7 Ethical Issues Raised by Recent Developments in Neuroscience: The Case of Optogenetics

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7.1 Introduction

New tools for recording and manipulating neuronal activity in humans and animals are developing at a rapid pace. Driven in part by public and private funding for ambitious neuroscience research (Insel, Landis, & Collins, 2013; Bargmann & Newsome, 2014; Brose, 2016; Yuste & Bargmann, 2017; Musk & Neuralink, 2019), these tools offer the promise of transforming our understanding of the brain in health and disease. Discussion of the ethical implications of these technological advances, however, has often lagged, despite increasing recognition of these ethical implications by the emerging field of neuroethics (Farah, 2010; Illes & Hossain, 2017). In order to maximize the benefits and minimize the risks of applying these novel methods, it is critical to identify and address the ethical issues early (Goering & Yuste, 2016; Greely, Ramos, & Grady, 2016; Ramos et al., 2019). We focus here on the ethical implications associated with the clinical application of optogenetics—an approach that allows neural activity to be controlled with light (Bi et al., 2006; Boyden et al., 2005; Deisseroth, 2015). While optogenetics is only one of several recent transformative neurotechnological developments, it is perhaps among the closest to clinical application. Indeed, clinical trials using optogenetics to treat retinitis pigmentosa, in which opsins (light-sensitive proteins) are expressed in the retina to restore vision, are underway (Simunovic et al., 2019), and there is great interest in applying optogenetics to a range of psychiatric and neurological disorders (Deisseroth, 2012; Delbeke et al., 2017). In this chapter, after briefly describing optogenetics and its potential clinical applicability, we focus on the ethical issues associated with its clinical use.

To appreciate the significance of optogenetics, it may be helpful for some readers to review very briefly here some fundamentals of neuroscience

(neuroscience experts may wish to skip ahead). Neurons communicate information via action potentials, which occur when positively charged ions enter the neuron. Ions cross the cell membrane passively through open channels, which can be opened or closed by factors such as chemical compounds, temperature, and light, and can be actively pumped across the membrane as well. Light-gated channels and pumps are found in a variety of microbial species, in which they promote survival (e.g., by allowing the organism to navigate toward a food source). Advances in molecular biology and genetics have allowed researchers to clone the genes encoding these light-sensitive channels and pumps (among many other proteins) and to express them in cells in which they are not normally found. Expressing light-sensitive ion channels in the cell membrane of a neuron, for example, allows the flow of ions across the membrane to be controlled by light, which can be delivered to the brain via an optical fiber. In this way, optogenetics allows for the manipulation of activity of genetically specified populations of neurons with light, providing unprecedented control of specific neural circuits (Deisseroth, 2015). Depending on which light-sensitive protein is expressed, and in which types of neurons, specific groups of neurons can be activated or inactivated with high temporal resolution. For example, neuronal expression of channelrhodopsin-2, a blue-light sensitive cation channel protein found in some algae (Boyden et al., 2005), allows these neurons to be activated by blue light. Light causes the channel to open, allowing cations to enter the neuron, resulting in an increased rate of action potentials. When archaerhodopsin-3, a proton pump found in the single-celled organism archaea (Chow et al., 2010), is expressed in neurons and exposed to yellow light, protons are pumped out of the neuron, ultimately decreasing the rate of action potentials. Channelrhodopsin-2 and archaerhodopsin-3 therefore allow the activity (the rate of action potentials) of neurons to be increased or decreased, respectively, and are only two of a rapidly expanding set of optogenetic proteins for controlling cellular processes.

Additional molecular tools allow for the expression of optogenetic proteins restricted to specific types of neurons based on, for example, what neurotransmitter they release or what downstream brain regions they project to (i.e., send axons; Luo, Callaway, & Svoboda, 2018). For example, suppose one wanted to activate only those neurons in one brain area (say, area A) that project to another brain area (say, area B). There are several approaches by which channelrhodopsin-2 can be expressed in only those area A neurons

that project to area B, and not in other area A neurons. Delivering blue light to area A (e.g., via an optical fiber) then activates only that subset of area B–projecting neurons (Gradinaru, Zhang, et al., 2010). This level of specificity is critical because neurons in any given brain area frequently project to many different brain areas, and each projection may have a specific function. Similarly, neurons in any given area may release different neurotransmitters, which may also mediate specific functions. Finally, because light delivery can be controlled with high temporal and spatial precision, neural activity in specific brain regions can be modulated at a relevant timescale for the processing that occurs in neural circuits (i.e., milliseconds).

