Methodological Issues of Human Experimental Research with Hallucinogens

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Human experimental research with hallucinogenic drugs is potentially able to identify linking variables between the psycho(patho)logical conditions and neurobiological alterations involved in both pharmacologically induced and naturally occurring acute psychotic states. A number of methodological aspects should be considered when planning modern experimental studies with hallucinogenic drugs. The issues of subject selection, repeated measures, and adequate control groups are discussed in this paper. Examples of recent experimental studies are presented which take these aspects into account. The first study examined psychopathological changes, facial expression and semantic priming effects during a psilocybin-induced state. In the second study, semantic priming effects after intake of psilocybin, 3,4-methylenedioxyethylamphetamine (MDE), and d-methamphetamine were investigated. Results confirmed time-dependent effects of psilocybin and the restriction of increased priming effects in the psilocybin group.

Introduction

Human experimental research with hallucinogenic drugs is becoming a crucial part of contemporary biological psychiatric research. Aside from its value as a basis for addiction research, it may provide us with important insights into basic brain mechanisms involved in normal and pathologic mental conditions such as the naturally occurring "endogenous" psychotic states. Furthermore, it may enable us to identify linking variables between psycho(patho)logical conditions and neurobiological alterations (*Callaway*, 1992). The history and rationale of hallucinogenic drug research in psychiatry is summarized elsewhere in this issue (*Gouzoulis-Mayfrank* et al., 1998).

Despite the controversial nature of hallucinogenic drugs, we have witnessed an encouraging renewal of human experimental research during the last 10 years. Recent work has been performed both with classic hallucinogens such as mescaline, psilocybin and dimethyltryptamine (DMT) and with a phencyclidine congerer, the dissociative anesthetic ketamine. Studies with the NMDA-antagonist ketamine have mostly been performed within the framework of the model psychosis paradigm and the glutamate hypothesis of schizophrenia (for reviews see: *Gouzoulis-Mayfrank* et al., *Hermle* et al., *Vollenweider, Abi-Saab* et al., 1998). In this paper we will focus on some methodological aspects of human experimental research with hallucinogens and related substances.

The Selection of Subjects for Hallucinogenic Drug Experiments

The first methodological issue concerns the selection of experimental subjects. In the USA, DMT and methylendioxymethylamphetamine (MDMA) experiments have been performed with "experienced users" (*Strassman* and *Qualls*, *Strassman* et al., 1994; *Grob* et al., 1996). In Germany, hallucinogen experiments have mostly been performed as "self-experiments" by physicians and psychologists, who had only minimal or no previous experience with drugs. These differences are a result of the divergent traditions and past histories of research as well as of the different ethical considerations in the two continents (*Strassman*, 1995).

Nevertheless, the degree of familiarity with drug effects might influence both psychological and neurobiological effects: therefore, more uniformity in subject selection criteria would be desirable. In our view, persons with a few past experiences but no regular use of drugs are ideal subjects for hallucinogenic drug sessions: on the one hand, they are less at risk of being overwhelmed by the possibly dramatic effects and have a "bad trip" than completely drug-naive volunteers. On the other hand, their reactions are not substantially predetermined by frequent past experiences. A good alternative to this selection process is to run a preliminary drug session without technical examinations for the subjects to become familiar with the drug effects. In Switzerland, this procedure is followed by *Vollenweider* et al. (1997). Nevertheless, careful selection, screening, preparation, supervision, and follow-up visits of subjects are important.

The Strength of Repeated Measures

A main methodological strength of the model psychosis paradigm with hallucinogenic drugs is the possibility of performing studies before, during, and after the intoxication period. Intraindividual controls can be obtained with this procedure and the variability of data can be minimized. However, hallucinogenic drug effects are variable across and within subjects and even within single sessions of one subject.

Distinct phases of the psychedelic state with different prevailing behavioral or psychopathologic phenomena and subjective experiences have been described in the older literature

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(*Heimann*, 1961). Thus, it may be difficult to link assessments made at different time points within a single drug session to each other. This problem can be dealt with experimental designs with multivariate repeated measures during the course of one intoxication period.

