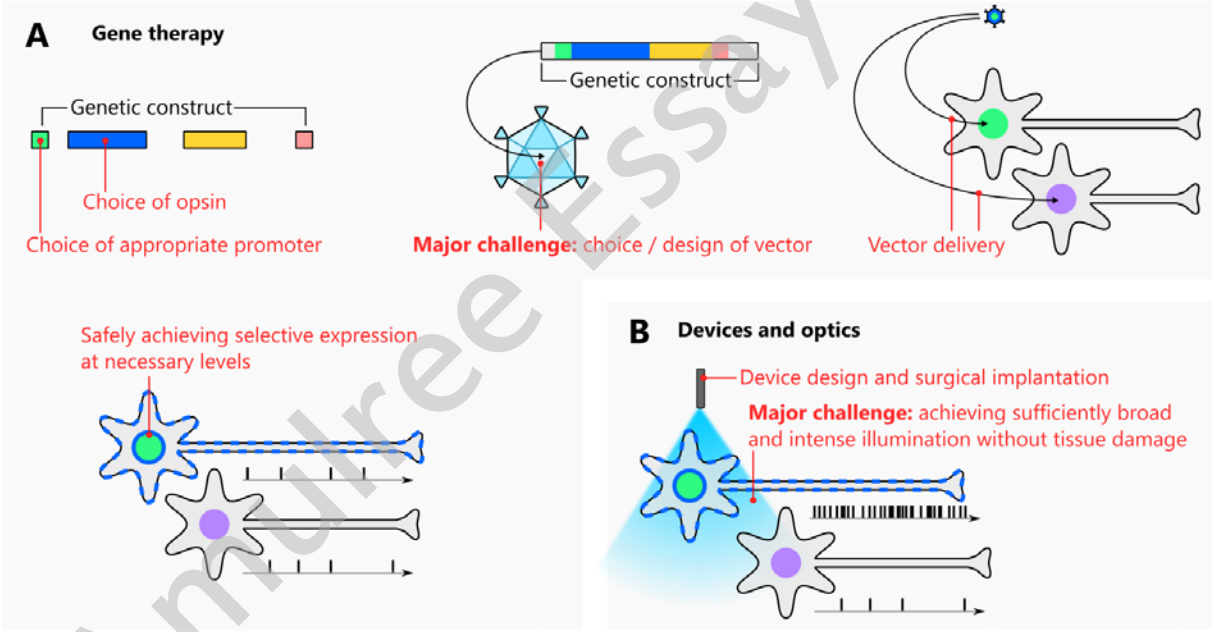

Figure 6 | Potential impediments and open questions at each stage of a simple optogenetic protocol. These are grouped into two technological categories: (A) those relating to gene therapy, and (B) those related to technological and optical limitations. These groups are examined in Sections 3.2 and 3.3 respectively. Non-technological issues are explored in Section 3.5.

As both gene therapy (GT) and cerebral implants are clinically established, one might suppose that many impediments to OTs have already been resolved. However, optogenetics was demonstrated in *ex vivo* human neurones only two years ago (Andersson et al., 2016). I will now present how many remaining hurdles, not all of them technological, are inhibiting progress in translational work.

3.2 Successful human optogenetics depends on successful gene therapy

Many of the studies presented earlier rely on transgenic animals that express recombinases in certain cell types to restrict opsin expression. In human patients, all of them wild-type, this crutch is removed. More subtle methods must be used for expression control, and all employ some form of GT. This approach still suffers from associations with leukaemia and the death of volunteers during early trials (Kotterman et al., 2015). We will return to the resultant misgivings in section 3.5.

A leading delivery vector for GT is adeno-associated virus (AAV), recently approved for clinical use after successful human trials (LeWitt et al., 2011). Therapeutic strains are nonintegrating, forming episomal concatemers that exist outside the host genome, precluding genotoxicity (Morrison, 2018; Kotterman et al., 2015). Viral vectors generally outperform others in penetrance and concatemers are stable in postmitotic cells like neurones. The principal drawback to AAV is the capsid-limited genetic payload of ~5 kb. For many PD-related cell types, there is no specific promoter that is sufficiently compact to incorporate into an AAV-delivered construct.

Attempts to find novel promoters aside, use of a physically larger capsid such as that of a nonintegrating lentivirus addresses this problem. With an increased coding limit, greater promoter choice is afforded. However, no known promoter is uniquely and highly-expressed among dopamine neurones and larger particles diffuse poorly in brain parenchyma. Vector engineers are therefore transitioning from promoter reliance to engineering vector tropism instead. Choi et al. (2010) present a solution in the form of designer “bridge” proteins that connect capsids with arbitrary cell surface markers, thus enabling selective transfection. Such markers could potentially exist for OT target cell types.

