Blood Flow and Cerebral Laterality in the Mescaline Model of Psychosis

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The psychological, neuropsychological, and neurometabolic effects of the hallucinogenic agent mescaline were investigated in 12 normal male volunteers. Between 3½ and 4 hours after drug intake, mescaline produced an acute psychotomimetic state, as measured by the BPRS and PDS-P. The APZ questionnaire revealed the specific effects of mescaline in the visual system. Neuropsychological effects were studied with a face/non-face decision task with known right hemisphere advantage, in which mescaline induced a decrease in functioning of the right hemisphere. In functional brain imaging using SPECT, mescaline produced a "hyperfrontal" pattern with an emphasis on the right hemisphere, which was correlated with mescaline-induced psychotomimetic psychopathology. Our findings question the validity of the concept of hypofrontality as an explanation for acute psychotic symptomatology.

Introduction

Hallucinogenic agents such as mescaline can produce psychosis-like syndromes in humans that resemble the initial manifestations of schizophrenia. Experimental investigations of peyote in volunteers were reported for the first time in 1895 by *Prentiss* and *Morgan*. From the turn of the century to World War II, a number of thorough investigations on mescaline were conducted (*Heffter*, 1898; *Knauer* and *Maloney*, 1913). In particular, the psychopathological effects of mescaline were described in unsurpassed detail by *Beringer* (1927). *Beringer* was one of the most important pioneers of experimental psychiatry in Germany. In the 1920s *Beringer* conducted a series of experiments with 60 volunteers using mescaline under controlled conditions. The term "artificial model of psychosis", later abbreviated as "model psychosis" has its origin in the early work of *Beringer*.

Hallucinogens, such as 3,4,5-trimethoxy-phenalkylamine (mescaline), LSD, psilocybin, etc., were widely used to produce changes in perception, thought and mood, which were thought to resemble schizophrenia to some extent (*Hermle* et al., 1992a, b).

In the last 25 years we have witnessed a tremendous increase in the number and versatility of methodological tools, whereas the subject of psychiatric inquiry has been restricted to spontaneously occurring (endogenous) psychotic states. One way of validating basic concepts such as "hypofrontality", "vulnerability", "limbic-system-involvement", etc. is to look for parameters indicative of these concepts in experimentally induced psychotic states, using psychoactive substances.

Although we are aware of the dissimilarities between experimentally induced psychotic states and schizophrenia, several authors have questioned the arguments usually given to support such a "disparate" view (*Chapman*, 1966; *Hoffer* and *Osmond*, 1966; *Winters*, 1974; *Gouzoulis* et al., 1994).

Notwithstanding the differences, the similarities between substance-induced schizophrenic-like states and (endogenous) schizophrenia quite possibly point to similar pathogenetic pathways (*Vollenweider* et al., 1997). In line with the vulnerability model of *Zubin* and *Spring* (1977), we assume that various etiological factors may contribute to a psychotic state. Hence we believe that it makes sense to use findings and research strategies currently used for the investigation of schizophrenia to study experimental psychoses.

The aim of the present study is to shed some light on an experimental psychosis with the currently available psychopathological, neuropsychological, and biological assessment strategies.

In our investigation we refer to the following neuropsychological and neuroimaging findings in the research of schizophrenia:

There is strong evidence that schizophrenia is related to impaired hemispheric function. Since *Flor-Henry's* (1969) proposal of left-hemisphere dysfunction in schizophrenic-like psychoses in epileptic patients, researchers have tried to assess right and left-hemisphere functions in patients with schizophrenia. Using divided visual field studies, many of them have found a dysfunction of the left hemisphere (*Beaumont* and *Dimond*, 1973; *Tomer* et al., 1982). A few authors have claimed a dysfunction of the right hemisphere (*Schweitzer*, 1978; *Venables*, 1984, *West*, 1984; *Cutting*, 1985/1990; *Oepen* et al., 1988). Others have found dysfunctions in both hemispheres: *Magaro* and *Page* (1983) and *Gruzelier* (1984) proposed that chronic schizophrenic patients or patients with mainly negative schizophrenia, mainly suffer from left-hemisphere dysfunction whereas acutely ill, productive schizophrenic patients with positive symptoms suffer from right hemisphere dysfunction. This considerable heterogeneity of findings in schizophrenic patients has been attributed to the heterogeneity of the symptomatology, as well as to the diversity of methods (see *Nasrallah*, 1986).

