

circuit elements with light. Although optogenetics is still in its infancy, its use has already revealed important and novel information on neural function that was inaccessible with traditional techniques.

For optical excitation of neural tissue, the algae protein, Channelrhodopsin-2 (ChR2), can be introduced into neurons by various genetic techniques, such as viral transfection (Boyden *et al*, 2005). Targeting neuronal subtypes has been achieved by expressing ChR2 under the control of cell-specific promoters (Adamantidis *et al*, 2007) or by using cell-specific recombination to drive expression in neuronal subpopulations expressing CRE recombinase (Atasoy *et al*, 2008; Tsai *et al*, 2009). Illuminating ChR2 with blue light (~480 nm) results in the absorption of a photon by the ChR2 cofactor, all-*trans*-retinal. This leads to a conformational change in the ChR2 complex allowing it to pass monovalent and divalent cations, resulting in the depolarization of neurons at resting membrane potentials. Activation of ChR2 can be used *in vitro* to excite cell bodies to induce firing of neurons at relatively high frequencies (Figure 1a; Boyden *et al*, 2005; Tsai *et al*, 2009). Alternatively, direct activation of axons and synaptic terminals expressing ChR2 can be used to probe afferent-specific synaptic transmission and strength (Figure 1b; Petreanu *et al*, 2007; Atasoy *et al*, 2008). *In vivo*, light can be introduced into specific brain regions expressing ChR2 via a fiber optic cable coupled to a guide cannula to directly excite specific neurons with high temporal resolution during behavior (Figure 1a; Adamantidis *et al*, 2007; Tsai *et al*, 2009). For the first time, this allows for activation of genetically defined neuronal subpopulations on a physiologically relevant timescale without directly altering the activity of neighboring cells.

Transient inhibition of circuit components could potentially be even more valuable for assaying the neural basis of behavior. By introducing the bacteria-derived light-sensitive chlor-

ide pump Halorhodopsin (NpHR) into select neurons, optical inhibition of neural activity is now possible on a millisecond timescale (Zhang *et al*, 2007). NpHR, which is maximally activated by yellow light (~590 nm), yields an inward chloride conductance capable of hyperpolarizing neurons and inhibiting firing. NpHR can potentially be used in combination with ChR2 to selectively inhibit or excite subpopulations of neurons with different wavelengths of light during behavioral tasks. Taken together, these emerging tools may help reshape systems neuroscience and greatly aid our understanding of the neural circuitry underlying addiction and psychiatric disease.

Garret D Stuber¹

¹The Ernest Gallo Clinic and Research Center, The University of California, San Francisco, CA, USA
E-mail: gstuber@gallo.ucsf.edu

DISCLOSURE

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Neurocartography

Although it has been appreciated since the work of Cajal that the brain is comprised of neurons connected toge-

ther in elaborate circuits, there has been only scant progress in mapping these circuits in detail. Here, we describe why it has been so difficult and why we believe things are about to change. Finally, we briefly discuss what value we believe these maps will have for basic and clinical neuroscience.

Probably the principal reasons why detailed circuit maps do not already exist are both the sheer number of objects that would have to be cataloged and the miniscule size of each. Each human brain contains an estimated 100 billion neurons connected through 100 thousand miles of axons and between a hundred trillion to one quadrillion synaptic connections (Shepherd, 2003) (there are only an estimated 100–400 billion stars in the Milky Way galaxy). The largest of these neural wires, myelinated projection axons, are typically smaller than 20 μm . The finest, axonal and dendrite branches, are smaller than 0.2 μm , effectively precluding even the highest resolvable conventional light microscope from tracing and identifying such connections. The raw data for the Atlas of Human Connections would require approximately 1 trillion Gigabytes (an exabyte) and could not fit in the memory of any current computer. Indeed, all the written material in the world is a small fraction of this map. By way of comparison, the entire Human Genome Project requires only a few gigabytes. Until recently, there really was no practical way to store the information needed for even a single brain map and there were no tools to make the maps in any case.

