Behavioral optogenetics in nonhuman primates; a psychological perspective

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A B S T R A C T

Optogenetics has been a promising and developing technology in systems neuroscience throughout the past decade. It has been difficult though to reliably establish the potential behavioral effects of optogenetic perturbation of the neural activity in nonhuman primates. This poses a challenge on the future of optogenetics in humans as the concepts and technology need to be developed in nonhuman primates first. Here, I briefly summarize the viable approaches taken to improve nonhuman primate behavioral optogenetics, then focus on one approach: improvements in the measurement of behavior. I bring examples from visual behavior and show how the choice of method of measurement might conceal large behavioral effects. I will then discuss the "cortical perturbation detection" task in detail as an example of a sensitive task that can record the behavioral effects of optogenetic cortical stimulation with high fidelity. Finally, encouraged by the rich scientific landscape ahead of behavioral optogenetics, I invite technology developers to improve the chronically implantable devices designed for simultaneous neural recording and optogenetic intervention in nonhuman primates.

1. The behavioral compass

In systems neuroscience the loosely defined term "behavior" encompasses almost any "output" of the brain's function. Objectively, motor nerves carry this output by either moving muscles or secretion. As simple as it sounds though, interpretation of patterns of motor nerve activity is complicated, not possible without considering contingencies with the sensory state as well as the internal state of the brain. A simple muscle twitch in the diaphragm can signal the beginning of yet another repetitive breathing movement or can be part of a repertoire of motor nerve activity that tells the story of a half-forgotten dream.

The entire science of psychology has evolved to describe and interpret behavior, but systems neuroscience aims at understanding the internal brain mechanisms that transform brain states into behavioral outputs. This effort, if successful, will bridge the gap between behavioral phenomena and their underlying neural mechanisms, a bridge that can unify the sciences of psychology and neuroscience at least at the theoretical level. Moreover, the role of behavior in systems neuroscience is fundamental in that almost any neural phenomenon in any brain circuit is understood in the context of how it eventually affects the brain's output (Johnson, 2000). For instance, as far as the retina is from the motor end of the system, lateral inhibition in the retinal bipolar neurons is understood in the context of how it contributes to vision as a behavior. Arguably and almost by definition if a neural phenomenon does not eventually affect or modulate behavior in any way at any timescale, it is an epiphenomenon. In this sense, behavior serves as a compass that gives direction and context to the functional description of neural phenomenology.

In order to link internal brain activity to the output function, besides careful observation and measurement of the neural state, we need tools to specifically and reversibly perturb it. This is critical for claiming causal relationship between a neural phenomenon and a given behavior. Specifically, artificial perturbation of a neural sub-state is sometimes the only way to decorrelate it from the covarying neural events, making it the only way to infer causal relationship between the sub-state of interest and a given output (Jazayeri and Afraz, 2017; Barack et al., 2022). As much as they are needed, tools that perturb the neurons with the accuracy, specificity and scale demanded by the neuroscientists are not yet available. In practice, every perturbation tool in the arsenal of systems neuroscience comes with its own limitations. This was the context when the promise of optogenetics for improvement of neural perturbation entered systems neuroscience more than a decade ago (Fenno et al., 2011; Bernstein and Boyden. 2011). Optogenetics provides the possibility of activation or inactivation of neurons with fine temporal precision at multiple spatial scales. It also allows targeting of specific cell types in order to delineate their roles in the functional circuitry of the brain. These potentials of optogenetics are not yet fully realized but they have been constantly improving in the past decade or so. Since its dawn, optogenetics has grown to be a standard experimental tool in many areas of systems neuroscience (Yizhar et al., 2011; Diester et al., 2011; Deisseroth, 2012; Häusser, 2014; Boyden, 2015). It has also been adopted and developed for nonhuman primate research (Chernov et al., 2018; De

et al., 2020; Diester et al., 2011; Han et al., 2009; Han, 2012; Ruiz et al., 2013; Nassi et al., 2015; Klein et al., 2016; Galvan et al., 2016; Mac-Dougall et al., 2016; Galvan et al., 2017; Nurminen et al., 2018; Deng et al., 2018; Ju et al., 2018; El-Shamayleh and Horwitz, 2019; Khateeb et al., 2019; Fabbrini et al., 2019), which sits at the gateway of potential uses of optogenetics for medical purposes in humans. Nevertheless, adoption of optogenetics in nonhuman primate physiology has not been as smooth as expected (Gerits and Vanduffel, 2013; Inoue et al., 2021; Bliss-Moreau et al., 2022), cluttering the dream of using the advantages of optogenetics for helping humans. Specifically, scientific observation of the potential behavioral effects of optogenetic intervention in nonhuman primates has been challenging. There are a number of studies that have demonstrated various behavioral effects of optogenetic neural perturbation in nonhuman primates (Jazayeri et al., 2012; Gerits et al., 2012; Cavanaugh et al., 2012; Ohayon et al., 2013; May et al. (2014); Dai et al., 2014; Inoue et al., 2015; Afraz et al., 2015; Acker et al., 2016; Stauffer et al., 2016; El-Shamayleh et al., 2017; Fetsch et al., 2018; Andrei et al., 2019; Nandy et al., 2019; Ebina et al., 2019; Amita et al., 2020; Watanabe et al., 2020; Maeda et al., 2020; Rajalingham et al., 2021; Chen et al., 2022; Azadi et al., 2023a). These studies range from demonstrating the behavioral effects of neural perturbation in the primary visual cortex (Jazayeri et al., 2012) to the frontal eye fields on the motor end of the system, where the impact of optogenetic neural perturbation on saccade latencies (Gerits et al., 2012) and saccade generation (Inoue et al., 2015) is demonstrated. These studies are promising for the future of optogenetics but their number is far less than expected in more than ten years of research, the reported effect sizes are small in many cases (not in all cases though) and there probably exists a large number of unpublished null results (Gerits and Vanduffel, 2013; Tremblay et al., 2020; Bliss-Moreau et al., 2022). Small effect size cannot be used as an excuse to dismiss the value of potentially important effects that are small in nature. However, whenever a larger behavioral effect can be theoretically expected, it is desired, because large effects typically come with less statistical challenges and concerns regarding repeatability. As a result, the neuroscience community is still skeptical about the effectiveness of optogenetics in the study of complex behavior in large brains.