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The incidence of low cerebral blood-flow patterns in frontal regions in patients with schizophrenia led to the concept of "hypofrontality", in contrast to hyperfrontal blood-flow patterns in normal controls (*Brodie*, 1984). Researchers using Positron-Emission Tomography (PET) have been partly able to replicate "hypofrontality" as a major finding in schizophrenia (*Delisi*, 1986; *Buchsbaum*, 1987; *Siegel* et al., 1993). Others did not find evidence of hypofrontal patterns in schizophrenia (*Sheppard*, 1983; *Wiesel*, 1985; *Gur*, 1987). Small sample sizes, the variability of the schizophrenic syndrome and, in particular, different testing conditions (e.g., eyes closed or open, cognitive behavior of patients during neuroimaging investigation, patients with or without neuroleptic treatment, different image processing equipment, and a variety of tracer substances) may be responsible for these differences (*Vollenweider* et al., 1997a).

In accordance with findings of right-hemisphere (RH) dysfunction in schizophrenia we hypothesized that the RH function is impaired during the course of the experimental psychosis.

Methods

Subjects

Twelve physically and mentally healthy male volunteers (age ranging from 27 to 47 years; mean: 35.5 years) were included in an open study. Each volunteer gave written informed consent. Subjects were carefully selected one to two months before the experiment by clinical interviews and personality inventory (Freiburg Personality Interview, FPI, *Fahrenberg* et al., 1984) to ensure that they had no personal or family history of psychiatric disorders in first degree relatives. All subjects had undergone an extensive physical screening program to exclude physical disorders. None of the subjects met the DSM-III-R criteria for alcohol or substance abuse. Two volunteers had taken tetrahydrocannabinol once or twice some years previously.

Each subject had been without any medication for at least two months prior to the study, and had not been subject to excessive caffeine intake or stressful lite events during the month prior to the study.

The participants of this study were all academics: nine physicians, one student and one engineer.

All volunteers were right-handed as determined by the Edinburgh Handedness Inventory (*Oldfield*, 1971). Laterality coefficients were + 80 and above.

Substances

3,4,5-trimethoxy-phenalkylamine (mescaline) was synthesized in the Institute of Pharmaceutics, University of Tübingen, FRG, and prepared as powder. Each volunteer received 0.5 g mescaline-sulfate with some liquid, a dose commonly taken for experimental use in previous years (see *Beringer*, 1927).

The study was approved by the local ethical committee at the University of Freiburg, FRG. Permission was obtained from the Federal Health Administration (BGA, Berlin) for the use of 6 grams of mescaline sulfate.

Psychometric Scales

All subjects were examined by one experienced psychiatrist and one psychologist. To evaluate the psychological effects at baseline (1 hour before substance intake), and $^1/_2$ hour, $1^1/_2$ hours, $3^1/_2$ hours and 7 hours after ingestion of mescaline the Brief Psychiatric Rating Scale (BPRS, *Overall* and *Gorham*, 1976) and the Paranoid Depression Scale (PDS, *von Zerssen*, 1986) were used (see *Hermle* et al., 1992).

In the days following the experiment subjects completed the Questionnaire for the Assessment of "Altered States of Consciousness" (APZ) with its dimensions Oceanic Boundlessness (OSE), Dread Ego-Dissolution (AIA), and Visionary Restructuralization (VUS) (*Dittrich* et al., 1985).

Neuropsychological test and neuroimaging procedures

Following each psychometric assessment, the subjects were required to perform a visual half-field task on a Gerbrands 3-channel tachistoscope. A face/nonface decision task with known right hemispheric (RH) affinity was used (*Regard* and *Landis*, 1986). Standardized faces and nonfaces were presented simultaneously on each side of a fixation point (Fig. **1**).