An example of such a study with a repeated measures design is described below: to investigate time-dependent effects of psilocybin in normals, a human behavior study was conducted applying a multimodal behavior analysis and physiological recordings (*Schneider* et al., submitted).

The subjects were 12 healthy physicians, all men, mean age 40±7.8 (±SD). Participants underwent comprehensive assessment procedures for medical, neurological, and psychiatric history, and results revealed them to be healthy, on no medication, and having no history of affective illness or schizophrenia in first-degree relatives. A laterality questionnaire revealed that 11 subjects were right-handed. Written informed consent was given by the participants before taking part in the study. Permission was obtained for the use of psilocybin in this study from the local IRB at the Medical School of the University of Tübingen and federal agencies.

Subjects received, in random order, a capsule containing either 0.2 mg/kg body weight of psilocybin (range: 12.5 – 17.5 mg) or placebo, on two sessions one to three weeks apart at approximately the same time of day (11.00 a.m.). Blood was drawn 11 times during the experimental session: – 5, 30, 45, 60, 80, 120, 165, 200, 240, 270, and 360 min. relative to the drug intake. The main metabolite psilocin was quantitatively analyzed in the blood plasma. Symptom ratings at – 60, 35, 65, 170, 300, and 360 min. included the Brief Psychiatric Rating Scale (BPRS; *Overall* and *Gorham*, 1962) as well as other scales not reported here.

For behavioral analysis a semi-standardized interview was recorded at – 25, 85, 185, and 330 min. Each subject was asked questions about his/her general well-being and how he/she was coping with his/her current situation. The interview lasted about three minutes. After the initial questions, a period of 2.5 minutes was taken for behavioral analysis. The reason for the late onset of the analysis was to ascertain that the participants had already adjusted to the experimental setting.

With small round stickers (diameter: 2.0 mm) attached to different regions of the face, the activity of facial movement was assessed with a computer-based analysis of facial action (*Schneider* et al., 1990, 1992). The specially constructed scanning unit had a resolution of 1024 × 2048 pixels (horizontal × vertical), and scanned 10 pictures per second. The yoked computer eliminated head movements and computed the X- and Y- coordinates for each facial action point with the help of four points of reference. The distance a point moved within the specified time was recorded and standardized (averaged across one second).

In this study we assessed the mobility of 12 facial action points: Four facial action point stickers were placed 1 cm above the inner/outer right and left eyebrow respectively, two 3 cm below the outer edges of the lower eyelid, two about 1 cm away from the nostrils, two close to the lip corners as well as about 1 cm above and below the midline of the mouth.

In addition, a lexical decision paradigm, similar to previous studies, was used in a computerized version (*Spitzer* et al., 1993). The subject had to decide whether a given string of characters was a word or not. In order to investigate how far semantic activation spreads, word pairs of different semantic distance were presented 200 ms apart. In this paradigm, the first word is called the prime and the second word the target. The effect of the semantic relation between prime and target on the reaction time (RT) of the lexical decision of the target is the critical variable in this task. RT is normally shorter when prime and target are semantically related (i.e. chair – table) compared to unrelated pairs (i.e. chair – cloud). This effect is called semantic priming (SP). When the relation between prime and target is indirect (i.e. chair – (Table) – leg) RT is generally slightly shorter than with unrelated pairs, but longer than with directly related pairs. This minor effect is called indirect semantic priming (ISP). The lexical decision task was performed at – 30, 50, 150, and 220 min. Mean SP and ISP were calculated both in milliseconds and as percentage scores. Due to technical problems, it was only possible to report results of only eight subjects here.

Between subjects, maximal plasma concentration (c_{max}) of psilocin yielded a wide deviation of 7.5 to 19 ng psilocin/ml plasma with a significant peak at one hour after drug intake (Fig. **1**).