We, along with other groups throughout the world (Denk and Horstmann, 2004), have come to realize that just as the human genome project required automation, the key to generating neural wiring diagrams lies in automating the tedious tasks of reconstructing the fine details of neuronal interconnections. A number of recent technical advances suggest that the reality of making a complete brain map is fast approaching. We are developing a

number of new techniques for tracing and cataloging brains, beginning in smaller animals with smaller brains as a precursor to the first human map. Because the diameter of the finest wires and synaptic connections requires electron imaging to resolve, we have automated the previously labor intensive process of brain sectioning and subsequent imaging by an electron microscope. The approach we settled on uses a novel microtome to turn the large volume of brain into a linear continuous strip of very thin tape (a process not unlike paring an apple). This tape is then automatically imaged in a scanning electron microscope with enough resolving ability to trace the smallest neuronal processes (Kasthuri *et al*, 2009). To trace the longer pathways that interconnect different brain regions, we developed a method to label each individual nerve cell a different color to identify and track axons and dendrites over long distances (Livet *et al*, 2007). Finally, we and our collaborators have been developing computationally intensive algorithms that are now for the first time automatically tracing neuronal processes and we hope eventually identifying synaptic connections in such data sets. Hand in hand with technical advances is the revolution in computing that seems to be continuing unabated (<http://www.intel.com/technology/mooreslaw/index.htm>). About 30 years ago, White *et al*, (1986) labored for over a decade to manually catalog the connections of the approximately 300 neurons comprising the nervous system of a single simple worm *C. elegans*. Their Herculean cartographic effort has not been equaled since, but we think will soon become relatively commonplace.

We believe that the payoff these maps will provide for neuroscience will be enormous. Many neuroscientists understand that the fundamental unit of organization of neural tissue is the synaptic connections linking neurons together. Indeed, neurons in various mammalian species seem quite similar, despite the obvious differences in behavior. The 'magic' that makes one species different from

another is in how these very similar neurons connect with each other. For humans, these maps would have special significance because an Atlas of Connections (ie, the human connectome) would represent a blueprint of ourselves, including imprints of all those things that are not in our genome, such as all the things we have learned throughout our lives. In addition, it is possible that many neurological disorders, such as the Autism spectrum disorders or schizophrenia, may be the result of misrouting of neuronal wires. Detailing these 'connectopathies' might give us insights into the underlying abnormalities in what are presently quite mysterious cognitive illnesses. Finally, as with all first glimpses into aspects of the natural world previously hidden, we imagine that a considerable number of surprises await us. For example, we do not have a good idea regarding how much the pattern of connections in one brain resembles the pattern in another. Are there deep organizing principles behind the ordering of our brains, or is each brain fundamentally unique? We predict that this effort will span many decades and just as the Hubbell telescope peers into a mysterious outer space, this effort will provide the first deep look into the inner space of our minds.

Narayanan Kasthuri¹ and Jeff W Lichtman¹

¹Department of Molecular and Cell Biology, Center for Brain Science, Harvard University, Cambridge, MA, USA

E-mail: jeff@mcb.harvard.edu

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Modafinil: an anti-relapse medication

Relapse to drug-seeking after abstinence is the most challenging problem in treating drug addiction. Therefore, the demand for anti-relapse medications is high. Clinical trials have reported that modafinil, a wake-promoting agent used to treat sleep disorders such as narcolepsy, is effective in treating cocaine dependence. Although a weak stimulant, sites of action and behavioral effects of modafinil appear to be different from those of cocaine or amphetamine. Modafinil blunts the reinforcing as well as cardiovascular effects of cocaine. More importantly, modafinil decreases cocaine use and relapse rates in cocaine addicts (Dackis *et al*, 2005; Hart *et al*, 2008). Larger multi-center clinical trials of modafinil have found modestly positive outcomes (Anderson *et al*, 2009). In addition, modafinil showed promise in a small group of methamphetamine-dependent subjects and in pathological gamblers with high impulsivity. However, it appears that modafinil may only be effective in cocaine addicts without alcohol dependence (Anderson *et al*, 2009). Modafinil also is reported to increase negative affect and withdrawal symptoms associated with nicotine dependence. These findings indicate consideration of smoking and alcohol abuse in using modafinil as an anti-relapse medication.

Despite clinical uses of modafinil, its mechanism(s) of action is still unclear. Using an animal model of relapse, we recently found that modafinil blocked reinstatement of an