The shortcomings of optogenetics in nonhuman primate experiments have been justly attributed to two major technical issues: effectiveness of targeting/expression of optogenetic constructs and safe yet potent delivery of light to the targeted cells in a large brain. The former problem is partly inherent to nonhuman primate research because the number of experimental animals is typically far less compared to, for example, rodent studies, a factor that limits the throughput of experimental iterations needed for development of better gene delivery tools, opsins and promoters. There have been many impressive efforts on this front that are beyond this short review (e.g. Han, 2012; Lerchner et al., 2014; Yazdan-Shahmorad et al., 2018; Khateeb et al., 2019; Fredericks et al., 2020). There is also a noble attempt at making an open platform for data sharing between nonhuman primate labs across the globe in order to compensate for the lack of numbers in each individual research group. In fact, here I use the opportunity to encourage all experimentalists to share their data in this platform (Tremblay et al., 2020) as it immensely speeds up the search for better viral vectors and genetic constructs.

On the second front - effective and safe delivery of light into large primate brains - there have also been many exciting developments ranging from optical fiber based technologies (Pisanello et al., 2014; Sileo et al., 2015; Sparta et al., 2012; Tsakas et al., 2021), to direct optical targeting (Ruiz et al., 2013; Yazdan-Shahmorad et al., 2016; Shewcraft et al., 2019) and chronically implantable LED arrays (Kwon et al., 2015; Steude et al., 2016; Rajalingham et al., 2021). This challenge, covering large physical areas, is not limited to light delivery, as mentioned earlier, virus delivery is also subject to the same limitations. Neither the challenges imposed by large brains are specific to all nonhuman primates. The marmoset brain, for instance, is small enough and flat enough capable of adopting many promising techniques from the rodent research arsenal into nonhuman primate research (Ebina et al., 2019; MacDougall et al., 2016; Le Bras, 2020, Jendritza et al., 2023). Optogenetics in large brains is, above all, a human problem. Larger brains of species such as macaca mulatta, provide the testbed for the challenges in the delivery of light and virus at a wide range of spatial scales. The ability to perform optogenetics at multiple spatial scales, besides its technical value, opens the door to a deeper question about neural circuits. This question can perhaps be simplified this way: How can one generalize the neural/behavioral effects of perturbation of ~1 mm^3 of neural tissue in a ~1000 mm^3 brain (mouse) to a large ~100, 000 mm^3 brain (monkey) and to a gigantic ~1,300,000 mm^3 brain (human)? One could argue, a 1 mm^3 perturbation in the mouse brain should be scaled up 3 orders of magnitude (to an area size of a bean, and coincidentally, size of the entire mouse brain) in order to expect comparable behavioral results in the human brain. This argument is obviously naive, as the brain is far too complex to lend itself to such a linear correction only for volume. Nevertheless, the question of how the organization and specification of brain circuitry interacts with its mere size remains an open, theoretically important question. Recent efforts in technique development are promising, but there is a long way to go until we gain scalable optogenetic control over large areas.

Although both of these fronts justifiably demand further development, in this short write up, I aim at opening a third front in order to address the problem of behavioral optogenetics in nonhuman primates: improvements in the measurement of behavior. Behavior is measured using different paradigms and the choice of paradigm affects our expectations and interpretations of the results. I will bring examples from the study of visual behavior and argue that even with the current limitations of optogenetics in nonhuman primates it is possible to utilize psychophysical paradigms that provide rich and reliable measurement of behavior in nonhuman primates.

