History, Rationale and Potential of Human Experimental Hallucinogenic Drug Research in Psychiatry

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Systematic scientific interest in psychedelic substances has a tradition of about 100 years. Numerous human experimental studies have confirmed the existence of a common nucleus of experiences in hallucinogen-induced states and the acute stages of schizophrenic psychoses. However, the degree of resemblance between endogenous and drug-induced psychotic states has been an issue of controversial debate. After the scheduling of psychedelics in the 1960 s, human research became highly restricted worldwide and scientific interest in this field faded. The debate about the appropriateness of the psychedelic state as a model for endogenous psychosis therefore seemed to have little practical relevance. Currently there is a revival of scientific interest in human experimental psychedelic research. Consequently, the appropriateness of hallucinogen-induced states as models for psychosis needs to be reappraised. The arguments for and against are summarized in this paper. In conclusion, the drug-induced model psychosis is shown to be a useful model for acute psychotic stages, but not for the nosological entity schizophrenia.

Historical Background – Origins of Scientific Interest and the Early „Mescaline" phase of human experimental research with hallucinogens (ca. 1910 – 1943)

Systematic scientific interest in the effects of psychedelic drugs in humans began about 100 years ago. It emerged after the discovery of peyote by the German toxicologist *Lewin* (1888). *Lewin* learned about the ritual use of the peyote cactus by Indian tribes in Mexico, and realized that this cactus must contain very powerful psychotropic substances. He and his colleague *Heffter* made the first chemical analyses of the plant and isolated four alkaloids, including mescaline (*Heffter*, 1898). *Heffter* himself and a few more scientists performed experiments on themselves with dried parts of the cactus („mescal buttons"), and gave the first reports on its psychological effects (*Heffter*, 1898; *Ellis*, 1897; *Prentiss* and *Morgan*, 1895; *Mitchell*, 1896). During the second decade of our century, *Spaeth* (1918) succeeded in synthesizing mescaline. This was an important step in terms of availability and standardization of dosage for subsequent, systematic research.

However, the availability of the compound alone was not sufficient to catalyze the psychiatric research which followed. In this respect, the influence of *Emil Kraepelin* at the Munich Psychiatric Department was decisive. *Kraepelin*, the father of modern biological psychiatry, was a major proponent of human experimental research strategies with psychoactive agents. He was fascinated by the possibility of altering experimentally the mental state of healthy humans, i.e. of inducing artificial mental disorders and studying them under standardized conditions. As early as 1892 *Kraepelin* published his experiments on the „influence of drugs on simple psychological processes" (*Kraepelin*, 1892).

With *Kraepelin* as an influential figure and given the availability of peyote and mescaline, the first early phase of psychiatric experimental research with this hallucinogen emerged. This phase lasted up to the 1940 s and provided extremely detailed, elaborate descriptions of the mescaline state in healthy volunteers. The first studies by *Knauer* and *Maloney* (1913) were performed in Munich. The important studies by *Mayer-Gross* and *Stein* (1926) and *Beringer* (1927) followed in Heidelberg. *Zucker* (1930) studied the effects of mescaline in schizophrenic patients. The study by *Stockings* (1940) of healthy volunteers is considered a classic.

Of these early studies, the one by *Beringer* (1927) is the most extensive and detailed phenomenological description of the mescaline state in about 60 volunteers.

Fig. 1 Kurt Beringer and his team at the Department of Psychiatry of the University of Heidelberg

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Beringer described disturbances of perception and predominantly visual hallucinations, but also acoustic and other perceptional alterations, including characteristic synesthesias. He mentioned the profound alteration in time perception, and described the „specific state of consciousness". Next to psychomotor inhibition, the latter includes a dream-like state with preserved orientation, waning and waxing of the experience, simultaneous contradictory feelings (i.e. feeling separated from one's self and others **and** feeling united with others and the universe), profound passivity and a peculiar narrowing of consciousness to a few subjects, i.e. to small perceptional details only. *Beringer* underlined the importance of passivity as a core feature of the state. He described variable alterations in thought and mood, but what he considered most typical was inhibition of thinking and will, poverty of thought content and speech, and a „hebephrenia-like" euphoria, as well as rapid shifts in mood. In some cases he described accelerated thinking and richness of ideas, as well as intense positive or negative feelings or blunting of affect which went as far as a complete absence of emotions.