By providing such cell-type specificity and spatiotemporal specificity, optogenetics has enabled researchers to examine whether activity in specific cell types is necessary and/or sufficient for a range of functions, from stimulus representation to neural circuit dynamics to complex social behavior, transforming how basic neuroscience is performed as well as our understanding of neural function (Yizhar, 2012; Yoshihara & Yoshihara, 2018). Given the circuit-based nature of many psychiatric and neurological disorders, optogenetics offers the potential to transform clinical care as well in ways that are not possible with current standard treatment options. Pharmaceuticals, for example, have themselves transformed psychiatric treatment over the last several decades via the development of drugs that up- or downregulate neurotransmission (Ban, 2006). However, the relatively slow time course of drug effects—on the order of hours—as well as the frequency of off-target effects, limits the efficacy of this approach. Direct current delivery, on the other hand, can provide millisecond-level modulation of neural activity, but affects all nearby neurons rather than only the desired type (Henderson, Federici, & Boulis, 2009; Nowak et al., 2010; Delbeke et al., 2017). Thus, these and other current approaches lack the necessary combination of temporal resolution and cell-type specificity to treat circuit-level disorders optimally.

Deep brain stimulation (DBS), a treatment for Parkinson's disease (PD) and other movement disorders approved by the Food and Drug Administration (FDA), provides an illustrative example of the shortcomings of traditional approaches and the potential clinical application of optogenetics (Lin, Deisseroth, & Henderson, 2011; Delbeke et al., 2017). In DBS for PD, current is delivered to a particular brain region (typically the subthalamic nucleus [STN], a component of the basal ganglia) in order to normalize its pathological activity and mitigate parkinsonian motor symptoms

(Kringelbach et al., 2007). We will subsequently refer to this therapy as "electrical DBS" (eDBS) to differentiate it from optogenetic DBS discussed below. Although eDBS typically relieves some parkinsonian symptoms, its mechanism of action is surprisingly poorly understood (Herrington, Cheng, & Eskandar, 2015), hindering improvements to the therapy. Standard models of basal ganglia function predict that the parkinsonian STN is hyperactive, suggesting that eDBS works by reducing STN activity. Typically, however, delivering current is thought to increase, not decrease, activity. One possible explanation is that eDBS somehow modulates the activity of axons projecting to the STN rather than STN neurons themselves, even though the delivered current presumably affects all nearby tissue similarly. By allowing specific neurons (e.g., STN neurons) to be manipulated in a known direction (e.g., excited), optogenetics avoids these problems, offering the potential to understand the mechanism of action of eDBS and identifying beneficial stimulation parameters, both of which would improve eDBS therapy (Gradinaru, Mogri, et al., 2009; Kravitz et al., 2010).

There is thus intense interest in developing and applying DBS protocols that use optogenetics (which we will call "oDBS"). To be sure, there are many practical barriers to overcome before oDBS can be a viable treatment option, including the delivery of the genes encoding the opsin, achieving stable long-term opsin expression, and safe light delivery. While these methods are standard in animal models, establishing them in humans presents particular challenges (some of which are discussed below). Conceptual barriers also exist. While we understand a great deal about PD and its treatment at the circuit level (McGregor & Nelson, 2019), our current understanding is insufficient to determine exactly how activity should be altered to relieve parkinsonian symptoms (i.e., what pattern of activity in which cell types would be required, and how frequently the stimulation protocol might need to be revisited in response to plasticity in the affected circuits). However, our technological capabilities and conceptual understanding are advancing rapidly. For example, it was recently demonstrated that "upconversion" nanoparticles, which absorb light of one wavelength and emit light of another, can be used to activate opsins (Chen et al., 2018). This is an important advance with translational relevance, as it would allow opsins normally sensitive to short-wavelength (e.g., blue) light to be activated by long-wavelength (e.g., red) light, which can penetrate through the skull and relatively deep into the brain and therefore be delivered noninvasively

(Feliu, Neher, & Parak, 2018). Thus, while there remain obstacles to overcome, it is critical to examine the ethical issues associated with oDBS (Gilbert et al., 2014). We next describe the normative ethical issues associated with clinical trials for oDBS and with the potential for widespread adoption of optogenetics in clinical care, and briefly discuss how these issues can and should be informed by empirical data.