Psychopathology corresponded very well with increased plasma levels of psilocin, facial action, and cognitive disturbance. With psilocybin, subjects experienced significant psychopathology, as illustrated in Fig. **1**. The BPRS-summary score reached a maximum at 170 min. (34.5 ± 9.0 SD) with formal thought disorders as the most prominent feature, beginning approximately 45 min. after drug intake (max at 65 min.: 9.6 ± 3.5). Three hours later, self-reported affect and observer rated anergia, anxiety, and depression were at a maximum.

In terms of facial expression, the drug effect began by showing facial movement characteristics similar to acute schizophrenics studied earlier (*Schneider* et al., 1992). When averaged across 12 facial action points, the initially significant increase was later followed by decrease in facial action over the time of the experiment, relative to placebo condition (mm/s) : – 25 min.: 0.45 ± 1.85; 85 min.: 1.64 ± 1.37, 185 min.: 0.45 ± 1.11, and 330 min.: – 0.31 ± 1.40. With changed affect, facial action was reduced.

While there was a nonsignificant increase in indirect semantic priming under placebo, the increase under psilocybin was significant. Data suggest an increased availability of remote associations under psilocybin. This finding may be interpreted as a confirmation of the anecdotally reported "consciousness broadening" effects of hallucinogens. Alternatively, it may be interpreted as a decreased ability to use contextual information for the focusing of semantic processing (*Spitzer* et al., 1996)

With the application of a multimodal behavior analysis and physiological recordings, this study showed time-dependent effects of psilocybin on healthy subjects, as was described

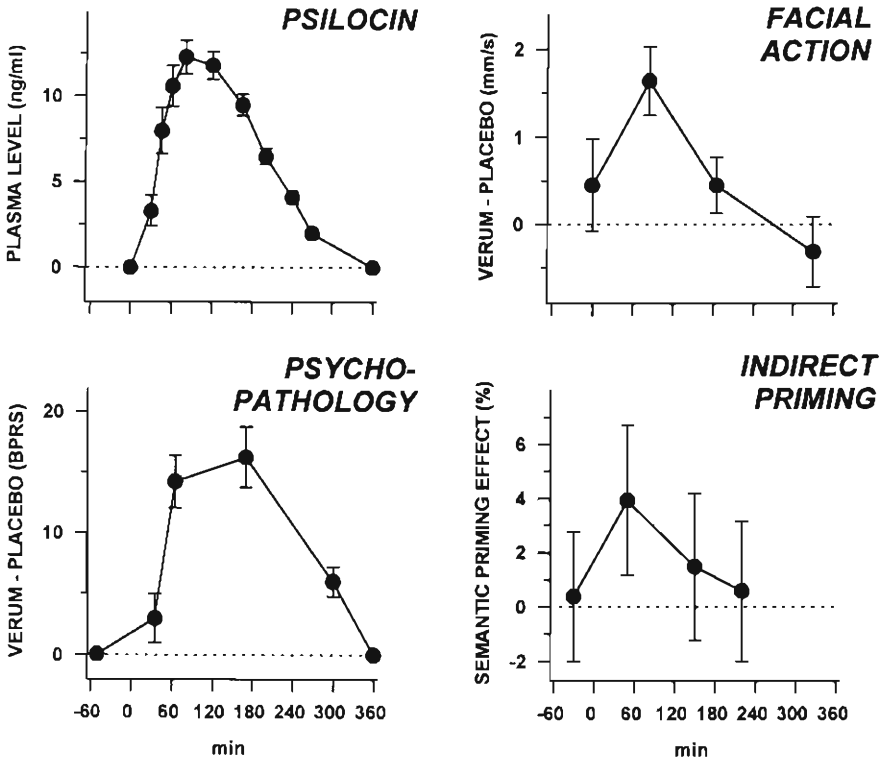

Fig. 1 Blood level of psilocin, facial action intensity, psychopathology (BPRS, summary score), and indirect priming effect in healthy subjects, receiving 0.2 mg/kg body weight psilocybin (±SE). 0 corresponds to the drug intake. Scores are presented relative to placebo condition.

earlier (*Heimann*, 1961). Measurements of the BPRS revealed a prominent covariation between plasma levels of psilocin, the main metabolit and psychopathology. At peak plasma level, thought disorders and cognitive disturbances were at a maximum. With a more depressive and anhedonic affect at the end of the study, the initially increased facial action manifested a decrease and indirect semantic priming returned to the predrug level.