Beringer considered the experience of the mescaline-state as very valuable for psychiatrists, because it enabled them to understand their psychotic patients better. With respect to the relationship between personality and experience he was disappointed by his results, because he found the drug effects to be unpredictable. However, he was aware of the methodological limitations of his personality assessments, and thought that better methods might emerge in future that would allow psychiatrists to assess personality features and motivational factors more precisely. He hoped that it might then become possible to find correlations between these aspects and drug effects. Beringer considered the mescaline state as unique compared to the states induced by other drugs. And, finally, he felt that the mescaline state very much resembled the experience of schizophrenic patients *at the beginning and during the acute phases of their psychosis, but not during chronic stages of the disease*. In other words, he regarded the mescaline state as a model for acute schizophrenia. This distinction between the different stages of endogenous psychoses is important, because it deals very early with the general criticism that hallucinogen-induced states present more differences from than similarities to schizophrenia (*Hollister*, 1962).

Other contemporary researchers gave less detailed but generally similar descriptions of the mescaline state. An interesting feature of the classic paper by *Stockings* (1940) is that he found acoustic hallucinations to be very frequent under mescaline. He described hallucinations of music and voices, quite similar to the typical hallucinations of schizophrenics. Like *Beringer*, he also described the fact that schizophrenics frequently experience visual hallucinations during the acute phases of their disorder. Stockings considered the drug-induced state an excellent model for psychosis. In his view, „the drug is of greatest importance as a method of approach to the understanding of the nature of mental disorder" (*Stockings*, 1940).

However, the influence of this early research with mescaline on the further development of the psychiatric discipline and the development of psychiatric theories remained limited.

The Second „LSD" Phase of Systematic Human Experimental Research with Hallucinogens (1943 – 1960 s)

The second phase of research began with the discovery of LSD by Albert Hofmann at Sandoz Pharmaceutics in Basel in 1943. It was dominated by work with LSD, although other psychedelics, which were discovered successively, were also studied. Research flourished up to the 1960 s and became extremely influential, and it is impossible to give a comprehensive review of the literature of that period. Research did not remain exclusively psychiatric in a narrow sense, but included extensive psychoanalytically oriented studies of consciousness and personality (*Linton* and *Langs*, 1962,1964), research into religious – mystical experience (*Pahnke* and *Richards*, 1966), and research into the utility of psychedelics as adjuncts for psychotherapy (*Abramson*, 1967; *Grof*, 1967, *Bastiaans*, 1979, *Leuner*, 1962). Following the tradition of the earlier, mescaline phsase, psychiatric studies used hallucinogens as models for psychosis. These studies utilized neuropsychological and neurophysiological tests, as well as standardized psychometric assessments (*Rinkel* et al., 1952, 1955, *Heimann*, 1961; *Rosenbaum* et al. 1959, *Fischer* et al. 1962,1969). Some researchers administered hallucinogens to schizophrenics in an attempt to specify the analogy between drug-induced state and endogenous psychotic experiences. Although the results obtained from such studies were contradictory, hallucinogens were used as screening tools, i.e., as diagnostic aids for "latent schizophrenia" cases (*Photiades* and *Anastassopoulos*, 1960; *Sedmann* and *Kenna*, 1965).

There were two main reasons for the attractiveness and enormous influence of human hallucinogenic drug research during this research phase: first, LSD and other indol hallucinogens have fewer somatic side-effects than mescaline. This makes experiments easier to conduct. Secondly, LSD is an extremely powerful drug, acting in the microgram dose range; accordingly, it seemed reasonable to assume that an analogous endogenous compound might be related to the etiology of schizophrenia. Given the chemical similarity of hallucinogens and endogenous transmitters, model psychosis research resulted in significant hypotheses about the etiology of schizophrenia, which regarded the disease as an autointoxication with endogenous hallucinogen analogs: the transmethylation, indol, serotonin, and adrenochrom hypotheses of schizophrenia (*Osmond* und *Smythies*, 1952; *Hoffer* and *Osmond*, 1959; *Nestoros* et al., 1977) were the theoretical background of extensive research activities, which, however, failed to confirm the hypotheses.

Nevertheless, researchers of that time noticed not only the similarities, but also differences between experimental and endogenous psychotic states. Some researchers, such as *Hollister* (1962), claimed that hallucinogen-induced states were not suitable as models for psychosis. A summary of Hollister's arguments (1962) disputing the comparability of the two states is given in Table **1**.