Viruses targeting the brain cannot simply be introduced into the general circulation due to interdiction by the blood-brain barrier and the risk of an inflammatory response. Intracerebral injection is therefore required. Although this approach is fraught with risk, it conveniently confers immune privilege. Thus, the major immunogenic concern with exogenous proteins is diminished by restricting opsin expression to the brain. Introducing any vector to specific brain regions demands stereotaxic techniques that are challenging in mice and primates, but even more so in humans owing to greater brain volume and higher standards for safety.

Although optogenetics can be implemented in human tissues, it is not known whether there is a maximum tolerated membrane concentration for opsins or if this varies between cell types. Though none of the animal studies covered here allude to opsin toxicity, such uncertainty surrounding the long-term safety and duration of GTs accounts for some of the trepidation towards clinical trials. Crucially, if adverse effects result from OTs, the underlying genetic changes are impossible to discontinue as one might during a pharmaceutical trial.

3.3 Optogenetics is limited by efficiency and scalability in the primate brain

Though the inefficient membrane trafficking of early opsins has since been remedied, cells with high opsin expression still suffer from light insensitivity (Gradinaru et al., 2010). Light delivered from traditional 'flashlight' fibre tips undergoes immediate divergence. 470nm blue light, routinely used with ChR2, is then scattered at lipid-water interfaces and absorbed by oxyhaemoglobin. Brain parenchyma is dense with both. Consequently, incident light can be attenuated to 1% over a mere 1mm of neural tissue (Galvan et al., 2017; Aravanis et al., 2007).

These effects have confounded illumination of large brain volumes. Though this is unimportant in the rodent brain, scale has beleaguered optogenetics in primates (Figure 7A). The GPi, an example BG target structure, has a volume of ~0.8mm^3 in rats, compared to a 240mm^3 volume in humans (Hardman et al., 2002).

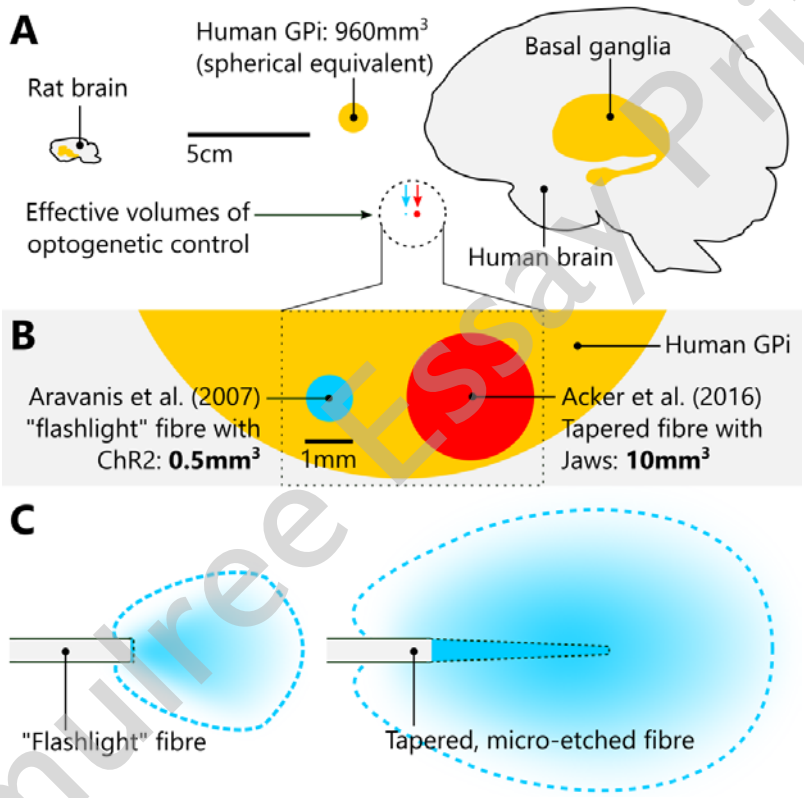

Figure 7 | (A) Scale diagram of human and rat brains compared with volumes of optogenetic control. BG size highlighted in yellow alongside the spherical volume equivalent of the human GPi. (B) Magnified volumes of control achieved with experimental optogenetics compared to the GPi. Aravanis et al. (2007) and Acker (2016) worked with rats and rhesus macaques respectively. (C) Use of a tapered fibre enables diffuse illumination of a greater volume from a larger light-permeable surface (dotted lines).

