that differ from non-addicted subjects; (3) acute effects of novel compounds on brain activation patterns in addicted subjects while performing these tasks could provide additional information about the pharmacodynamics, and hence the potential utility of these compounds for treatment of addictions. The potential usefulness of this approach has been shown by a recent study showing that an acute dose of methadone reduced fMRI brain activation associated with heroin-related stimuli in opiate addicts (Langleben *et al*, 2008); however to date, phMRI has not been routinely used as a tool for medication development for addictions.

Basic science advances in understanding addiction raise hope for a future with more effective therapeutic strategies for this chronic, relapsing brain disorder. Yet, the progress of candidate medications on the pathway to patients is slow and of the numerous compounds studied for treatment of addictions, few have reached the FDA approval (Vocci and Elkashef, 2005). Novel brain imaging methods, such as phMRI, offer the potential to provide important information about medications for addictions, which could aid in the development of pharmacotherapies for addictions.

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DISCLOSURE

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Sex-related functional asymmetry in the limbic brain

At a macroscopic level, the brains of both men and women are very similar. However, closer inspection shows striking differences between the sexes in the structure–function relationships in the brain. Interpersonal, emotional, and occupational success depends critically on effective navigation of the social world. At the same time, individuals of each sex have different goals—only women bear children, and this basic function likely sets the agenda for the individual and societal goals of many women. Men do not bear children and may be driven by an agenda emphasizing acquiring and maintaining resources and power. Thus, sex differences in social-emotional regions of the brain might be adaptive. The limbic regions of the brain and closely connected regions, especially the ventromedial prefrontal cortex (VMPC) and amygdala, are important for social-emotional processing. Furthermore, as nearly all brain regions have homologous versions in each hemisphere, this may be a substrate on which divergent selection resulted in sex-related functional asymmetry.

Studies of neurological patients have shown that the right VMPC and amygdala appear to be critical for social-emotional functioning and decision making in men, whereas the left VMPC and amygdala appear to be more important for these functions in women (Tranel *et al*, 2005; Tranel and Bechara, 2009). For example, a man with a unilateral right VMPC lesion, who was well educated and had worked successfully as a minister, was entirely unable to return to any form of gainful employment after his brain damage. He requires supervision for daily tasks and demonstrates severe disturbances in behavior and emotional regulation, including impulsivity and poor judgment. By contrast, a man with a unilateral left VMPC lesion was able to return to his job at a grain elevator and remains successfully employed there. He is remarkably free of disturbances to his social life and emotional functioning (Tranel *et al*, 2005). Moreover, preliminary evidence from the Trust Game, a multiplayer neuroeconomics task, suggests that women with left VMPC lesions and men with right VMPC lesions trust others less (ie, they invest less in others) and display more frequent acts of negative interpersonal reciprocity (ie, they return less than the amount invested). Similarly, women with lesions to the left amygdala and men with lesions to the right amygdala appear less risk averse than do men and women with lesions to the opposite amygdala. This evidence converges with other research, including (1) fMRI studies showing similar patterns of lateralized activations in these regions in response to social and emotional paradigms (eg, Killgore and Yurgelun-Todd, 2001; Cahill *et al*, 2004); (2) studies showing sex differences in orbitofrontal-dependent behavioral paradigms, such as the Iowa Gambling Task (eg, Overman, 2004); and (3) studies showing increased functional connectivity with the right amygdala of men and with the left amygdala of women (eg, Kilpatrick *et al*, 2006). Altogether, such evidence suggests that the right VMPC and amygdala in men as well as the left VMPC and amygdala in women are important for social-emotional functions. Potentially, the left limbic dominance observed in women reflects a need for expertise in interpersonal relationships (eg, the need to bear and rear children, maintain in-group

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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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

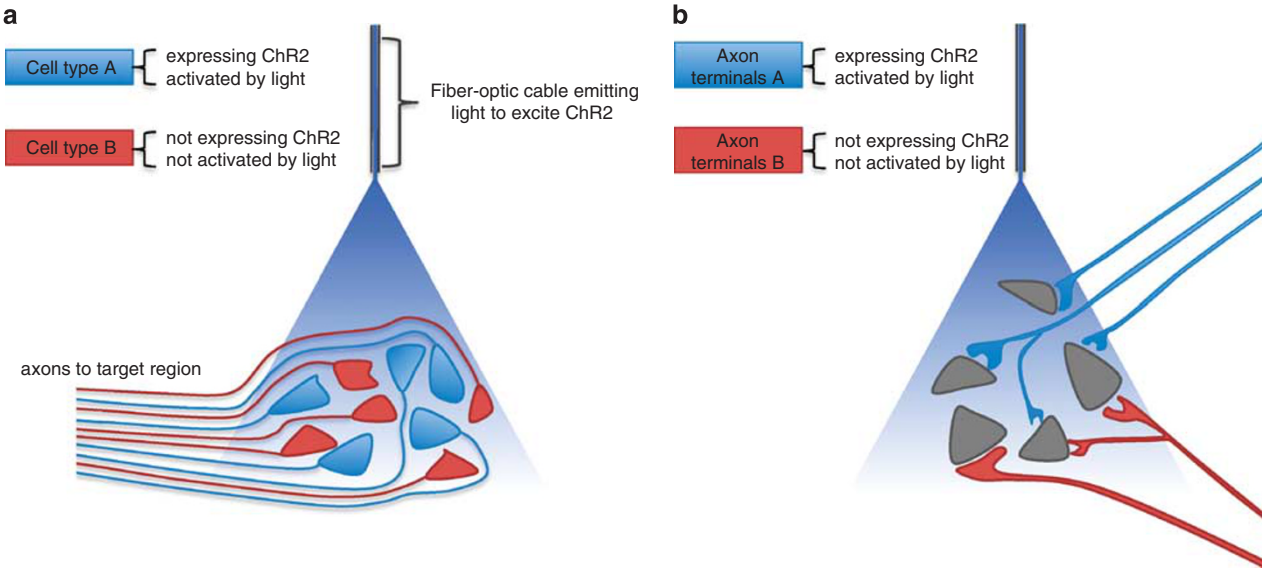

Figure 1. Activation of genetically defined neurons or axon terminals in heterogeneous tissue. (a) Neurons expressing ChR2 (cell type A) are activated upon illumination with blue light. Optical stimulation of neurons expressing ChR2 leads to selective modulation of firing in these neurons, whereas neighboring 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*.