Before diving into a more in depth analysis of methods for measuring behavior, I would like to note that some features that are perceived as weakness of optogenetics might in fact turn into points of strength if reliable measurement of behavior is established. Limited by expression rate and other factors, optogenetic perturbation of neurons is not typically as potent as electrical stimulation or some chemical interventions. For instance in our 2015 study, optogenetic silencing omitted ~33% of the spikes that would have been driven without illumination, gently modifying the stimulus driven neural response (Afraz et al., 2015) but muscimol, the comparable chemical silencing tool, practically takes out 100% of the stimulus driven spikes, as well as the background activity in the injection zone (Arikan et al., 2002). This lack of efficacy is not a necessary feature of all optogenetic set ups, but is not necessarily a bad feature either because unlike strong perturbations, it does not push the neural state too far from its natural manifold (Jazayeri and Afraz, 2017). Another apparent weakness of optogenetics is the limited penetration of light into the neural tissue. For instance, the power of a ~10 mW beam of green (~530 nm) light, scatters down to ~1 mW after traveling ~1 mm in the neural tissue (Afraz et al., 2015). This limits the number of neurons that can be perturbed at high densities using a single light source. Luckily, the brain tissue is more transparent to longer wavelengths, for instance, red (~650 nm) light penetrates the tissue ~5 times more than the blue (~440 nm) light (Lehtinen et al., 2022). This problem is thus being addressed by the development of red-shifted opsins that harness the deeper penetration of larger wavelengths of light into the neural tissue (Zhang et al., 2008; Bansal et al., 2022) as well as building platforms for scalable light delivery onto the cortex (Kwon et al., 2015; Yazdan-Shahmorad et al., 2016; Rajalingham et al., 2021). Nevertheless, one could argue that smaller spatial spread means better spatial resolution, and that if more sensitive measurements of behavior manage to capture the behavioral consequences of neural perturbation at a smaller scale it would be easier to eventually theorize the results at the single neuron scale.

2. The projective field

Let's start this section with a personal story. During the year 2013 and most of 2014, at every work day, I carefully lowered an optical fiber into the inferior temporal (IT) cortex of macaque monkeys in order to measure the effect of optogenetic silencing of face-selective neurons on visual perception. There was no way to measure the perceptual effects of cortical stimulation directly and as a whole, so I aimed at measuring what the most viable hypothesis suggested; IT face-selective cells are probably involved in face recognition behavior, thus their inactivation must take a toll from a face discrimination task. The face sex discrimination task was chosen as the representative of face discrimination behavior because of its evolutionary importance and its generalizability to every face. Soon, we learned that reversible silencing (using ArchT) of face-selective neurons takes a statistically significant yet very small toll of ~2% from the behavioral face discrimination performance (Afraz et al., 2015). This established partial causality, but this small effect size did not provide the desired dynamic range for deeper experimental investigation of the behavioral effect. It also left me with an existential question: Is the perceptual effect of neural perturbation in ~1 mm^3 of cortical tissue this small? Or is there a large perceptual effect that I can't capture with my measurement tool? Perhaps my measurement has gotten too far from what I intended to measure, with too many assumptions on the way, missing the main perceptual effects of the cortical intervention. This question can be boiled down to a practical one: Does the monkey clearly perceive the effect of optogenetic neural perturbation, but manages to ignore it and perform mostly unaffected on the discrimination task? Or alternatively, the monkey barely even notices the cortical perturbation impulse, as much as is reflected by the ~2% behavioral effect. In other words, does the observed 2% effect represent a small byproduct of an otherwise large but unmeasured perceptual effect or is it fairly representative of the amount of total perceptual change induced by brain perturbation. If the former statement is true, it means that my experimental design has missed a potentially large reportable perceptual effect that is not specific to my task of interest, in exchange with a small effect specific to my task. That's fine, but what was the "potentially large" missed effect?

