always an agonist, partial agonist, or antagonist/inverse agonist) had been accepted for a half-century. Two decades ago, it became clear that a single G protein-coupled receptor (GPCR) could have promiscuous G protein interactions. This suggested that some drugs might cause differential effects on signaling via a single receptor, and within a few years, there were data showing such 'anomalous' functional responses—in the extreme, a ligand acting at a single receptor being a full agonist at one function and an antagonist at another (Kilts *et al*, 2002).

Strikingly, most laboratories engaged with this phenomenon recognized its implications, each proffering a unique name (eg, agonist-directed trafficking of signaling, biased agonism, etc), with *functional selectivity* emerging as the apparent consensus. The naming quandary, the involved mechanisms, the impact on understanding drug action, the relevance to drug discovery, and even the implications for teaching have been reviewed recently (Urban *et al*, 2007), now including the first book on the subject (Neve, 2009). It appears that this is a universal phenomenon for all GPCRs and other drug targets, and that many drugs may cause such differential signaling.

The question is whether functional selectivity is an interesting artifact for the specialist, or a mechanism that affects psychoactive drug action and drug discovery. The data suggest that both are true (Kilts *et al*, 2002; Smith *et al*, 1997). As an example, a recent publication examined the impact of functional selectivity on valvulopathy, which was thought to be due to 5-HT_{2B} agonist-induced mitogenic action in the heart. Clinical drugs were selected for their 5-HT_{2B} agonist profile in traditional assays, and then functionally profiled. Of this group, ropinirole was differentiated from the other compounds by its signaling profile, possibly explaining why it has a decreased risk of valvulopathy (Huang *et al*, 2009). To our knowledge, this is the first example for the differentiated side-effect profiles of functional selectivity.

Of direct neuropsychopharmacological relevance is the dopamine mechanism of action of aripiprazole. The most commonly disseminated hypothesis is that aripiprazole causes 'dopamine stabilization' through D_2 partial agonism. Conversely, other data have shown that aripiprazole, although sometimes a partial agonist, can also be a D_2 pure antagonist or full agonist depending on the assay system. As we have reviewed recently (Mailman, 2007), the original *in vivo*/*ex vivo* data from the drug's discoverers are consistent with D_2 functional selectivity, but not with simple partial agonism. Functional selectivity would thus predict that D_2 ligands selected as partial agonists in a single common functional assay may not be similar clinically. From this perspective, the failure of preclamol or bifeprunox to have adequate antipsychotic efficacy may not be surprising.

The level of complexity added by functional selectivity also provides opportunity. In the short term, it permits a greater understanding of the differential neuropsychopharmacology of drugs once thought to be functionally similar, and may permit discrimination of potential drug candidates. In the long term, scientific advances showing how individual signaling pathways affect cellular function (and subsequent physiological responses) will provide a mechanistic foundation for the discovery of rationally chosen functionally selective drugs.

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DISCLOSURE

In addition to income from his primary employer, Dr Richard Mailman has an equity interest in Biovalve Technologies and Effipharma, which creates a potential conflict of interest that has been monitored by committees at his current and previous employer. In the past three years, Dr Mailman has also been compensated for providing scientific opinions relevant to legal or public policy matters that are not related to the topic of this commentary. Except for his primary employment, Dr Vishakantha Murthy declares that no compensation or support has been received from any entity over the past three years for research or professional service. This work was supported by grants MH040537 and MH082441.

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Induced pluripotent stem (iPS) cells and their future in psychiatry

One of the most significant challenges in neuroscience for the twenty-first century is to understand the molecular and cellular basis of neuropsychiatric disorders. Despite extensive research, the last several decades failed to yield clearly validated new drug targets or therapeutic mechanisms for major psychiatric disorders (Hyman, 2008). One important limitation is the lack of pathogenically and physiologically reliable animal and cellular model systems of psychiatric disorders. This challenging situation is now changing through the advances that followed Shinya Yamanaka and his colleagues' successful generation of pluripotent stem cells in 2006, so called 'induced' pluripotent stem (iPS) cells, from