Increasing light intensity extends illumination and effective neuromodulation range at the expense of tissue heating. As brain temperature must be maintained within a delicate range, this is undesirable: irreversible damage begins in mammalian brains 3°C above the physiological baseline. Nonspecific changes in neuronal activity begin even below this, forfeiting any benefits from OT specificity (Kiyatkin, 2010). Because of this, thermal effects render the 470nm-ChR2 experimental pairing unsuitable for clinical use. There are several

proposed solutions to this problem, clustered broadly into attempts to increase opsin sensitivity and attempts to increase illumination volume.

Engineered opsin variants with red-shifted activation spectra represent a hybrid approach. Red light undergoes dramatically less absorption and scattering in neural tissue than shorter wavelengths whilst depositing less energy at any given intensity. Acker et al. (2016) substantiate this in NHPs, achieving 10mm^3 of reliable control *in vivo* using the red-shifted opsin Jaws. This channel is actuated at lower irradiances than its blue counterparts, further increasing effective neuromodulation range. As Jaws also has slow inactivation kinetics, lower illumination duty cycles may be used. As a result, safe tissue heating of <1°C was recorded. Another part of their success is attributed to a novel tapered fibre which broadens illumination and reduces focal heating (Figure 7C) whilst minimising fibre insertional damage. Although this study illustrates the importance of wavelength, opsin, and fibre design for OTs, 10mm^3 is still dwarfed by the volume of the human GPi, shown to scale in Figure 7B. In contrast, modern DBS influences brain volumes exceeding 100mm^3, and the gross neuromodulatory volume achieved is correlated with therapeutic outcome (Maks et al., 2009). If this correlation holds for OTs, insufficient illumination volumes could threaten their comparative efficacy.

Optogenetic protocols using multifibre illumination represent one remaining solution for OT modulation of entire human nuclei. However, this approach confers cumulative insertional trauma from each additional fibre, as I will now discuss further.

3.4 The hardware and protocols for optogenetic neuromodulation aren't yet mature

Implantation of an optoelectronic device to deep brain regions is accompanied by several risks, many of them comparable between existing DBS leads and fibreoptic cables. However, modern fibreoptics are thinner and more flexible than DBS leads, and insertional trauma is proportional to device diameter. The fibre used by Acker et al. has a maximum diameter of 250µm, compared to the 1270µm diameter of some DBS leads[4]. Even thinner fibreoptics may be manufactured at the cost of reduced light delivery. A compromise must therefore be reached between insertional trauma and illumination. Surgery also introduces a less variable risk of infection that remains a primary source of DBS postoperative complication (Williams et al., 2010). Because of their essential similarity, we should expect similar risks of trauma and contamination in OTs.

PD DBS consistently results in better self-reported patient outcomes than the best medical therapies alone across RCTs, but a greater number of surgical patients experience serious adverse events (Sharma et al., 2012). For example, the PD SURG clinical trial reports 42 adverse surgery-related events and one death in a DBS cohort of 183 over the first postoperative year (Williams et al., 2010). These combined risks would discourage routine use of OTs for PD.

Despite these dangers, the relative clinical effectiveness of DBS over pharmacotherapy validates surgical approaches to PD. This will need to be proven for OTs as well: to compete, optoelectronics must meet similar or higher standards for reliability, biocompatibility, and efficacy to DBS. Animal implementations are neither designed to these specifications nor used chronically. As the most protracted animal experiments last only a few years (Yazdan-Shahmorad et al., 2016), there is little evidence for the long-term performance and safety of optoelectronics.

[4] Taking the Medtronic model 3389 as a market-leading example.

Protocol choice raises further questions. Optogenetics has enjoyed widespread research adoption and therefore rapid advancement in recent years: new opsins, vectors and devices are developed monthly. Whilst this is beneficial to research, the rate of progress disincentivises commitment to translational studies due to the obsolescence risks assumed by any venture.

Furthermore, there is no consensus on the most effective neuromodulation target, expanding the decision pool in Figure 8. Although some studies referenced in this paper have produced effective symptomatic relief in animal models, their targets and outcomes have differed. Investigating which target-protocol-technology combination optimises outcomes is necessary to confidently propose a translational attempt. Small differences can produce wildly divergent effects: prolonged photoactivation with ChR2 can, counterintuitively, silence neurones through depolarisation block in a similar manner to high-frequency DBS (Herman et al., 2014). Such emergent network behaviours complicate design and make ensuring OT safety more difficult. Essentially, we should not expect physiological activity from neurones pushed beyond physiological bounds. There may also be unexplored consequences to introducing artificial, synchronous network activity to BG networks. Adverse outcomes seem especially plausible considering that at least some PD symptoms result from increased network synchronicity (Wang et al., 2016). Without sufficient data, committing to any particular method for translational study is difficult.