With this story in mind, let's now generalize the case. Nonhuman primates do not talk, so we typically read their behavioral output as binary responses expressed via hand or eye movements in the context of a pre-trained task. This substantially limits our ability to interrogate perception because we need to force all of our questions into one or a few dimensions which the monkey has learned to report. In order to systematically dissect the issue, let's borrow and expand upon a concept defined by Lehky and Sejnowski in the 80s (Lehky and Sejnowski, 1988); the projective field. In a neural hierarchy, for every neuron there exists a receptive field, defined by the input that the neuron receives from its upstream connections. For every neuron, there also exists a projective field that describes how the neuron projects to the downstream units. Given that we have defined behavior as "any" output of the brain here, it is possible to extend the projective field of neurons into behavioral domains. So let's define the behavioral projective field of a neuron as the set of all possible behavioral measurements that are affected by alteration of that neuron's activity. Fig. 1 summarizes this notion. Neural perturbation induces a behavioral effect, represented by the "projective field" vector in Fig. 1 b. This effect has shadow projections on various psychophysical measures, in fact it is by definition constructed of them. In this formulation, the effect sizes observed in a brain perturbation experiment highly depend on the alignment of the psychophysical axis of measurement with the projective field vector. Translating my 2014
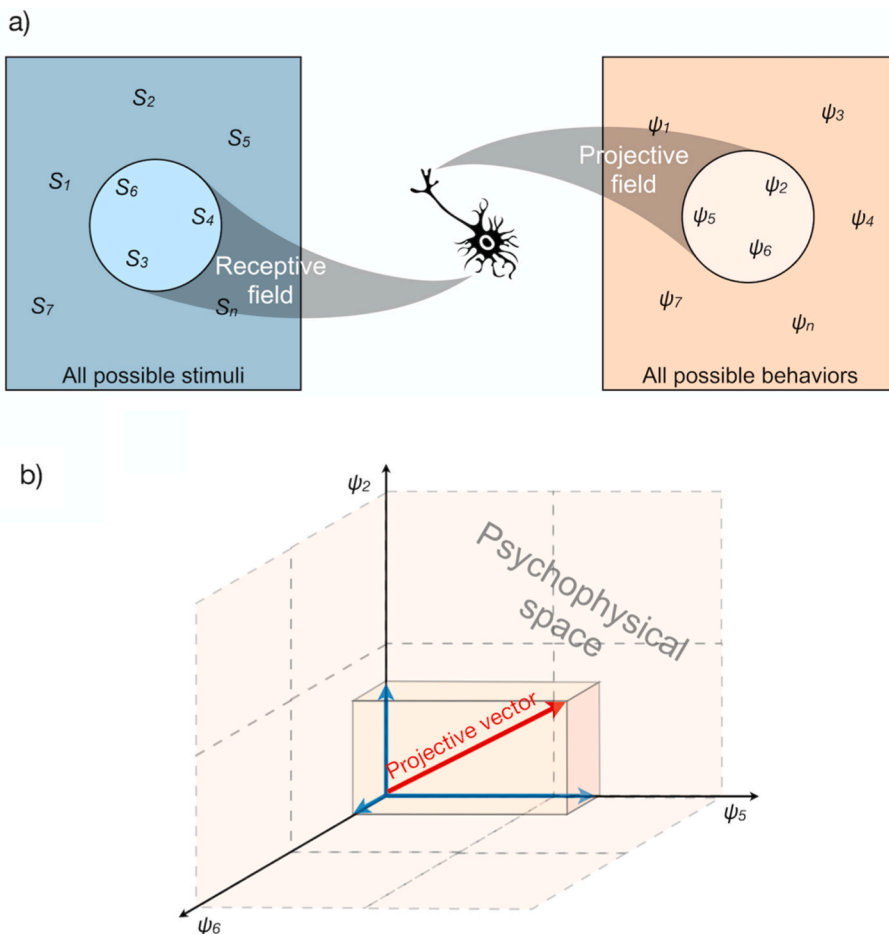
Fig. 1. Projective field. a) The activity of a neuron anywhere in the sensory cortex can be perturbed by a subset of external stimuli. Parts of the sensory space that influence the responses of the neuron are defined here as the "receptive field". Note that the sensory space includes non-spatial aspect of the stimulus as well. Similarly, perturbation of the activity of a neuron can induce various behavioral changes. The subset of all psychophysically measurable behaviors that are altered following perturbation of a neuron is referred to as the "projective field" here. b) All tasks are not equally affected by perturbation of a given neuron. The behavioral alteration vector casts shadow projections of various sizes on different measurement axes. Conversely, the projective vector can be constructed, with behavioral measurement on multiple axes.

question into this language, I wanted to know if the projective field of the targeted face-selective cells was aligned with my face sex gender discrimination measurement axis, thus the observed 2% effect represented the true size of the projective field vector. Or, if there exists a large projective field vector with a small (~2%) shadow on the face sex discrimination axis. This question is quite important when interpreting the effect sizes obtained from a behavioral optogenetics experiment. The absence of a satisfying answer for this question, reflects on a practical bias among us neuroscientists: we are relatively open-minded when studying the receptive fields, in that we test the responses of neurons against numerous stimulus dimensions, but projective fields are typically measured in non-explorative ways on impoverished sets of behavioral measures. These behavioral measurements are typically designed to support or reject a hypothesis, informed by the response properties of the cell, such as in Afraz et al., 2015 and 2015, and not to explore the projective field in an independent manner. As a result, we do not ask the brain what it does, we only ask if it does what we have hypothesized. This methodological bias doesn't necessarily come from lack of interest, it partly reflects the heavy cost and logistic limitations of training nonhuman primates on behavioral tasks. Now, is there a way to go around this problem and create rich high-dimensional measurements of the behavioral in order to better estimate the behavioral projective fields of neurons or neural assemblies?

The most direct answer to this demand is increasing the task dimensionality by increasing the number of behavioral choices (Majaj et al., 2015) or the number of tasks, for example by training the monkeys on reporting a perceptual choice as well as their confidence about it (Kiani and Shadlen, 2009). This helps with anchoring the behavior with more parameters thus better estimating the projective field. Nevertheless, training nonhuman primates on multiple tasks is time consuming and might not be possible for more than a handful of tasks.