The Need for Adequate Controls

The major methodological problem of adequate controls for hallucinogen experiments has already been discussed in the older literature. The effects of hallucinogenic drugs are so pronounced that blinding in placebo-controlled experiments cannot be warranted. Therefore, designs with "active placebos" exerting at least some peripheral autonomic effects, but lacking effects on the central nervous system, are desirable. On the other hand, the psychological effects of hallucinogenic drugs are complex and include alterations in perception, mood, drive, and cognition. Accordingly, it is difficult to link neurobiological effects to distinct psychological components, making designs that indude related substances with predominantly stimulant or emotional effects reasonable. Typical stimulants such as d-amphetamine and d-methamphetamine are suitable control substances for experimental purposes. Entactogens (3,4-Methylenedioxymeth-amphetamine = MDMA and the MDMA-like substances MDE and MBDB) typically induce a more subtle state with predominantly pleasant emotional effects, but have also some hallucinogenic and stimulant properties (*Grob* et al., 1996; *Gouzoulis-Mayfrank* et al., 1996). Therefore, they occupy an intermediate position between hallucinogens and stimulants and constitute a further reasonable control group for hallucinogen experiments.

This principle of multiple drug controls was applied in a recent double-blind study conducted by our group. Thirty-two healthy volunteers (physicians and psychologists, mean age: 34, range: 27–47) participated after undergoing screening procedures similar to those in the above mentioned psilocybin study. They received p.o. either the typical hallucinogen psilocybin (0.2 mg/kg, n = 8), an entactogen (2 mg/kg MDE, n = 8), a stimulant (0.2–0.4 mg/kg d-methamphetamine, n = 8), or placebo (PLA, n = 8) in a randomized order. The doses used in this study are typical recreational doses that induce significant, but not extremely strong effects in most subjects. Assessments included standardized psychometric measures, assessments of semantic priming effects, covert orienting of attention and working memory, evaluation of regional cerebral metabolism using positron emission tomography (PET), assessments of neuroendocrine effects and of sensorimotor gating (prepulse inhibition of the acoustically elicited startle reflex).

The effects of the drugs on semantic priming are reported here. In the previous placebo-controlled study with psilocybin, we demonstrated a larger semantic priming and particularly a larger indirect semantic priming under psilocybin compared with the placebo condition (*Spitzer* et al., 1996). However, one might argue that this was due to unspecific influences such as general activation, tension, or emotional effects. We hypothesized that semantic priming (SP) and indirect semantic priming (ISP) are increased under psilocybin only; but not under MDE and methamphetamine. Subjects were administered equivalent versions of the lexical decision task one hour before ingestion and again about 90 minutes after ingestion of the respective drug. Mean reaction times (RT) were calculated for each subject and condition (unrelated, directly related, indirectly related word pairs). Semantic priming and indirect semantic priming effects were calcu-

lated as the difference of RT (SP = RTr–RTn, ISP = RTi–RTn) both in ms and as percentage values. Further analysis was performed by means of repeated measures analysis of variance and t-tests.

Psilocybin and MDE caused substantial overall slowing of RTs. Variance of the data was strong, especially in the psilocybin and MDE groups. Thus, differences in priming effects did not reach statistical significance across drug groups. However, there was a trend towards an increase in indirect priming after psilocybin ($P = 0.094$), but not after MDE or methamphetamine (Fig. 2). Inspection of the data of individual subjects revealed an outlier with a dramatic decrease in indirect semantic priming after administration of psilocybin. After elimination of this outlier, the increase in indirect semantic priming after psilocybin was significant. Moreover, after discarding the data of this proband indirect semantic priming correlated highly with psilocin plasma levels (AUC psilocin and indirect semantic priming: $r = 0.943$). In conclusion, the data demonstrate a trend toward increased indirect semantic priming after psilocybin, but not after methamphetamine and MDE.