			X					5
Single			Y		GPi			10
Multiple	tapered	fibres driving	photoexcitation	of Z cells in the	STN	using Jaws and	burst illumination at	20 Hz
	flashlight		photoinhibition			ChR2	tonic	50
	rounded		G-proteins			HaloR		100

Figure 8 | The decision pool for OT design. Additional options are available for each variable shown here, and others (wavelength, surgical method, vector choice, dosing, and promoter) are not shown.

3.5 Financial and sociological concerns inhibit adoption

We have explored several impediments to designing a real-world OT but can set these aside for the remainder of the section. Supposing that an enterprising group were to commit to development regardless of these, many additional challenges would be encountered.

A company launching the first OT trial would meet several first-mover disadvantages. Firstly, clinical studies are necessarily subject to stricter standards of regulation and safety than animal research. To commence trials, an OT would face the combined regulatory hurdles of a GT and implanted device. Such regulation has necessarily prevented many promising treatments from reaching market. Moreover, if the first clinical foray results in disaster, the reputation of the field suffers in a way that may permanently disincentivise follow-up studies. Hence, the safety (and ideally, success) of any trial would have to be all but guaranteed before investment. The optogenetic knowledgebase is not yet complete enough to assure this.

Development would also take place parallel to the advancement of other therapies against which OTs must compete. Improvements in DBS technology, for instance, could obviate the need for further work towards an OT at any time.

During clinical trials, disruptive technologies face resistance due to transition costs and the need for popular acceptance. Both professional and patient opinion of unfamiliar treatments must be won gradually through reassuring clinical results, and the success of any new therapy depends on public perception. Medical professionals would likely find OTs complicated to

implement and difficult to recommend. The initial cost of training staff must also be considered. Patient attitudes are even more relevant: whilst acceptance of implanted devices is higher than ever, public opinion of GT remains cautious (Gaskell et al., 2017). Familiarity comes slowly, but comparative presentation like the term "brain pacemaker" for DBS devices may expedite it.

Even if all these issues were surmounted, the developing company would need to both recoup their expenses and commercialise the product. The development costs of any therapy are therefore unavoidably reflected in the cost of treatment to the healthcare provider or private client. OTs combine two technologies whose individual prices strongly suggest that OTs will not be cost-effective (Table 3).

		Costs		
Treatment	**Period**	**Pharmaceutical**	**Surgical**	**Gene therapy**
Best medical therapy	First year	£3,600	None	None
DBS + medical therapy	First year	£3,300	£9,100	None
Voretigene neparvovec (retinal dystrophy)	One-off, (per eye)	Minor	Minor	£298,500
Alipogene tiparvovec (lipoprotein lipase def.)	One-off	Minor	Minor	£779,400
'Strimvelis' (ADA-SCID)	One-off	Minor	Minor	£514,400
Optogenetic therapy	First year	Comparable to DBS + medical	Comparable to DBS + medical	May compare with gene therapies today

Table 3 | Costs of treatment modalities. Costs of medical therapy alone and DBS + best medical therapy from McIntosh et al. (2016). Costs of comorbidity treatment and non-pharmaceutical, non-surgical costs incurred by PD are not included. Prices for gene therapies with reference to Nature Biotechnology News (2018) and Touchot and Flume (2017). Exchange rates from USD and EUR calculated April 2018 and rounded to the nearest £100.

Firstly, the expenses of surgery and optoelectronic devices must be factored into the cost of OTs. It is important to recognise the costs incurred during installation as well as postoperative management, maintenance, and the event of device failure. An estimate of these can be made from DBS, whose uptake is limited in part by its price. A 6-year follow-up study to the PD SURG trial calculated an incremental cost per quality-adjusted life-year of £70,537 for DBS (McIntosh et al., 2016). Conservatively assuming similar costs for the surgical component of OTs (on the basis of discussion in Section 3.4) would suggest that provision to the 1% of over-60s affected by PD is unrealistic, especially when considering the relative simplicity and economy of pharmacotherapy (Lees et al., 2009).

More crucially, the prices of GTs remain extremely prohibitive. This renders them risky investments and difficult marketing prospects - none of the orphan drug examples given in Table 3 have been successfully commercialised. Furthermore, the ongoing costs and lasting efficacy of GT are obscure due to the recency of clinical trials.

Being a combination of GT and implanted device, the predicted costs of OTs remain unavoidably high. One must ask whether OTs are economically plausible, given that they are not disease-modifying and that patient lifespans will not be greatly extended with their use. Although OTs may reduce recurrent antiparkinsonian drug costs due to their efficacy, this seems an insignificant saving considering the upfront expense. An apparently overwhelming ethical objection to OTs arises when reconciling patient benefits, however great, with such expense if the same resources could be more effectively allocated. It is possible, however, that a subset of the patient population whose PD is particularly unmanageable through conventional means would stand to benefit regardless of the price.