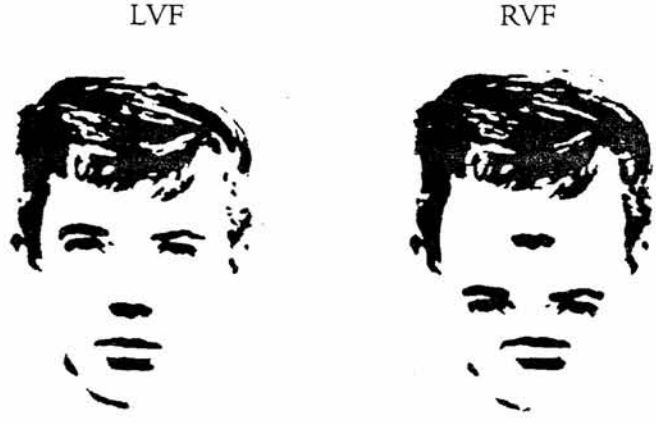

Fig. 1 Face/nonface stimulus material as used in the experiment.

In each trial, a fixation cross was shown first for 650 ms, followed by the face/nonface stimulus, showing a face and a nonface simultaneously in the right and left visual field, respectively. Exposure time was 60 ms. This was followed by the presentation of a mask (pattern of random lines and dots) for 6 s. The subjects had to press a lever ipsilateral to the target stimulus (i.e., face) with their index finger as fast as possible. The run consisted of 36 trials: 12 trials with targets (faces) in the left visual field (LVF), 12 trials with targets in the right visual field (RVF), and 12 trials with bilateral nontargets (nonfaces). The order of the trials was initially randomized, and then left constant for all subjects.

Single photon-emission computed tomography (SPECT) using ^{99}mTc-hexamethyl-propyleneamineoxime (HMPAO) displays

regional cerebral bloodflow (rCBF) directly (*Sharp* et al., 1986). As a lipophilic agent, HMPAO crosses the blood-brain barrier by passive diffusion and is retained intracellularly as a hydrophilic complex for several hours. Because of its long retention in brain tissue, HMPAO allows rCBF studies with the wide-spread rotating gamma camera system.

Four-and-a-half hours after mescaline intake, brain metabolism for each subject was investigated using ^{99}mTc-HMPAO SPECT. SPECT was performed 15 min. after an intravenous injection of 740 MBq ^{99}mTc-HMPAO under resting conditions (eyes closed, dim light).

For final evaluation 18 regions of interest (ROI) were drawn semiautomatically according to *Musalek* et al. (1988) and *Prodreka* et al. (1987). Transversal sections were reconstructed by a filtered back projection in 128 × 128 matrices. Following the filtering of projections, 18 ROIs were drawn in each hemisphere on 4 adjacent 22 mm-thick cross-sections.

For evaluation of relative regional cerebral blood-flow (rCBF) distribution in the brain, a regional index (RI, ratio between counts/voxel of one ROI and mean counts/voxel of all ROIs) was calculated.

SPECT scans produced under mescaline were then compared intraindividually with SPECT scans of the same subjects under control conditions, which were obtained 14 days prior to the study.

Experimental procedure

Fasted subjects arrived at the hospital at 7:30 and were examined one at a time. After baseline measurements had been obtained, mescaline was given orally with some liquid at 8:30. Thereafter, the subjects were allowed to drink water and to eat some fruit. Tests and assessments were carried out by an experienced psychologist. For the entire experimental session (10 hours) and the durarion of the drug effects (approximately 12 to 15 hours), respectively, subjects were under permanent supervision by either the psychologist or a psychiatrist.

In a separate experiment, the same procedure was performed without mescaline in a sex and age-matched control group of volunteers. Care was taken that the times of measurement were the same as in the first study.

Statistical analysis

The time-course psychometric data were analyzed by the Friedman Rang Analysis of Variance (ANOVA) for BPRS total score, anergy (ANER), anxiety/depression (ANDP), thought disorder (THOT), activity (ACTV), and hostility (HOST). To assess self-rating and observer rating, Pearson correlation was used to compare these two measures. The APZ questionnaire was analyzed by means of two-tailed Student's t-test.