Besides training the animals on tasks that require explicit or categorical reports, another fascinating possibility is to utilize the natural dimensionality of some analogue outputs of the brain in order to measure the behavior implicitly without introducing training biases. It has been shown that the positioning of the hand and fingers before making perceptual decisions can encode the final perceptual decision (Song and Nakayama, 2008; Vaziri-Pashkam et al., 2017). Patterns of eye movements are high dimensional and full of information with regard to the perceptual state (Land, 2006; Yu et al., 2012), this information can be possibly harvested in the context of behavioral experiments without any training cost. Machine learning has made it possible to analyze the complex body movements of animals in order to decode various chemical states of the brain (Wiltschko et al., 2020), this can be added to the tools in our observatory of behavior. These implicit readings of behavior clearly demonstrate how wide and inclusive the concept of "behavior" is. Projective field, by its definition, inherits this lack of specificity. In that sense, if stimulation of a neuron leads to a wide range of measurable behavioral effects ranging from perceptual effects to variations in pupil size and positioning of the body, we have to include all of these phenomena in our projective field vector. This is useful because it reminds us that a neuron may contribute to the neural function at multiple domains and scales. However, to make the concept practical, we can operationally define projective fields within specific behavioral domains. Following, I will use the concept, in the domain of visual perception/behavior.

Is there a way to estimate the size of the projective field vector directly? In depth review of the existing literature on behavioral optogenetics in nonhuman primates reveal a few experiments resulting in quite large effect sizes; experiments in which the animals are incentivized to detect and report existence of brain perturbation directly. For instance, using similar behavioral paradigm as in a previous electrical stimulation study (Murphey and Maunsell, 2007), May et al., 2014, trained macaque monkeys to detect and report optogenetic stimulation in the somatosensory cortex; an experiment that revealed very large (near ceiling) effect sizes. This clearly shows that the perceptual event induced by optogenetic stimulation of the cortex is quite sizable and easy to detect by the animal. Consistently, Jazayeri et al., induced eye movements by optogenetic stimulation of the primary visual cortex (Jazayeri et al., 2012). This is probably because the saccades are initiated following easy detection of the phosphenes induced by the cortical perturbation, although the possibility of reflexive eye movements cannot be ruled out. Recently, we have also tested to see if macaque monkeys can detect even weak optogenetic impulses delivered to their IT cortex when incentivized (Azadi et al., 2023). We observe massive behavioral effects as the monkeys can easily detect and report optogenetic stimulation at illumination levels comparable to the 2015 study (Afraz et al., 2015). Specifically, the animals reached above 90% performance (>40% increase from the chance baseline) in the detection task, while optogenetic perturbation led to only ~2% performance change in the 2015 study. This clearly answers my existential question: even small optogenetic perturbations lead to sizable behavioral effects because they can be easily detected and reported by the animals. But now, if there are large perceptual effects induced by optogenetic perturbation of the cortical activity, what are they? How can we describe and constrain them? Is it possible that the brain is rewired to detect the optogenetic perturbation without invoking a visual percept? Cortical Perturbation Detection (CPD) task has proven very sensitive in detecting behavioral effects, but it is not specific and does not describe the stimulation-induced-event. Is there a way to bring specificity to this task? In the section that follows, I will briefly report and review a few examples of our attempts at describing the perceptual projective fields of neurons using a simple CPD task in IT cortex (see Fig. 2).

3. A photography project

In order to bring specificity to the CPD task we combined it with machine learning aiming at taking "pictures" of the visual hallucinatory event induced by optogenetic stimulation of IT cortex. Pictures are highly specific and bias free, is it possible to capture the perceptual alteration induced by the brain stimulation in the form of a picture? Following is a compressed report of the steps we took to achieve this. The related paper is currently under review for publication, but the details of the experiments described here can be found in the BioRxiv version of the paper (Shahbazi et al., 2022). We first trained macaque monkeys to detect and report an optical impulse, 200ms in duration, delivered to their central IT cortex via an implanted array of LEDs (Rajalingham et al., 2021; Azadi et al., 2023b). Prior to array implantation, we injected the cortical area under the array with AAV5 carrying C1V1, an excitatory construct (Fredericks et al., 2020). The animals were trained to hold fixation on an image for ~1 s (slightly different in different experiments), midway through the image presentation the optogenetic stimulation impulse was delivered to the cortex in half of the trials, randomly chosen. The same set of images appeared equally in both stimulation and nonstimulation conditions, carrying no information regarding the stimulation condition. Following image presentation, the animals made saccades to one of the two consequently presented targets in order to report whether or not a trial contained cortical stimulation. They were rewarded only for making the correct choice. The animals learned this task easily and quickly to the point that we had to drive the LEDs at 1–4% of their maximum power, at levels lower than used in Afraz et al. (2015) (~10 mW optical output power), in order to bring the monkey down from ceiling performance. Did they actually "see" something during the stimulation trials or their brains rewired the target area directly to behavior to bypass perception?