7.2 Normative Ethical Issues Associated with Clinical Optogenetics

Clinical optogenetics requires genetic engineering in order to express opsins in neurons, as well as the direct modulation of neural activity. As such, several of the associated ethical issues are similar to those of gene therapy and eDBS. We review these briefly here, highlighting differences specific to optogenetics, before focusing on novel ethical issues. While we concentrate here on clinical applications of optogenetics, it is possible that optogenetics could at some point be leveraged to enhance cognitive function, following the familiar shift from restoration to enhancement seen with other therapeutic approaches. Such use would involve many of the same ethical issues as would clinical applications, while also introducing additional issues discussed in the cognitive enhancement literature (e.g., access and equity; Farah et al., 2004).

7.2.1 Ethics of Opsin Expression in Patients

Expressing opsins in neurons requires introducing DNA encoding the opsin protein to the neurons of interest, which can be accomplished in several ways. Critically, these methods require only somatic editing and not the more ethically fraught germline editing (in which the exogenous DNA is passed to future generations). Genetically modifying somatic cells to treat diseases is generally considered potentially ethical as long as standard issues are addressed (i.e., safety, risk–benefit calculation, protection of vulnerable subjects, informed consent, patient monitoring, and equity of access; National Academies of Sciences, 2017; Cavaliere, 2019; Coller, 2019), including by the public (Condit, 2010; Robillard et al., 2014). To the extent that introducing opsin DNA is seen as therapeutic, we would expect the same normative ethical issues and empirical attitudes.

However, in contrast to cases in which gene therapy is used to repair faulty genetic information (i.e., resulting from genetic disorders), in the

case of optogenetics, the opsin is not itself therapeutic but instead provides a *tool* for therapy by providing the neurons with an enhanced functionality to be controlled by light. There does not appear to be a deep normative distinction between these cases, given that the ultimate purpose of the opsin expression is therapeutic. However, one might be concerned about some of the morally relevant consequences differentiating a therapy itself and a tool that could be used for therapy in that the tool (in this case, gene editing for opsin expression) could be used for other purposes (see below). Moreover, attitudes toward gene therapy differ for restoring, as opposed to enhancing, function (Robillard et al., 2014). So, it is possible that the gene therapy required for optogenetics would be met with some resistance that is worth understanding and addressing. Empirical data addressing this question would therefore be useful.

7.2.2 Ethics of Directly Manipulating Brain Activity in Patients

oDBS involves the direct manipulation of brain activity. As such, many of the ethical issues raised by eDBS apply to oDBS as well (and some are not applicable; e.g., oDBS may not require an invasive implant for light delivery). These issues include balancing the benefits of therapy with the risks of unintended effects of stimulation, informed consent in a patient population in which medical decision making may be impaired, the potential for enhancement rather than restoration of function, and potential changes to personality and agency (Schermer, 2011; Skorburg & Sinnott-Armstrong, 2020). In the case of closed-loop eDBS, in which stimulation parameters are adapted based on recorded brain activity, privacy is an additional concern (Zuk et al., 2018). We do not identify any ethical issues related to the direct manipulation of brain activity that are novel to oDBS. On the contrary, given that oDBS (including closed-loop oDBS) has the potential to be more effective than eDBS due to its cell-type specificity, some of the above concerns may be mitigated. For example, unintended effects, including personality change, may be less likely to occur.

7.3 Novel Ethical Issues with Optogenetics: First-in-Human Clinical Trials

Perhaps the nearest clinical application of optogenetics to a neurological disorder is oDBS (e.g., for movement disorders such as PD). In light of this, a novel ethical issue raised by optogenetics involves considering the ethical

requirements for clinical trials of oDBS (Gilbert et al., 2014). Following the framework of Emanuel, Wendler, and Grady (2000), we focus on aspects unique to oDBS of several criteria that such trials would need to meet.

7.3.1 Fair Subject Selection

Which patients would be most appropriate for first-in-human oDBS trials? While for the reasons described above oDBS holds high potential for improvement over eDBS, the latter is already sufficiently effective and safe, has been approved by the FDA for certain conditions, and is in widespread clinical practice. Thus, the rationale for subjecting a particular patient to oDBS requires a potential relative benefit, or at least no detriment, of oDBS over eDBS for that patient. One promising population would be those for whom eDBS would otherwise be indicated but is not possible. For example, patients with structural basal ganglia abnormalities present a problem for targeting specific brain regions with the stimulating electrode (Kocabicak et al., 2015). This particular problem would be mitigated by oDBS, in which, as long as opsin expression can be sufficiently restricted to a particular type of neuron (an active area of research showing steady advancement), neither the viral injection nor the light delivery needs to be as spatially restricted to achieve therapeutic success.