Neurometabolic data were evaluated as follows: one ANOVA for repeated measurements for the combined ROIs in SPECT data was calculated with the intra-subject factors "anterior/posterior" (ANT POST), "left/right hemisphere" (LH RH), "with/without mescaline" (MESC). A separate ANOVA for repeated measures was calculated to compare cortical with subcortical (i.e., limbic) regions and "left/right" hemisphere. A repeated measures ANOVA with the group factor "with/without mescaline" and the intra-subjects factor "repetition" was decomposed for linear, quadratic, and cubic trends. Two-tailed significance levels of $p \leq .05$ were adopted (*Hermle* et al., 1992).

Results

Neuropsychological and psychopathological measures

Ingestion of 0.5 g mescaline resulted in psychotomimetic effects as well as in pronounced changes in hemisphere balance. With repeated testing, RH-performance (t_0–t_3) in the LVF deteriorated steadily as psychopathology increased (measured by BPRS and PDS; see Fig. **2**). The changes in asymmetry in hemisphere functioning across the five points of measurement (t_0–t_4) were not significant but there was a tendency towards significance (MANOVA; $F(4,44) = 2.3$; $p = .074$). At the same time LH-performance in the RVF improved to a level

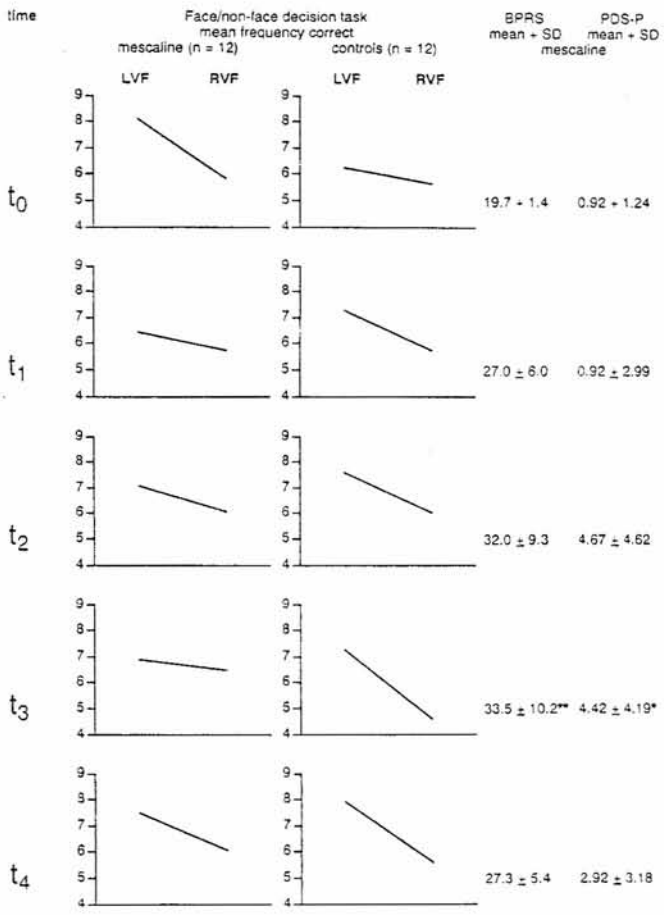

Fig. 2 Effects of mescaline in healthy male volunteers (n = 12), compared to a control group matched for age and sex without mescaline. Changes in tachistoscopic hemifield advantages. Total scores on BPRS, PDS-P (delusional ideas) are shown for baseline (t_0) and times t_1–t_4. Under mescaline, right hemisphere, left visual field (LVF) performance of correct face decision deteriorates steadily with increasing psychopathological features (assessed by BPRS and PDS) while right visual field (RVF) performance remained stable. Without mescaline, no decrease in LVF performance was noticed.

