Opinion

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Optical and chemical discoveries recognized for impact on biology and psychiatry

Karl Deisseroth[1,2,3]

Karl Deisseroth was awarded the 2017 quadrennial 4 million euro Else Kröner Fresenius Prize today for the "discoveries of optogenetics and of hydrogel-tissue chemistry, and for developing circuit-level insight into depression". In this opinion, he was invited to discuss the impact of optogenetics and hydrogel-tissue chemistry [1–10] on understanding the structure and function of the brain in health and disease.

See also: **E Schnapp & H Breithaupt** (May 2016)

How do diseases of the brain, such as major depression or schizophrenia, change an individual's ability to manifest subjective mental states? These diseases not only create dysregulated negative or aversive states, but the very same experiences that once brought joy, reward, and motivation, fail to do so, giving rise to the common and crippling symptom of anhedonia. More broadly, we could ask the following question: How does the brain interpret specific experiences under different circumstances—for distinct individuals, or during distinct adaptive behavioral states? These are fascinating and difficult questions, long at the core of our shared human experience, that are now accessible to modern psychiatry and neuroscience—raising hope for alleviating human suffering and for understanding brain function.

The development of optogenetics (controlling specific neural circuit elements during behavior using microbial opsin genes, fiberoptics, and generalizable cell targeting tools), from 2004 to 2009, ultimately enabled considerable progress in answering these questions [1–3]. By way of example, a 2012 paper identified specific cellular connections—spanning the entire adult mammalian brain from medial prefrontal cortex to the lateral habenula, or to the dorsal raphe nucleus—that are causally involved in precise bidirectional tuning of motivational behavior in response to depression-related challenges [4]. And in a more recent paper, we described specific circuit-dynamical underpinnings of anhedonia itself [5].

When we set up an experiment to elicit recruitment of midbrain dopamine neurons in the freely moving rat in operant fashion by the rat pressing a lever, we observed that some animals pressed the lever much more than others, up to hundreds of times per day. It revealed not only that the dopamine neuron recruitment was a source of primary reward and motivation, but also that this behavior quantitatively varied between individuals [5]. In accounting for this variability, we found that the extent of activation of a distant subcortical structure, the ventral striatum, by midbrain dopamine neurons contributed to the observed behavioral differences [5].

This brainwide activity relationship was interesting in itself, but we soon observed something even more interesting. When we optogenetically elevated activity in the medial prefrontal cortex of these rats (based on the observation that human patients suffering from depression often show elevated activity in homologous prefrontal regions (reviewed in ref. [6]), we observed anhedonic behavior. Even more strikingly, this intervention accessed the same long-range multi-region dynamical pattern that had been found to contribute to naturally occurring individual variability earlier, in diminishing the ability of elicited midbrain dopamine neuron activity to recruit ventral striatum [5].

This observation—that naturalistic and brainwide behaviorally relevant activity patterns can be causally elicited by optogenetic intervention—raises intriguing possibilities for the field. Relevant to this opportunity, we have developed new methodologies for precise observation and control of brainwide activity states, for example using the brain-spanning and multi-site approach of frame-projected independent-fiber photometry to match or modify the native timing and amplitude of local or global activity patterns across acute or chronic timescales during free mammalian behavior [7]. These advances allow exploration of a virtually limitless range of ideas and hypotheses regarding the causal and global circuit dynamics of adaptive and maladaptive behaviors, including states related to depression, anxiety, and altered social behavior.

Interdisciplinary collaboration has been the hallmark of these efforts, characterized by joint efforts among physicians, biologists, physicists, materials scientists, biochemists, chemists, and chemical engineers. On the smallest of spatial scales in biology, chemical and biophysical analysis of the microbial opsins themselves at the atomic level has been a priority in my laboratory for more than a decade, driven by curiosity about these remarkable molecules, as well as by the opportunity to create new functionality for neuroscience via molecular analysis and design [1].

Our work in chemistry and biochemistry also led to the second discovery recognized by the 2017 Prize, described as hydrogel-tissue chemistry (HTC) [8–10]. The talented

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scientists in my laboratory were able to overcome a key limitation for the structural analysis of biological tissues: generally stated, the linking of deep content to deep context. From 2009 to 2016, they developed a new approach by which an intact metazoan animal tissue (reconsidered as its positionally defined constituent biomolecules) effectively becomes a reactant or "meta-reactant" in a chemical process. Various polymers and gels have long been used to physically support biological tissues for sectioning and histology, and hydrogels had long been explored as a substrate onto which cells could be seeded or printed to create tissues or organs. In contrast, with HTC the hydrogel is built from within each cell of a tissue simultaneously: specific tissue components are anchored (via molecular linkers) to gel monomers, and then, crosslinkers are triggered to cause polymerization and gelation. Subsequent selective removal of unlinked tissue elements from the tractable new composite hydrogel-tissue material is then possible [8,9], allowing high-resolution optical access and permeability for macromolecular probes. Since 2013, many forms of the original HTC concept have been described [9,10], spurring considerable innovation and many intriguing experimental insights into biology.

For example, this approach has been used to obtain brainwide cellular-resolution activity-trace information after defined behavioral experiences in freely moving mice. One form of HTC, called CLARITY [9], was used to transform the intact brains of large cohorts of mice that had experienced positive (appetitive) or negative (aversive) experience or neither. This was combined with a novel method called CAPTURE [10] to label and quantify the brainwide projections from the medial prefrontal cortex that were strongly activated during these experiences [9,10]. These experiments revealed that the projection from the medial prefrontal cortex to the lateral habenula—similar to the projection that we had identified earlier as favoring passive-coping or depressive-like responses [4]—was recruited more robustly by negative experience [10]. In contrast, the projection from the medial prefrontal cortex to the ventral striatum/nucleus accumbens was more strongly recruited by positive experience, which suggests a possible mechanism by which the prefrontal cortex could exert influence in the ventral striatum and reward-related responses in anhedonia [5]. In addition to this brainwide anatomical perspective, the HTC approach [8] also enabled molecular interrogation of recruited prefrontal cells; selective expression of the NPAS4 transcription factor [10], which is involved in regulating adaptive responses to experience, was revealed in positive-experience prefrontal cells.

Looking to the future, registering all of these datastreams together in single subjects (local and global wiring, molecular cell typology, and natural causally important changes in neural activity during behaviors of interest) will continue to deepen our understanding of adaptive inner states and behavioral state transitions that are central to the expression of psychiatric disease symptoms and, more broadly, the experience of life.

It is worth noting, in closing, a topic of timeliness: the importance of public support for basic research, which has considerable relevance to our discoveries recognized by the 2017 Else Kröner Fresenius Prize. The tentative first steps that eventually led to optogenetics [2] and HTC [8] were neither part of disease-related research, nor even constrained in terms of specific applications to basic science. Exploratory early-stage research is a vulnerable target for budget cuts: an easy target and easy to dismiss. We and many others have discussed how to balance funding of early versus late-stage research (e.g., http://www.pnas.org/content/112/47/E6413.full), and we have repeatedly suggested that scientists must communicate to the broader public that any specific goal of a research portfolio—be it disease treatment or national interest—is best served with a major basic research component where direct links between research and goal are not known, or even knowable [3]. As a society, we must also work harder to prevent discouraging or dismissing scientists at the early stages of their careers with the wrong signals or inconstant support. Just as with early-stage research, junior scientists are full of promise, unconstrained and vulnerable. The fullest reckoning of our community's success can be measured in theirs.

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