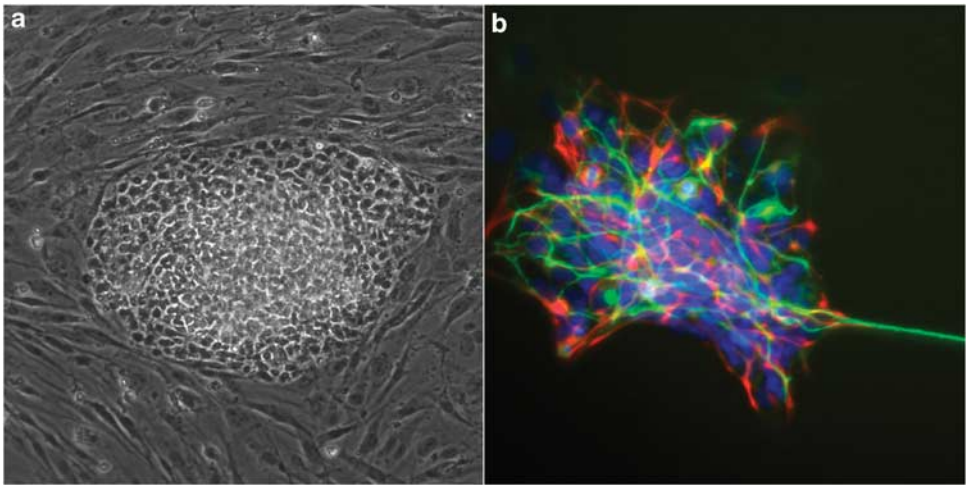

Figure 1. Human iPS cells derived from human newborn fibroblasts by direct protein delivery. (a) These protein-induced human iPS colony shows a typical human ES cell morphology. (b) They can differentiate into all three germ layers including neuroectodermal lineage cells such as nestin-positive neural precursors (red) and Tuj1-positive neurons (green). Nuclei were stained with DAPI (blue).

somatic cells by retroviral transduction of four transcription factors (ie, Oct4, Sox2, Klf4, and c-Myc) (Takahashi and Yamanaka, 2006). Furthermore, 1 year later, several groups showed that human iPS cells could be generated from human tissues by similar methods, paving the way to generate disease- and patient-specific iPS cells (Takahashi *et al*, 2007; Yu *et al*, 2007; Park *et al*, 2008). Until these advances, the biological dogma was that the developmental process is unidirectional in that a totipotent zygote becomes more and more restricted until terminally differentiated tissues are generated. These new breakthrough studies showed that epigenetic reprogramming by defined factors could reverse this process.

iPS cell technology is a tantalizing new method of generating genetically matched pluripotent stem cells *in vitro*. Unlike conventional methods that generate embryonic stem cells from zygotic embryos, it does not require killing of embryos, thus avoiding the associated ethical dilemma. These iPS cells provide useful tools to study the molecular and cellular mechanisms of development and differentiation, particularly early human development. Furthermore, iPS cells derived from patients could be extremely useful for investigating the physiological, cellular, and molecular mechanisms underlying the disease process, which may lead to ideal platforms for drug screening. This new approach may be especially important to advances in psychiatry because (1) the underlying pathogenic mechanisms of mental disorders are largely unknown, (2) cellular models for disease mechanism study are extremely limited, and (3) rational treatments are lacking in most cases.

Several major obstacles must be overcome for iPS cell technology to make a full impact in psychiatric disease research. First, most iPS cells have been derived by retroviral or lentiviral introduction of reprogramming factor-encoding genes, resulting in multiple chromosomal disruptions, any of which may cause genetic dysfunction and/or tumor formation. This could be particularly problematic in psychiatric diseases that may have relatively subtle pathogenic mechanisms. Secondly, reprogramming transgenes (in particular, c-Myc and Klf4) are closely associated with oncogenesis, raising the possibility that iPS cells generated by these factors may be prone to tumor formation. Currently, most iPS cells contain the reprogramming transgenes in their chromosomes although their expression is mostly silenced. Reactivation and/or residual leaky expression of these transgenes may trigger altered cell physiology and/or abnormal differentiation properties. To address these issues, recent studies used non-integrating vectors (eg, adenovirus or episomal vectors) or excisable vectors (eg, *piggyBac* transposon and Cre-recombinase excisable viruses (Yamanaka, 2009)). As these DNA vector-based manipulations are not completely free from potential chromosomal disruption, we recently developed a new method to generate human iPS cells by direct protein delivery without the use of virus or DNA transfection (Kim *et al*, 2009). These transgene- and DNA-free iPS cells (Figure 1) could be useful not only for disease mechanism study, but also for future customized cell therapy of neuropsychiatric disorders.