Hollister argued that schizophrenics are mostly withdrawn, while subjects on psychedelics like to speak about their experiences while intoxicated. Further, he argued that in both conditions subjects experience somatic sensations; however, their subjective interpretation is different: schizophrenics generally suspect alien forces, while sophisticated subjects on

Table 1 Arguments disputing the comparability of hallucinogen-induced and endogenous psychotic states (summarized from: Hollister 1962)

	schizophrenia	hallucinogen-induced states
withdrawal	+	–
subjective interpretation of bodily sensations	"alien forces"	psychodynamic
concern about failure to communicate	–	+
hallucinations	mainly acoustic; considered real	mainly visual; recognized as hallucinations
delusions	common	rare
catatonic features	common	rare

drugs give psychodynamic explanations of their experiences. A further argument was that subjects on drugs are disturbed when they have difficulties expressing their experiences, while schizophrenics are not concerned by this. *Hollister* underlined the different modality of the predominating hallucinations in the two states. A further distinction was that schizophrenics believe that their hallucinations are real, while intoxicated subjects know that they are not. And, finally he argued that delusions and catatonic features are rare in drug-induced states, but quite frequent in endogenous psychoses. The counter-arguments to Hollister's arguments are discussed in the next section.

In 1957 a new anesthetic, phencyclidine (PCP, Sernyl®), was developed. During the first clinical trials patients demonstrated severe postoperative psychiatric abnormalities including hallucinations, bizarre behavior, excitement and violent behavior. At the end of the 1950 s, *Rosenbaum* and colleagues (1959) began to perform experiments with subanesthetic doses of this new anesthetic. They concluded that PCP is a better psychotomimetic than LSD and the other classical compounds, since it mimics core schizophrenic symptoms such as thought disorder, negativism, hostility, attentional abnormalities, bodily sensations, and apathy, while inducing fewer visual hallucinations. However, this view is not generally accepted. Subsequent studies concluded that PCP produces a delirious state rather than one resembling schizophrenia (*Pearlson*, 1981). This issue has remained a matter of debate until today. PCP was never marketed for human use, but ketamine, a related dissociative anesthetic was made available and is still employed both clinically and for experimental purposes (*Krystal* et al., 1994; *Malhotra* et al., 1996; *Lahti* et al., 1995a, 1995b; *Vollenweider* et al., 1997). Knowledge about the NDMA-antagonistic properties of the dissociative anesthetics PCP and ketamine (*Anis* et al., 1983) led to the glutamate hypothesis of schizophrenia, which is being widely discussed at present (*Kornhuber* et al., 1989; *Carlsson* and *Carlsson*, 1990; *Javitt* and *Zukin*, 1991; *Olney* and *Farber*, 1995).

The issue of the adequacy of the psychedelic state as a model for endogenous psychosis was still being debated when the situation changed during the mid-1960 s. Up to that time the drugs had been in the laboratories, in the hands of specialists, and other people knew little about them. The hippie subculture and psychedelic drug abuse after the mid-1960 s had enormous cultural and public health implications worldwide. Hallucinogenic substances were scheduled in the United States and in Europe. Human research with these substances became highly restricted worldwide and was discredited. Accordingly, scientific interest in psychedelics faded at the end of the 1960 s, and the discussion about the suitability of the psychedelic state as a model for endogenous psychosis seemed to be of little practical relevance.

Current Human Experimental Hallucinogenic Drug Research – Rationale and Promises

During the past 10 years scientific interest in human hallucinogenic drug research has begun to grow again. The main areas of current interest are the pharmacology of the drugs, i.e., understanding the mechanisms of action of substances of abuse, and the model psychosis strategy within biological schizophrenia research (*Hermle* et al., 1992, 1993a and b; *Krystal* et al., 1994; *Malhotra* et al., 1996; *Lahti* et al., 1995a and b; *Strassman* and *Qualls*, 1994; *Strassman* et al., 1994, 1996; *Ensslin* et al., 1996; *Spitzer* et al., 1996; *Gouzoulis* et al., 1992, 1993; *Gouzoulis-Mayfrank* et al., 1996; *Vollenweider* et al., 1997a, b; *Schneider* et al., 1998).