4 Perspectives

4.1 The risk-to-reward ratio of clinical optogenetics remains uncalculated

I have argued in this essay how, despite their potential benefits for PD treatment, a serious proposal to develop OTs seems remote. For now, it is only possible to speculate how optogenetics compares to DBS or pharmaceutical treatments on many clinically-important metrics. Among these, improvement in patient quality-of-life is chief but also least clear. In public healthcare systems, this variable must always be balanced against a cost which seems prohibitively high for OTs. The two sides of the case to develop OTs are summarised in Table 4. There is currently no indication that OTs could ever challenge the convenience and relative economy of pharmacotherapy or even DBS. Optogenetics simply does not have the ability to reach most patients, and such factors have culminated in the abandonment of countless nascent treatments in the past. Even if OTs were to prove efficacious, we can look to DBS uptake as evidence that therapeutic impact is not the only important parameter when considering widespread adoption.

Category	Incentives	§	Disincentives	§
Developmental *Most certain*	Large opsin library with varied properties to select from	1.1 1.2	Rapid rate of progress introduces an obsolescence risk	3.5
	Single-component, making preliminary research simpler	1.1 1.2	Difficult to settle on any one combination of protocol elements	3.4
Clinical *Uncertain*	Unprecedented temporal and spatial resolution alongside cell-type specificity	2.1	No clear method of opsin restriction to several potential target populations in humans	3.2
	May be more effective over time than DBS	2.1	**Limitations on neuromodulation scalability in large brains**	3.3
	May improve side-effect profiles versus existing treatments	2.1	**Complicated to implement in humans; combined risks of GT and neurosurgery**	3.3 3.4
	Might be more therapeutically effective than DBS or pharmacotherapy	2.1	**Unlikely to ameliorate all symptoms, advantages remain uncertain**	2.2 3.4
			Possibility of unforeseen side-effects and cannot be withdrawn	3.2 3.4
			Not disease-modifying	3.5
			Public unfamiliarity with gene therapy	3.5
Economic *Most uncertain*	May reduce recurrent cost of medication	3.5	**Very high combined cost of surgery and GT**	3.5
			High cost to ensuring safety and running clinical trials	3.5

Table 4: Grouped incentives and disincentives to developing an OT for PD. Section references to pertinent discussion are included. Issues that are of central importance are bolded, namely those relating directly to cost per quality-adjusted life year and the ultimate value of treatment.

If OTs for PD have any hope of development, it lies in successful demonstrations in other clinical contexts. Section 3 establishes that deep brain implementations of optogenetics are fraught with problems. For this reason, more accessible body regions such as peripheral nerves and the retina have served as testbeds for clinical optogenetics. Here, both the technical challenges and risks of deep brain OTs are reduced. Consequently, the first OTs may be for diseases like retinitis pigmentosa for which the PIONEER trial will bring the first results in 2024. The outcome here will represent the first evidence for OT tolerability and efficacy. Success in these early attempts may foster the necessary excitement, technological advancement, and willingness to spend for more ambitious efforts. If developed, OTs for retinitis pigmentosa and other candidate diseases could serve as stepping stones to the development of the deep brain OTs critically examined in this paper.

4.2 Optogenetics indirectly enables new approaches to PD treatment

For now, it is considerably cheaper and more feasible to advance existing treatments using the findings of optogenetic investigations, as presented in section 1, than it is to champion OTs themselves. Certainly, optogenetics has transformed our understanding of the functional neuroanatomy of the healthy and diseased BG, and this evidence can be readily applied to DBS neuromodulation protocols. Doing so represents an indirect means by which optogenetic research has benefited PD treatment.

However, there remains a need for a technology that can exert versatile and specific control over neurocircuitry in PD and other diseases. Despite its many beneficial properties, optogenetics may not be the first to fill this niche: its development continues alongside other technologies that may do so instead. Directional DBS and pharmacogenetics are generating promising results and are in different ways more elegant than OTs (Pollo et al., 2014). Optogenetic research may indeed inform the development of an entirely new approach, possibly one that eschews the associated expense and risks of GT.

As a final remark, one should note that a hypothetical OT, like all existing treatments, would serve to ameliorate symptoms but would not address the neurodegenerative process itself. For a true disease-modifying treatment, a cure, we must look to prospective therapies that target PD at a more fundamental level than optogenetics can.

5 Bibliography

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