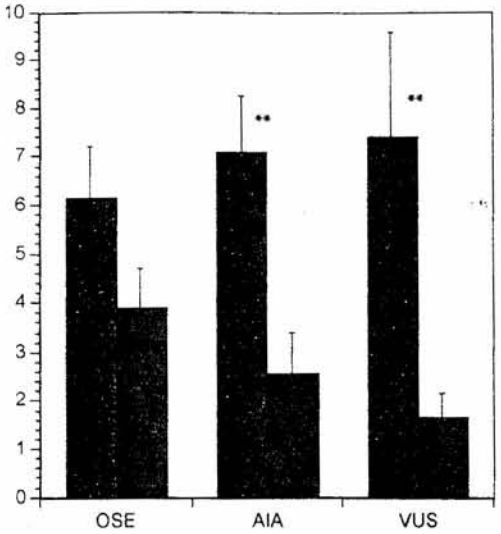

Fig. 3 Features of the APZ questionnaire mentioned under the influence of mescaline, MDE, and with placebo (see Table 1).
▒ mescaline, ■ MDE

of performance even exceeding that seen prior to the mescaline intake (t_0). At t_4 (430 min. after mescaline intake) hemifield asymmetry was back to baseline. Data from the control experiment with an age and sex-matched group without mescaline clearly demonstrate no decrease in LVF performance.

AI data on subjective drug experience under mescaline were compared with APZ data from a different placebo-controlled study on 3,4-methylenedioxyethamphetamine (MDE) (*Hermle* et al., 1992/1993). The differences between mescaline and MDE in the dimensions AIA ($df = 10$; $p = 0.005$) and VUS were highly significant ($df = 15$; $p = 0.000$). The difference in the APZ feature OSE was not statistically significant (see Table **1**).

Table 1 APZ scores (mean and standard deviation, SD) under mescaline (n = 12), as evaluated some days after drug intake, compared to 3,4 methylendioxyethamphetamine (MDE) and placebo

	Mescaline (n = 12) (mean ± SD)	MDE (n = 14) (mean ± SD)	Placebo (n = 14) (mean ± SD)
OSE	6.16 ± 3.63	3.92 ± 2.97	0.14 ± 0.36
AIA	7.08 ± 4.03	2.57 ± 3.08	0.07 ± 0.26
VUS	7.41 ± 3.65	1.64 ± 1.86	0.00 ± 0.00

Neurometabolic measures

Fig. **4** presents SPECT data of all 36 cortical and subcortical regions of interest with and without mescaline. Statistical procedures were performed on combined regions in order to evaluate anterior versus posterior (ANT/POST), left versus right (L/R), as well as limbic metabolic activity (see Table **2**). Fig. **5** summarizes the data "with mescaline" minus "without mescaline".

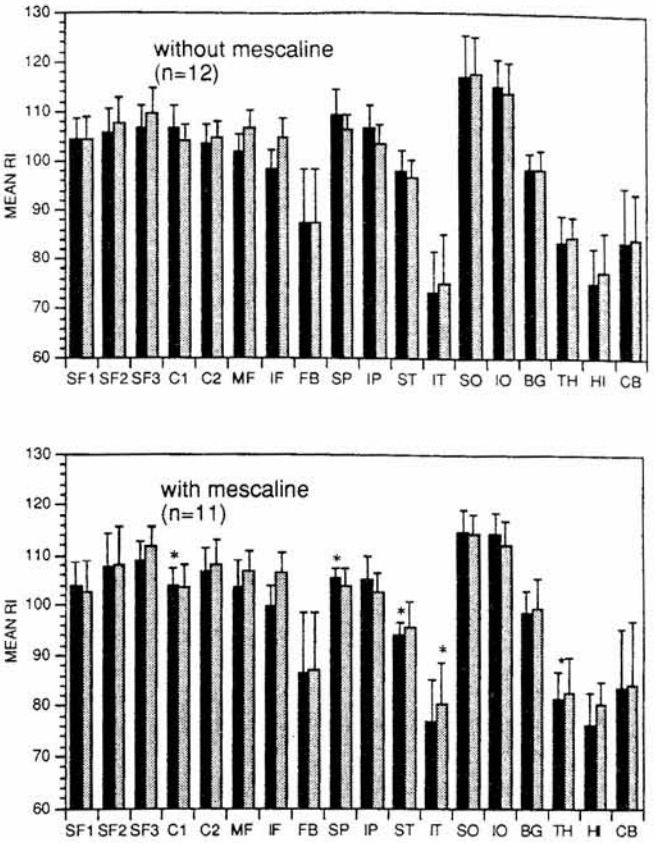

Fig. 4 ^{99m}Tc-HMPAO uptake in cortical and limbic ROIs with and without mescaline (n = 11 male volunteers; the data of one volunteer were lost for technical reasons). ROIs with significant changes under mescaline are marked with an asterix (*).
Cortical and limbic regions were combined as follows:
- Frontal cortical regions: superior-frontal (SF 1 – 3), central (C 1 – 2), medio-frontal (MF), inferior-frontal (IF), fronto-basal (FB)
- Posterior cortical regions: superior/inferior parietal (SP, P), superior/inferior temporal (ST, IT), superior/inferior occipital (SO, IO)
- Limbic regions: basal ganglia (BG), thalamus (TH), and hippocampus (HI)