We noticed that the behavioral performance of the animals for detecting cortical illumination highly varied depending on the image they were viewing at the time of stimulation. Viewing some images (systematically and repeatedly) helped the animal in noticing the cortical stimulation and some did the opposite (Azadi et al., 2023a). This suggests that the optogenetic impulse induces a visual perceptual effect as it interacts with the visual stimulus. This finding is consistent with
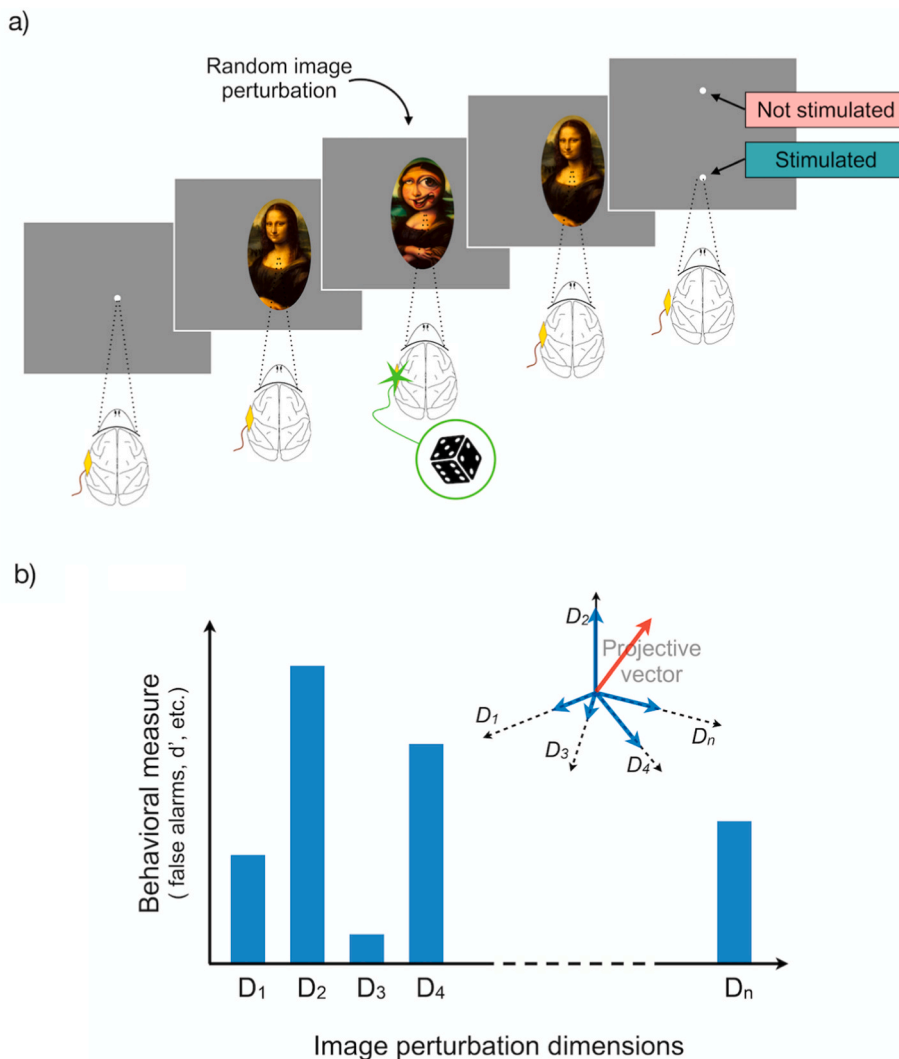
Fig. 2. The Cortical Perturbation Detection (CPD) task. **a)** The animal fixates on the screen, then an image is shown. A locus in the inferior temporal cortex is optogenetically stimulated randomly in half of the trials. The animal is rewarded for detection of this cortical stimulation impulse by making a saccade to one of the two consequently presented targets. We noticed that the performance of the animals in CPD highly depends on the properties of the image on the screen. This is because the animal detects a "visual perceptual event" to perform the task. This mental perceptual events interacts with the image and can be captured and described by perturbing the image on various visual dimensions. Using machine learning it is possible to find the one visual perturbation that maximizes the behavioral false alarm rate. We call such an image "perceptogram" (see text) as looking at it makes the animal think its brain is stimulated in the absence of stimulation. **b)** While the CPD task is very sensitive, it lacks specificity. Nevertheless, given the wide dynamic range provided by the large CPD effect sizes, also because of dependence of the task on the viewed images, it is possible to gain the lacking specificity by varying the visual stimulus across multiple image dimensions. This allows profiling of the projective vector over many possible tasks and dimensions of interest. A "perceptogram" is an example of projective field profiling in the image domain, but the basic logic holds for other domains, modalities and cortical regions.

two recent studies, revealing that optogenetic activation of neurons in the monkey primary visual cortex systematically interacts with behavioral detection of visual stimuli (Andrei et al., 2019; Chen et al., 2022), with the difference that here, the animal is tasked to detect cortical stimulation, also that we stimulated a high level visual area. We next raised a phenomenological question: why does detection of the stimulation-induced-event interact with passive viewing of visual stimuli? Is the stimulation induced event is an isolated additive perceptual element that interacts with the screen images only because of spatial overlap (e.g. a star being superimposed on other images, being more or less visible in different backgrounds), or if it is structurally incorporated in the perception of the screen image (e.g. a distorted version of the image being viewed). The "addition" hypothesis predicts that removing the screen image or decreasing its visibility (by removing contrast and opacity) would improve the behavioral performance in detecting the cortical event by decreasing the background visual clutter. The alternative hypothesis predicts that the animals actually depend on seeing the screen images in order to better detect the perceptual distortions. To our surprise, data strongly rejected the former hypothesis, the clearer the screen is, the harder it is for the monkeys to detect cortical stimulation, with the lowest performance recorded for when the animals fixate on a blank screen (Azadi et al., 2023a). In a separate experiment, reported in this issue of *Current Opinion in Neurobiology*, we noticed that the same is true for the size of the viewed objects as well; the smaller is the object on the screen, the harder it is for the monkey to notice cortical

stimulation (Lafer-Sousa et al., 2022). These findings clearly reveal the visual nature of the perceptual events induced by stimulation of IT cortex independent of their additive or distortive properties. Specifically, if the stimulation induced event was not visual (inducing an auditory or tactile sensation for instance) we did not expect its detectability to interact with the shape of the visually presented stimulus and to systematically depend on its visibility and size.