Concerning the first-named area of interest, the rationale for studying the human pharmacology of drugs of abuse is generally accepted. We know little about the actions of the drugs in humans, and this research is relevant as a basis for addiction research. But why is it reasonable, and why might it be useful to follow the model psychosis strategy today? The background of the new interest in this paradigm is related to the methodological problems and contradictory results of modern biological schizophrenia research. It is one expression of a general trend away from nosology-oriented and towards syndrome-oriented research strategies.

Clinical studies, neuropsychological tests, and long-term follow-up trials with psychotic patients are difficult to perform. Patients are heterogeneous in respect of nosological category, medication status and stage of the disease. Follow-up studies are difficult to realize. During the acute episodes of the disease, patients with prominent positive symptoms are hardly in a position to cooperate in the complex tasks required by studies. Moreover, patients may present with disorganized behavior and formal thought disorder, and their ability, to communicate their subjective experiences is limited. Most studies are therefore performed with patients in chronic or remitted states with various medications. It is doubtful whether these data can also be applied to other groups of patients, in particular to patients in acute phases of the disease.

The above arguments support the usefulness of the model psychosis strategy, provided that we accept that healthy people under the influence of medium doses of psychedelic substances experience similar phenomena to patients in the initial stages of acute psychoses. Healthy volunteers mostly maintain insight into and control over their behavior and are able to cooperate even in complex task procedures and to describe their subjective experience during and after the experiment. Subjects on hallucinogenic drugs can therefore be involved in sophisticated neuropsychological tasks and

undergo modern technical examinations such as PET and functional MR scans, or event-related potential studies. The experimental subjects can participate in tests before, during, and after the effect of the drug has faded. This approach allows intra-individual comparisons, thus minimizing the variability of data. These advantages can lead to important insights into the nature of psychotic processes.

From the methodological point of view, therefore, the model psychosis strategy offers an excellent opportunity for studying the shift from normal consciousness to the psychotic state both psychologically and neurobiologically. The model psychosis is a potential tool for validating basic neurobiological concepts thought to be related to the endogenous psychoses. However, it is most important to remember that the model psychosis is not meant as a model for schizophrenia as a disease. The model goes beyond nosological boundaries and is intended as a model for acute psychotic episodes with prominent positive symptoms.

Furthermore, taking into consideration the phenomenological and neurobiological heterogeneity of schizophrenic patients and the fact that schizophrenia is more a concept than a natural disease entity, any research approach looking for specifically „schizophrenic" disturbances is bound to miss its target. This principal methodological fact is sufficient to explain many of the contradictory findings in biological schizophrenia research.

Last not least, it is obviously impossible to obtain an adequate animal model for such complex alterations of the mind as psychosis. If we decide that we need models for the investigation of psychosis-related neurobiological phenomena, then we have to add human models to the animal models that are used in research.

The Psychedelic Drug-Induced "Model Psychosis": Is it an Adequate Model for Psychosis?

The decisive question is whether psychedelically induced states are adequate models for psychosis.

The criticism that is most frequently heard (see, for example, Hollister's comments in the 1960 s) can be summarized in a few statements: a typical psychedelic state presents with qualitative alterations of consciousness with mainly visual perceptional phenomena, synesthesias, complex changes in time, space, and body apperception, disturbances of the experiencing self and variable changes in thought and emotional processes. Ego-control and reality-adjustment is usually preserved, i.e., the consumer of a hallucinogenic substance knows that he is experiencing a psychedelic state and that his perceptions are not real. On the other hand, endogenous schizophrenic patients mainly present with acoustic perceptional disturbances, delusional phenomena, loss of reality adjustment, formal thought disorder, and negative symptoms such as social withdrawal, passivity, lack of interests, blunted affect and emotional responsivity. In other words, the two states are more dissimilar than alike (*Hollister*, 1962; see Table **1**).