RI = ratio between cts/voxel of one ROI and mean cts/voxel of all ROIs, ■ left hemisphere (LH), ▒ right hemisphere (RH)

In the left hemisphere a significant decrease in HMPAO uptake was found in the central region (C 1: $p = 0.014$), in the superior-parietal region (SP: $p = 0.039$), in the superior-temporal region (ST: $p = 0.013$), and in the thalamus (TH: $p = 0.011$). In the right hemisphere, a significant increase in HMPAO uptake was found in the inferior-temporal region only (IT: $p = 0.043$).

The interation ANT POST x L R is significant and points to different rCBF indices in anterior and posterior cortical regions. As illustrated in Fig. **5** and **4**, rCBF is more pronounced in right anterior cortical regions as opposed to higher rCBF in the left posterior cortical regions. This effect is independent of ingestion of mescaline.

The significant interaction MESC × ANT POST shows an increased HMPAO uptake under mescaline in the frontal cortical

Table 2 Cortical and limbic rCBF patterns with and without mescaline

Effects	Cortical F (1,10)	Signif.
L/R	3.98	0.74
ANT/POST × LI/RE	7.19	0.23*
MESC × ANT/POST	5.25	0.45*
MESC × ANT/POST × LI/RE	5.27	0.45*
Effects	**Limbic F (1,10)**	**Signif.**
L/R	4.34	0.64

ANT/POST: Anterior-Posterior Effect; L/R: left-right effect; MESC: Mescalin effect; *: $p < 0.05$

regions, while posterior cortical regions show a reduction in HMPAO uptake. The significant three-way interaction of MESC × ANT POST × LR reveals that in anterior cortical regions HMPAO uptake is more pronounced in the RH, while there is no difference in posterior cortical regions. In cortical and limbic regions, HMPAO uptake tends to be higher in the RH, and this tendency is also independent of mescaline intake.

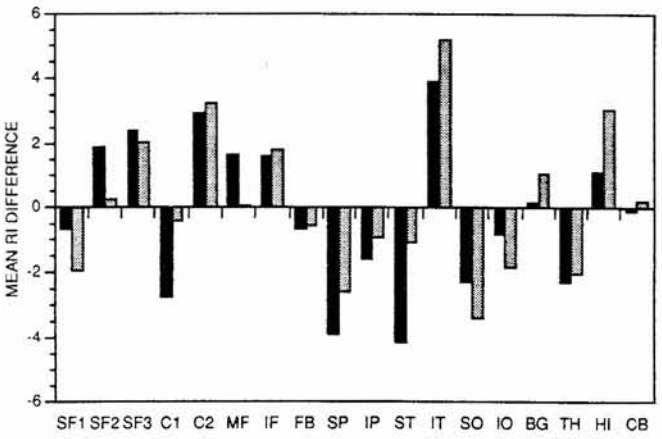

Fig. 5 Cortical and limbic rCBF patterns in 36 single ROIs; data "with mescaline" minus "without mescaline" (n = 11)
■ left hemisphere (LH), ▨ right hemisphere (RH)

Discussion

This study focused on the psychological, neuropsychological, and neurometabolic effects of mescaline in normal male volunteers. Significant psychotomimetic effects were revealed by the APZ questionnaire, an instrument which is unsurpassed with respect to its validity and reliability. Hallucinogenic effects mainly comprised dissolution of ego-boundaries, visual hallucinations and features of "oceanic boundlessness" often mixed with anxious passivity experiences. Compared to results from a study on MDE (*Hermle* et al., 1993), mescaline produced significantly more pronounced effects than MDE. While this general effect might be due to the particular doses used in the studies, the differential scores of the two substances in the three APZ scales reveal genuine differences in the psychological effects of the substances. In particular, mescaline is comparatively more effective in producing visual changes than MDE. It also induces more anxiety and passivity experiences.