Although trials testing the therapeutic efficacy of oDBS would need to be performed in patients, there may be advantages to performing parallel trials, in separate groups of subjects, to test the safety of opsin expression and the safety of light delivery. In principle, opsins can be activated by light of sufficiently long wavelength to be deliverable noninvasively through the skull (e.g., via LEDs on the scalp). Assessing the effects of increasing light power on brain tissue (absent opsin expression) can therefore be performed relatively noninvasively in healthy human subjects and will be able to build on work in preclinical studies in animal models. To assess the safety of opsin expression alone, although trials would require an invasive intracranial injection, they would not need to be paired with light delivery. Alternatively, if safety-related trials are performed in patients only, it may be advantageous to also test for efficacy in the same patients (Gilbert et al., 2014).

An important aspect of fair subject selection involves ensuring that vulnerable individuals are not targeted for risky research, and also that the rich and socially advantaged are not favored for potentially beneficial research (Emanuel et al., 2000). Subjects should be selected based on the scientific

goals of the study. In the context of oDBS, it is unlikely that vulnerable or stigmatized individuals would be specifically targeted (e.g., because of convenience). However, it may be true that vulnerabilities exist that should be managed during trial design and execution, and that the rich or socially advantaged may be favored as subjects, given that they may be presumed to be more open to advanced neurotechnologies such as oDBS. Thus, care should be taken for researchers and Institutional Review Boards to use an analytic framework for identifying and addressing vulnerabilities, such as the integrative-functional account (Racine & Bracken-Roche, 2019). This framework provides a toolkit that can be applied to any study protocol. Care should also be taken to recruit subjects from all socioeconomic groups so that the privileged are not prioritized and benefits and risks are fairly distributed.

7.3.2 Favorable Risk–Benefit Ratio

In addition to the risks and benefits associated with eDBS and gene therapy, a unique risk of oDBS is the potential for covert manipulation. Once the neurons of a patient are expressing the opsin, their activity is susceptible, by design, to being manipulated by light. As noted above, in the preferred clinical scenario, the light would be deliverable noninvasively, likely via long-wavelength light capable of penetrating deeper into the brain (Feliu et al., 2018). However, this means that other light sources of sufficient power could, in principle, activate these neurons as well. This leaves open the possibility that patients' brain activity could be manipulated covertly with imperceptible light that has no effect on individuals who are not expressing the opsin. Such manipulation could induce patterns of activity in opsin-expressing neurons that cause harmful motor or cognitive effects. The importance of this concern would grow as more patients express a particular opsin, which would be expected to occur if oDBS were to attain clinical viability.

This risk echoes more traditional concerns about the widespread ability to manipulate brain activity of groups of individuals (e.g., via chemical agents delivered to the water supply). In this case, however, the manipulating agent (light) can be delivered indiscriminately while only having an effect on the known targeted population, making this population particularly vulnerable (Racine & Bracken-Roche, 2019). Thus, ethical clinical trials for oDBS should include plans to minimize these risks while still maximizing the potential benefits at the subject and societal level. For example, if covert manipulation with external light sources is deemed too great a

risk, opsin expression levels can be titrated such that only sufficiently high-intensity light (i.e., that emitted by the implanted light source) is capable of manipulating neural activity.

7.3.3 Scientific Validity

In general, much more preclinical work must be performed in animal models before scientifically valid clinical trials can be performed. For example, despite a recent National Institutes of Health requirement to examine sex differences in preclinical studies (Clayton & Collins, 2014), to our knowledge there have been no studies on whether any oDBS-related variables (e.g., strength of opsin expression) depend on sex. One issue unique to oDBS, which may not be addressable in preclinical studies, is its long-term viability. oDBS requires that opsins remain stably expressed in the desired cell types, and that light be continually delivered to the brain with a constant (known) effect on neural activity. Typically, this approach would be expected to last for several years, similar to the time course of eDBS therapy. Little is known, however, about the stability of opsin expression over these timescales. The duration of the vast majority of studies in animal models is limited to months at most, and even at this timescale, age-related morphological changes in opsin-expressing neurons have been reported (Miyashita et al., 2013). While expression stability has begun to be examined in the retina (Ameline et al., 2017; Simunovic et al., 2019), to our knowledge, no studies have addressed this question in the brain structures required for oDBS (e.g., the STN). Beyond the stability of opsin expression alone, it is unknown whether there are long-term effects of chronically activating opsins, both on the health of the neurons themselves and on the circuits being manipulated, which may undergo activity-dependent plasticity (Zucker, 1999).