However, there are detailed clinical descriptions indicating the presence of „psychedelic", „dream-like" states with disturbances of visual perception, synesthesias, alterations in time and space perception and ecstatic-transcendental feelings in the initial acute stages of endogenous psychoses (*Beringer*, 1927; *Freedman* and *Chapman*, 1973; *Bowers* and *Freedman*, 1966; *Chapman*, 1960; *Gouzoulis* et al., 1994). As pointed out by early researchers such as *Beringer* (1927) and *Stockings* (1940), these subjective experiences cannot be observed directly and may be easily overlooked if no explicit interview takes place after remission of the acute episode. The real frequency of such phenomena in endogenous psychoses may therefore be underestimated in general. On the other hand, psychedelically induced altered states of consciousness not only exhibit alterations in visual perception, but also distortions of acoustic perception and acoustic hallucinatory phenomena (*Stockings*, 1943; *Leuner*, 1962). Moreover, reading the early, detailed studies and papers on hallucinogenic effects, one finds descriptions of withdrawal, blunted affect, and passivity, which resemble negative schizophrenic symptoms, as typical of the psychedelic state (i.e., *Beringer*, 1927). These phenomena may be even more frequent with atypical hallucinogens of the PCP type. However, in our experience, they are also frequent after classic hallucinogens such as psilocybin. *Beringer* (1927) described passivity as a core feature of the mescaline state. Last not least, the extent of ego-control, i.e. of insight into the artificial nature of the experience, varies in the psychedelic state. Vulnerable individuals may lose control and become psychotic even after ingestion of relatively low doses of psychedelics, such as the doses commonly taken for recreational use. With high doses, the ability to integrate the experience and preserve mental control diminishes in most humans, resulting in severely paranoid and even quasi-catatonic states (*Leuner*, 1962). In addition, if somebody is given psychedelics without his knowledge, then he cannot recognize the artificial nature of his state. When such experiments were performed, the effects were sometimes indistinguishable from acute paranoid-hallucinatory psychoses (*Fishman*, 1983). The situation of a patient with initial acute psychosis is comparable with that of somebody who has ingested psychedelic drugs unknowingly. Both experience pervasive alterations of perception, thinking and affectivity and know nothing about the origin of these alterations. Knowledge of the artificial nature of the state is therefore not a valid criterion for distinguishing between acute endogenous psychoses and psychedelically induced altered states of consciousness.

In summary, there is sufficient evidence that psychedelically induced altered states of consciousness (ASC) very much resemble the acute stages of endogenous psychoses with prominent positive symptoms.

So far, little effort has been spent on the standardized assessment of typical quasi-psychedelic phenomena in endogenous psychoses. The only study of schizophrenic patients that we are aware of (*Schroeter-Rosendahl*, 1980) demonstrated a coincidence between the clinical phenomena of the acute psychotic episodes and the items of the APZ (Abnormer Psychischer Zustand = Altered State of Consciousness = ASC), a questionnaire for the assessment of psychedelically induced states and other ASCs (*Dittrich* et al., 1985, 1998). During recent years, we have performed systematic studies with acute endogenous psychotic patients using the same questionnaire (*Gouzoulis-Mayfrank* et al., submitted). The results

confirm the findings of *Schroeter-Rosendahl* (1980) and extend their validity to schizoaffective and schizophreniform disorders. These data thus provide an additional argument supporting the comparability of ASCs of healthy humans and acute psychotic episodes.

One extremely interesting question is whether different psychedelic states might be models for different endogenous psychotic subsyndromes. This is not true for the classic hallucinogens such as mescaline, LSD, and psilocybin. They all induce similar states in humans, despite their differences in chemical structure. All classic hallucinogens probably act through direct mechanisms at the 5-HT_{2A} receptor site. The PCP and ketamine states may serve as more adequate models for chronic psychotic stages with prominent negative symptoms (*Abi-Saab* et al., 1988). Finally, the psychological profile of ecstasy (MDMA) might resemble more the phenomenology of atypical psychoses with prominent emotional and fewer perceptional symptoms (*Nichols*, 1986, *Gouzoulis-Mayfrank* et al., submitted). These issues still have to be clarified in future studies.

Conclusions

The present article summarizes several methodological arguments for the traditional approach of the experimental, psychedelic drug-induced, model psychosis strategy. This strategy offers a valuable tool for the investigation of psychosis-related phenomena using modern psychological and biological techniques.

The model psychosis paradigm is potentially valuable as a way of validating basic neurobiological concepts thought to be related to schizophrenia. With regard to standardization and control, such experimental studies with healthy volunteers have advantages over clinical studies with psychotic patients. They move a step nearer to symptom-oriented or syndrome-oriented biological research in psychiatry and explore phenomena related to psychotic subsyndromes which are more likely to present with biological homogeneity than endogenous patient samples.

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