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Advances in PET analyses of stress and dopamine

A deregulation of the stress response is a potential etiological factor in the development and relapse of dopamine (DA)-related human disorders, including addiction, drug-induced psychosis, and schizophrenia. Schizophrenia is characterized by a chronic relapsing nature and vulnerability to exacerbation following stress or dopaminergic drugs. Indeed, the most replicated finding so far in schizophrenia positron emission tomography (PET) research has been an increased DA release after the administration of amphetamine, and this DA increase has been associated with positive psychotic symptoms and active stages of the illness. As increased stimulant-induced DA release is a hallmark of sensitization, several pieces of evidence support the view that schizophrenia is associated with a process of dopamine sensitization (Laruelle and Abi-Dargham, 1999).

Psychosis sufferers themselves often cite a link between the experience of stress and psychotic symptoms. The stress-vulnerability model suggests that an endogenous, organic diathesis or vulnerability interacts with internal or external stressors in the development of psychotic disorders. However, the underlying neurobiological condition/event that results in an exaggerated response to stressors is unknown. One proposed mechanism is neurochemical sensitization of the DA system—*dopamine sensitization*—, whereby repeated exposure to sensitizing life stressors (or DA drugs) progresses into increased stress-associated DA release. Hence, during active periods of the illness (that is, prodromal phase, initial episode, and subsequent relapses), dopaminergic neurons may be hyper-responsive to environmental stimuli, and exposure to even moderate levels of stress (or DA drugs) produces excessive DA release, precipitating illness in vulnerable individuals and relapse in those with schizophrenia.

The phenomenon of DA sensitization to psychostimulants is subjected to cross-sensitization with stress. It is well established that repeated stress (maternal separation, social-defeat stress, foot shock, tail pinch, restraint) induces heightened sensitivity to low doses of dopaminergic drugs; and conversely, repeated dopaminergic drug exposure increases the stress response in animals. Consistent with these findings, prenatal and postnatal stress is associated with increased drug-induced DA release, and different types of acute and repeated stress increase DA release (Abercrombie *et al*, 1989; Kalivas *et al*, 1986). Similarly, recent studies in humans using PET have shown increased DA release after either a psychosocial or a metabolic stress task (Adler *et al*, 2000; Pruessner *et al*, 2004). However, this finding was not replicated in another study, which used a different stress paradigm, with no

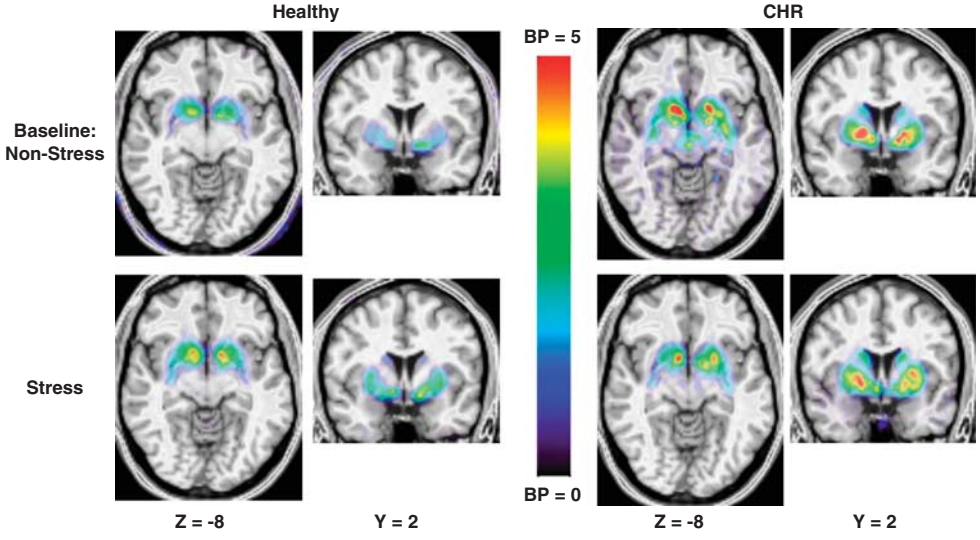

Figure 1. Representative figure showing decreased [^{11}C]-(+)-PHNO BP_{ND} in CHR following stress suggesting increased DA displacement, as compared with HV.