New LSD Research: Gene Expression within the Mammalian Brain

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As readers of this magazine will know, Bob Wallace, a great friend and a pivotal Heffter board member, died not long ago. One project of particular interest to Bob, and which shows how perceptive he was, is a new-technology LSD research program at Vanderbilt University.

Why did this research intrigue Bob? Despite research over the past 30 years, the mechanism of action of hallucinogenic drugs remains largely mysterious. Studies have focused primarily on how the drugs affect neurotransmitters. A team of researchers at Vanderbilt University—Drs. Charles D. Nichols and Elaine Sanders-Bush—has now for the first time used state-of-the-art functional genomic and molecular methods to investigate the brain's genetic response to LSD.

Heffter and the National Institutes of Health (NIH) jointly funded the work, and we are happy that this is the second time we have collaborated in funding a research project on hallucinogens with NIH. On a more personal note, Dr. Charles D. Nichols is the son of Heffter Board President Dr. Dave Nichols, and it is very pleasing to be able to report on the work of a second-generation neuroscientist studying LSD.

Genes are most familiar as the repositories of instructions that our sex cells carry so that they can build the next generation of human beings. But genes do a great deal more than that. They code for and control the myriad chemical functions that the body is carrying out in every cell all the time. It is the genes that switch on and off the cellular processes that ultimately control life and consciousness. Genomic technologies allow investigators to see for the first time how genes behave in response to a given molecule, allowing a new level of delicacy in understanding how cells function.

The investigators began by questioning whether some behaviors elicited by hallucinogens result from temporary changes in gene expression in the brain. After giving LSD to one group of rats, they extracted the expressed RNA (the molecules made from turned-on genes) from the brains of the LSD rats and from control rats. They compared the differences by analyzing the sample with the powerful technology of DNA microarrays—small glass slides, about thumbnail sized, that have about ten thousand gene sequences printed onto them using actual DNA. Each of these sequences represents a unique gene. The researchers have now screened two chips, which taken together represent some 15,000 expressed genes. Because the predicted number of genes in a human is only 30-40,000, these two gene "chips" may represent nearly half of the total genome!

Results to date show that LSD induces expression changes in a relatively small but important collection of genes. Many of these genes influence the way neurons change physically to alter functional abilities in the brain. At least one of the genes is involved in the process of growth and differentiation of various cell types, and has been shown to be necessary for memory consolidation. A common theme of many of the genes regulated by LSD is the process of synaptic plasticity. The genes that LSD affects may thus play an important role in learning and the storage of memories.

Genomic research opens a new frontier in understanding how hallucinogens work in the brain. And by combining the results of the gene studies with current signal transduction mechanisms, electrophysiology, and behavioral experiments, we may finally begin to grasp the larger picture of how the effects of hallucinogens are produced in the brain at the molecular level. This will in turn help us understand the physical substrate of behavior and cognition. ■