So far, we knew that optogenetic perturbation of neural activity at similar spatio-temporal scales that has led to very small behavioral effects in some other preparations, can lead to very robust behavioral effects if the monkey is directly asked to detect it. This finding is consistent with earlier results in the somatosensory cortex (May et al., 2014). Moreover, it shows that the effect detected by the monkeys is visual in nature. In sum, we learned that the neural sub-populations of the scale ~ 1 mm^3 in IT cortex have projective fields in the visual perceptual domain. The projective vectors of the stimulated IT sub-populations are large in the perceptual space because the monkeys find them very easy to detect and report. But we do not yet have a rich qualitative understanding of these visual events. Remains the burning question; what is it that the monkey sees?

The shortcoming of the CPD task is that it exchanges specificity with sensitivity, while it is most sensitive in detecting a behavioral effect, it is indifferent with respect to the quality of the perceptual events induced by cortical stimulation. We figured that it is possible now, to exchange specificity with time, and gain it back at the cost of collecting a large

number of low-specificity CPD trials. In a process named "perceptography" we attempted at high-dimensional pictorial reconstruction of the visual perceptual hallucinations induced by optogenetic stimulation. The CPD task remained the same from the perspective of the animals, but this time, we actually perturbed the images on the screen and utilized a machine learning pipeline in order to induce behavioral false alarms by altering the images at the time of brain stimulation. Images of objects were altered using a generative adversarial neural network and a learning system used the animals naturally occurring false alarms in order to find and augment image features that increase the probability of false alarms. After a learning process that took about ~40K behavioral trials for each cortical position and each base image, specific images were evolved looking at which made the monkeys think they were stimulated in 60–100% of the trials where no cortical stimulation was applied. We named these images "perceptograms" as they are graphical yet fully parameterized psychophysical equivalents of the perceptual state of being stimulated for the monkeys (Shahbazi et al., 2022). Perceptography, for the first time provides us with pictures directly associated (as judged by the monkey) with the perceptual events induced by cortical stimulation in a high level visual area. Perceptograms capture and reveal the visual quality of the events induced by optogenetic stimulation and open the door to linking the pictorially described response properties of neurons to pictorial descriptions of their projective field.

A notable side analysis that comes from CPD experiments, is about how the neural tissue interacts with optogenetic stimulation in the long term. A fully flexible and plastic neural network, optimizing for performance, is expected to only read out the stimulated cells for performing the CPD task, isolating them from the visual input. This is because only the stimulated neurons carry information for performing the CPD task and the natural neural activity adds only noise. Thus, an optimized read out mechanism should ignore the synaptic input from the rest of IT and vary only by the variance of the targeted cells. Under such a condition, we don't expect to learn much about the natural function of the visual system in the context of a CPD task. However, the results suggest this is not the case. Repeated optogenetic stimulation in IT cortex continued to interact with the visual stimulation in a similar manner over the course of many months; the detection profile of each area remained unchanged (Azadi et al., 2023a) and the perceptograms obtained from a single channel remained distorted and highly similar (Shahbazi et al., 2022). This shows the neural system has not isolated the stimulated neurons from the rest of the visual processing machinery, otherwise we expected a flat detection profile and no distortion of the base image in the perceptograms. All together, these lines of evidence suggest that the neurons that are optogenetically targeted remain a functional part of the visual processing circuitry at least over the course of many months. This is understandable because the neurons are being targeted only during the experiment sessions but for most of their functional life, they are contributing to the animals' natural vision.

The results reviewed here are specific to IT cortex but the basic logic and methodologies directly apply to any other low-level or high-level sensory processing brain area. Using the CPD task in the motor processing areas makes a curious thought because the sensory logic won't directly apply. I speculate that CPD in the motor context might reveal interesting phenomena and mechanisms related to volition. Weak electrical stimulation of the inferior parietal cortex in humans induces a strong desire to move a certain body part (depending on the exact cortical position) and strong stimulation in the same area makes the participants think they have already executed the movement in the absence of any physical movement. In contrast, stimulation of the premotor cortex induced a physical movement, but the participants were not aware of the movement (Desmurget et al., 2009). CPD might provide the opportunity for studying the phenomenology of such effects in nonhuman primates. Overall, this line of research is at its beginning and raises more questions than answers, but I reviewed it here as an example of how combining a CPD task with other parametric variations can uncover large behavioral effects of optogenetic cortical perturbation and richly describe them.