It is worth noting that in addition to the three ethical requirements discussed above (i.e., fair subject selection, favorable risk–benefit ratio, and scientific validity), Emanuel and colleagues' (2000) framework for ethical research includes four other requirements: social or scientific value (that the research improve health and well-being or knowledge), independent review (that the research be evaluated by individuals unaffiliated with the research), informed consent (that subjects are provided with information about the purpose of the research, the procedures, its perceived risks and benefits and alternatives, and that the subject understands this and makes a voluntary decision), and respect for enrolled subjects (including permitting withdrawal, protecting privacy,

maintaining welfare, keeping them apprised of changes in risk–benefit ratio, and informing them of research results). Although any research study using optogenetics should ensure that all seven ethical requirements are met, we do not discuss these four in depth because optogenetics research does not raise any unique challenges or questions in these domains.

However, it is perhaps worth making a few remarks about informed consent because one might wonder whether the conditions being treated in oDBS prevent patients from understanding the information sufficiently to give informed consent. As we indicated, the most likely first use (and trials) would be for oDBS for movement disorders such as PD (perhaps with patients with structural basal ganglia abnormalities that present problems for the targeting of specific brain regions required by eDBS). PD is known to produce minor cognitive impairment, such as difficulty in focusing and memory impairment. Informed consent processes should be developed that account for these sequelae, but there is no reason to think that patients will be unable to provide informed consent—and oDBS does not present unique issues here. Even if oDBS is used for psychiatric conditions such as depression or OCD, the normative stance is the same: while capacity for consent should be assessed, it should not be assumed that patients with these conditions are incapable of providing informed consent to participate in oDBS research, nor is it true that oDBS presents unique issues compared to other types of research with these populations. Empirical work can be helpful in understanding where potential gaps or weaknesses in understanding about oDBS research exist so that consent processes can be designed to address them (see below).

Some of the ethical concerns discussed above are limited not to clinical trials themselves but to the continued use of oDBS, should it ultimately succeed in clinical trials and receive regulatory approval. For example, the long-term effectiveness of oDBS must continue to be monitored after approval (i.e., in Phase IV trials). In addition, as noted above, the concern about covert manipulation would only grow with increased acceptance and adoption of optogenetics in clinical settings, and perhaps even in non-clinical settings in which manipulating brain activity is used for enhancement of normal function.

7.4 Empirical Data

Empirical data have the potential to inform some of the normative ethical questions discussed above (Sugarman & Sulmasy, 2010). In particular,

how do relevant stakeholders—patients, medical caregivers, and family members—perceive the potential risks and benefits of clinical optogenetics, particularly compared to the risks and benefits of eDBS? For example, eDBS requires an invasive permanent implant. oDBS would require a one-time invasive surgery (to inject the viral vector), but light could, in principle, then be delivered noninvasively. Is the invasiveness of eDBS and oDBS therefore perceived differently? Understanding these attitudes would help with the assessment of favorable risk–benefit ratio and design of informed consent processes in a way that includes the patients' and subjects' perspectives and not only the researchers' and ethicists' perspectives. While we may gain some insight into these questions by considering studies that have examined attitudes about eDBS and about gene therapy, to our knowledge, no empirical studies have focused on attitudes and understanding about clinical optogenetics. While it would be necessary for surveys and qualitative studies first to provide sufficient objective information about the "basics" of optogenetics to stakeholders before assessing their attitudes, concerns, and understanding (as is the case with any novel therapy), such studies could help to evaluate the ethics of clinical optogenetics.

7.5 Conclusions

Optogenetics offers the potential to manipulate neural circuit activity precisely, and there is increasing interest in harnessing this potential to treat a broad range of neurological and psychiatric disorders. Identifying and addressing the ethical issues associated with the first clinical trials and with the potential for widespread adoption of the technology, as we have attempted to do in this chapter, is a necessary step for realizing this potential.

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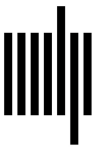

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