On the basis of studies with schizophrenic patients increased indirect semantic priming has been linked with formal thought disorder (*Spitzer* et al. 1993). However, until now it has not been possible to conduct studies with schizophrenic patients and adequate clinical controls, such as patients in manic states. Our data suggest that increased indirect semantic priming is indeed restricted to the thought disorder occurring in endogenous schizophrenic and schizophreniform psychoses and the hallucinogenic drug-induced model psychoses. General activation and alterations of emotional processes occurring in stimulant and entactogen-induced states are not sufficient to alter formal thought to this extent. We hypothesize that this is also not the case in comparable, naturally occurring states in patients with major affective episodes.

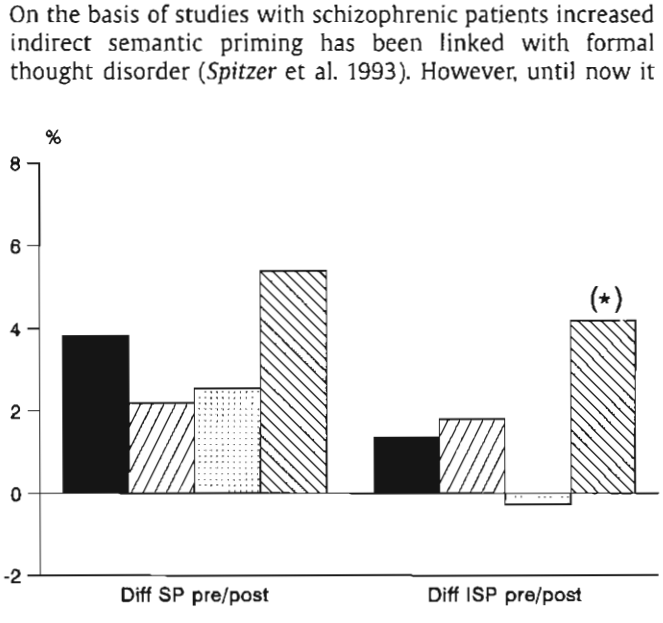

Fig. 2 Semantic priming and indirect semantic priming effects under psilocybin, MDE, d-methamphetamine, and placebo (each group; n = 8). Values represent the difference between predrug and postdrug effects. Priming effects are expressed as percentage values.

Future Directions of Human Experimental Research with Hallucinogens

From both the systematic and methodological point of view, the traditional approach of the experimental model psychosis offers a valuable tool for the investigation of psychosis-related phenomena with modern psychological and biological techniques.

The model psychosis paradigm is potentially able to validate basic neurobiological concepts thought to be related to the naturally occurring schizophrenia spectrum psychoses, such as hypofrontality, temporal lobe dysfunction, associative and working memory involvement, attentional deficits, etc. PET, SPECT and functional MR techniques are appropriate tools for the study of cerebral blood flow and metabolism in the hallucinogen-induced psychotic states. Suitable behavioral tasks for activation of specific regions of interest thought to be involved in schizophrenic processes should be used in combination with these modern functional imaging techniques and electrophysiological studies (ERP, MEG studies). As regards standardization and control, such experimental studies with healthy volunteers will have advantages over clinical studies with psychotic patients. According to the vulnerability model (*Zubin* and *Spring*, 1977) research has to go beyond diagnostic categories such as "organic" or "endogenous". Experimental studies are moving a step nearer to symptom or syndrome-oriented biological research in psychiatry.

The aim of these studies is to understand the basic mechanisms of action of hallucinogenic drugs and extrapolate the mechanisms in functional psychoses. Methodological considerations such as those discussed in this paper should be taken into account in present-day research. By means of carefully designed experiments we may be able to learn more about the biological nature of mental desintegration in the acute, naturally occurring psychoses.

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