cohesion, etc.), whereas the right limbic dominance observed in men could reflect a need for expertise in inter-group relations (eg, warfare, out-group relations, leverage of critical resources, etc.).

Sex-related functional asymmetry in the VMPC and amygdala may prove to be at the heart of the complementary social roles that both men and women have in human society. It is incontrovertible that men and women deserve equal opportunities to participate in society; it is also clear that men and women are neither biologically nor behaviorally identical. Sex-related functional asymmetry may be one way that evolution has capitalized on the capacity of homologous brain regions to process information differently and shaped our brains to meet the demands of both the sexes with unique reproductive and social roles.

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DISCLOSURE

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Dissecting the neural circuitry of addiction and psychiatric disease with optogenetics

Establishing the causal relationships between brain function and behavior is one of the most important goals in neuroscience research. Traditionally, this has been accomplished with electrical stimulation or lesioning techniques that nonselectively activate or ablate the neural tissue, or by microinjections of drugs, which often selectively activate or inhibit specific neurons, but do so on a timescale irrelevant to neuronal firing. Although these techniques have been crucial in defining the gross neuroanatomical pathways that mediate behavior, they have had limited success in determining the specific synaptic connections and cell types that mediate a given behavioral response. With the recent advances in the emerging field of optogenetics, it is now possible to selectively introduce light-gated ion channels and pumps into genetically defined populations of neurons to selectively stimulate or inhibit neuronal

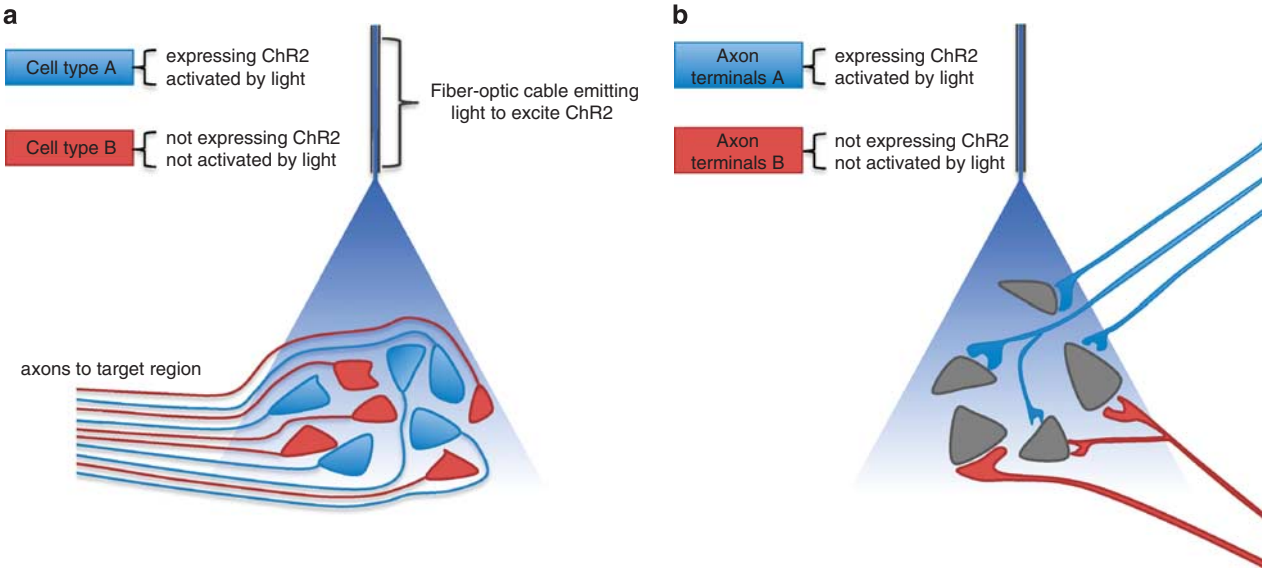

Figure 1. Activation of genetically defined neurons or axon terminals in heterogeneous tissue. (a) Neurons expressing ChR2 (cell type A) are activated upon illumination with blue light. Optical stimulation of neurons expressing ChR2 leads to selective modulation of firing in these neurons, whereas neighboring neurons are unaffected (cell type B). (b) Afferents from neurons expressing ChR2 are directly activated by light, whereas afferents from other neurons in close proximity that are not expressing ChR2 are unaffected. This allows for afferent-specific perturbation of synaptic function *in vitro* or *in vivo*.

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 chloride 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.

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Neurocartography

Although it has been appreciated since the work of Cajal that the brain is comprised of neurons connected together 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 ums. The finest, axonal and dendrite branches, are smaller than 0.2 ums, 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