4. There will be light

Optogenetics has progressed on many fronts in recent years thanks to the efforts of the global scientific community that are impossible to summarize in this humble note. We now have better expression of better genetic constructs, more practical and more accurate methods of light delivery and a deeper understanding of the physiology underlying optogenetic intervention in the neural circuits (Galvan et al., 2017; Sanzeni et al., 2022). There have been multiple cases of success in behavioral optogenetics and given the novel tools, such as machine learning, the psychophysical landscape of behavioral optogenetics in nonhuman primates looks tantalizing. However, the available technology for optogenetics experiments is still far behind the scientific demand. For example, while there are many interesting experimental devices around (Tamura et al., 2012; Ruiz et al., 2013; Ozden et al., 2013; Ledochowitsch et al., 2015; Park et al., 2015; Yazdan-Shahmorad et al., 2016; Welkenhuysen et al., 2016; Komatsu et al., 2017; Rajalingham et al., 2021; Wang et al., 2021; Zhou et al., 2022), currently, there is no off-the-shelf, chronically implantable platform that combines scalable patterns of illumination with simultaneous recording of the neural state (array single units, field potentials, etc.) packed in a device appropriate for the complicated anatomy of the large primate brain. The first demand of such a device is the ability to produce 2D surface patterns or ideally, 3D volumetric patterns of light in the neural tissue. Two dimensional patterns are easy to create using surface illumination (Ruiz et al., 2013; Park et al., 2015; Yazdan-Shahmorad et al., 2016; Shewcraft et al., 2019; Rajalingham et al., 2021). Three dimensional patterns are harder to induce as they require either multiphoton microscopy (Oron et al., 2012; Chen et al., 2018; Adesnik and Abdeladim, 2021) or physical penetration of tissue with an optical probe. There are currently many approaches using penetrating optical fibers or other probes (Diester et al., 2011; Kondabolu et al., 2015; Zhao, 2017; Shin et al., 2019; and else) to deliver light deep in the tissue. These approaches can be scaled up in order to support 3D patterning of light, although one inherent problem of penetrating approaches is tissue damage that might scale up to inappropriate levels if multiple parallel penetrations are attempted. The issue of tissue damage might be avoidable by using fine implantable mesh structures interwoven in the neural tissue (Zhao et al., 2023) or fine flexible silk optical fibers (Zhou et al., 2022). Either way, the ability to induce spatiotemporal patterns of neural perturbation opens the door to the study of how artificial stimulation interacts with the intrinsic patterns of neural activity (spatial and temporal), which in turn might allow a cultural change in how we use artificial stimulation for interacting with the brain. The potential interaction of stimulation with the internal neural state, demands the second requirement of the imaginary device exemplified here; neural recordings. Accurate measurement of the neural state in behavioral optogenetics experiments provide three critical lines of evidence: 1. Determining the intact (correlational) physiological properties of the target neurons in the absence of any optogenetic perturbation. This is a fundamental piece of the puzzle, if bridging a causal link between the neural state and the behavioral state is intended, one shall measure both at once. 2. Studying the neural impact of optogenetic intervention. Stimulation of the same volume of tissue with the same photometric energy may lead to different neural effects depending on the neural state at the time of stimulation and its dynamic interaction with the stimulation impulse (Mateo et al., 2011; Sanzeni et al., 2020; Bradley et al., 2022). Thus, monitoring the neural activity during stimulation can inform our interpretation of potentially variable behavioral effects across trials or conditions. 3. Guiding the experiments that require closed-loop interaction with the neural system. In such experimental designs, the amount and/or pattern of the neural perturbation is directly informed by the neural state, thus depends on its accurate measurement (Grosenick et al., 2015; Srinivasan

et al., 2018; Fernandez-Ruiz et al., 2022).

In the age of compact optical electronics, this under development of technology for optogenetics is not fundamental. The density of electronics compressed into the cellphone in my pocket, is much higher than what would make a dream tool for the neuroscientist, at this stage of science. Nevertheless, the combination of lack of funding, hope and interest among technology developers have held them back. Here, I invite the developers to spend more effort on making and improvement of the existing medical grade implantable devices, capable of producing different types of illumination (surface, deep layers, different wavelengths) at different scales (such as in arrays) with the ability for simultaneous neural recording and adaptability for the shape of a complex large brian. Such devices not only allow significant expansion of our basic understanding of the brain function, but also pave the road for functioning prosthetics for human brains.

One last note before closure! Above, I have put low-dimensional theory-driven methods of behavioral measurement in contrast with high-dimensional explorative methods with the claim that the latter is more sensitive than the former in detecting behavioral effects of optogenetics. This doesn't discredit the theory-driven experiments though. Theory-driven experiments test hypotheses, in that sense, even their small effects are quite informative as they test explicit theories. In contrast, exploratory experiments are less specific thus less strict in rejecting theories, but they are extremely useful to chart unknown territories and help us come up with the right theories to test. Encouragement of one approach is not discouragement of the other, because both approaches are needed in order to converge on the answer in an iterative, interactive and exciting process.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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