Psychedelic Research

the link between human and animal studies:

A Talk by Professor Mark Geyer, Ph.D at the Society of Neuroscience 1993 Annual Convention

BY JON FREDERICK

AT THE NOVEMBER, 1993 annual convention of the Society for Neuroscience, held in Washington, D.C., Mark Geyer, Ph.D., professor of psychiatry at U.C. San Diego, spoke at an evening dinner event on the importance of continuing basic research on psychedelic drugs in human subjects. His audience of about 100 scientists included many of the world's leading serotonin researchers. Dr. Geyer introduced his talk by reporting on his recent visit to a conference in Lugano, Switzerland, sponsored by the Swiss Academy of Medical Sciences, commemorating the 50th anniversary of Albert Hoffman's discovery of the psychoactive effects of LSD. This meeting was a major summit of both human and animal researchers in the psychedelic field, designed in part to address the issue of the safety and efficacy of LSD and related compounds as adjuncts to psychotherapy. The Swiss government is currently reconsidering the protocols and requirements under which human psychedelic studies have been conducted since 1988.

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Geyer was upbeat and encouraged by the diversity of human psychedelic research represented at this meeting. (reported in the previous MAPS newsletter). "The prospects for further studies are real, as long as we keep them rigorous, and society doesn't react in the way it did in the sixties and cause another cessation of this enterprise." In addition to studies in psychotherapy, research on the neurobiology and the basic psychological processes affected by hallucinogens were presented. "It seems to me that these kinds of databases will provide critical information that just hasn't been available to those of us who work with animals and would like to know whether what we're doing has any bearing on the interesting effects of hallucinogens in man," Geyer said.

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Startle response

To illustrate, Geyer presented some of his own work on the effects of hallucinogens on the startle response in rats. In Geyer's laboratory, startle chambers equipped with vibration sensors are used to measure the whole-body jump of a rat when startled by a puff of air or a sound. The startle response can be elicited in a number of species, including humans, which allows for the assessment of the relevance of animal models.

"I'm not particularly interested in the magnitude of a brainstem reflex to explain the complex and interesting effects of hallucinogens," Geyer said. "Rather, what interests me is the plasticity of behavior that can be illustrated and demonstrated in startle response paradigms." One form of plasticity which has been extensively studied in Geyer's laboratory is what has been called the simplest form of learning, habituation. Habituation is the decrease in response that is observed when an animal is exposed to the same stimulus repeatedly with no consequences. "It is a very simple, fundamental form of non-associative learning, without which, one cannot learn to discriminate stimuli, really. That is, if one can't learn what not to pay attention to, the flip side of that is one can't learn to pay attention to anything in particular." Essential to the selectivity of attention is the ability not to attend to some things, those for which there

are no important contingencies, Geyer said. Geyer suggested that changes in such "pre-attentive filtering mechanisms might explain some of the subjective phenomenology of hallucinogens. When the same air puff is administered to a rat every fifteen seconds or so, they quickly learn that there's nothing they can do about this, there are no contingencies, nothing else is going to happen, and so the startle response habituates. By contrast, after LSD, what is old becomes new. What is familiar is perceived as novel. Another way to say that is that there is a failure of habituation. Thus, rats treated with LSD show a failure of startle response habituation." This effect can also be observed with mescaline and can be blocked by serotonin-2 antagonist drugs such as ritanserin. (Serotonin-2 refers to a group of serotonin receptor subtypes that are distinguished from other subtypes based on their molecular structure and affinity for drugs such as LSD. A variety of studies have implicated the serotonin-2 subtype in the effects of psychedelic drugs.) Further studies in Geyer's laboratory have shown that, for a series of serotonin-2 antagonists, there is a correlation between their affinity at the serotonin-2 receptor and their ability to produce changes in the habituation of the startle reflex that are opposite to those of the hallucinogens. Meanwhile, drugs like MDMA (Ecstasy), which cause the release of serotonin into the synapse, act as indirect agonists, producing a failure of habituation similar to that observed with hallucinogens.

Prepulse inhibitor

Another form of sensory filtering that is studied in Geyer's laboratory is known as prepulse inhibition. Geyer explained, "Basically, what it means is that on some trials you present a loud stimulus and you get a startle response, but on other trials in the same session, you precede that loud stimulus with a very a weak subthreshold stimulus, and what is observed is that the startle response is robustly inhibited. Like habituation, prepulse inhibition is disrupted by LSD as well as indirect serotonin agonists such as MDMA. Both the habituation effects and the prepulse inhibition effects are not unique to hallucinogens, but they are produced by manipulations of serotonin systems and they might tell us something about what the function of the endogenous serotonin system is."

Parallel studies

Geyer has also studied habituation (and prepulse inhibition) of the startle reflex in human subjects, using headphones for the acoustic stimulus and measuring the eyeblink response using an EMG monitor. For example, normal habituation is observed in control subjects and depressed patients, while an impairment of habituation is observed in schizophrenic patients. "This paradigm would be practical for use in drug-treated volunteer subjects", Geyer said. "One of the things that excited me about the prospects of having real scientific studies resume in humans with these compounds would be that we might be able to do parallel studies between animals and man and thereby assess the relevance and validity of the animal models." •

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