Neuropsychological effects were studied with a face/nonface decision task with known RH advantage. Mescaline induced a decrease in RH function, and a slight increase in LH function. However, the mescaline-induced reversal of the normal hemifield asymmetry for the RH-specific task did not reach statistical significance ($p = .074$). In a separate experiment we were able to show that the differences in our neuropsychological measures were neither due to time-of-day nor to practice effects.

Functional brain imaging using ^{99}mTc-HMPAO SPECT showed a pronounced increase in rCBF under mescaline in brain metabolism in right anterior cortical regions. Hence, mescaline seems to produce a "hyperfrontal" pattern with an emphasis on the RH, which is correlated with mescaline-induced psychotomimetic psychopathology. No statistically significant influence of mescaline intake on the subcortical (limbic) system was found.

There is substantial evidence that other 5-HT2-receptor agonists such as psilocybin also induce a hyperfrontal activation pattern measured with PET and [18]-fluorodeoxyglucose (FDG) in 10 normal volunteers (*Vollenweider* et al., 1997). A marked increase in cerebral metabolic rate of glucose was found in the prefrontal cortex, the anterior cingulate, and the temporomedial cortex and the putamen. This finding is similar to the hyperfrontal activation pattern with mescaline, which also acts on 5-HT2 receptor.

From a general point of view, this study has systematic and methodological implications for research into experimental and endogenous psychoses.

Some of our brain imaging data seem to conflict with results from other groups of schizophrenic patients. The first results of brain imaging studies using xenon scintigraphy and PET in schizophrenic patients drew attention to "hyperfrontality" in schizophrenia (*Farkas* et al., 1984). Given large variety of existing functional brain imaging partly confirming and partly refuting these findings, we propose that in the next phase of research, multiple measurements of single subjects/patients should be taken. The contradictory results in the investigations of brain imaging hitherto are due to a number of factors inherent to different methods as well as the inhomogeneity of psychotic syndromes (*DeLisi* et al., 1986; *Kling* et al., 1986; *Gur* et al., 1987; *Leenders*, 1989).

The observation of hyperfrontality in the mescaline model psychosis corroborates other findings which, using SPECT, found positive symptoms in acute unmedicated first-episode schizophrenics (*Ebmeier* et al., 1993; *Parellada* et al., 1994), as well as a recent PET study of ketamine in normal volunteers (*Vollenweider* et al., 1997b).

This contradiction stems from the tendency to speak of schizophrenia without keeping in mind that we are dealing with a general term for very heterogenous psychopathological disorders. Therefore we can also conclude that various cortical and subcortical functional changes must occur. In

addition, hypo- and hyperfrontality are not specific findings but can be found in various mental states (e.g. hypofrontality can be found in depression and sleep). A further issue is that traditionally defined anatomical brain regions have been studied, which need not have any significance for functional relationships. To reduce these methodological problems, functionally related rather than anatomically related brain regions must be investigated in the near future.

Up to now it has only been possible to deduce a epiphenomenal theory from the PET and SPECT findings we have obtained. In other words, the changes with respect to rCBF and brain metabolism have no etiological significance.

The neuropsychological findings of the present study, i.e., the decrease in right hemisphere performance in the face/nonface decision task, concur with the results of earlier tachistoscopic testing with acute schizophrenic patients (*Oepen* et al., 1988). Acutely psychotic schizophrenic patients show a decrease in right hemisphere performance. This is in line with the abovementioned findings of a deficit in the right hemisphere or in both hemispheres in acute psychosis: the latter cannot therefore be interpreted as due to a purely left-hemisphere dysfunction. This finding needs to be discussed as follows: there is strong evidence that face/nonface recognition is processed in the temporal lobe, and not in the frontal lobe. Moreover, the relationship between cortical activation and neuropsychological performance is complex and not linear.

In conclusion, SPECT results and neuropsychological findings, if taken together, do not allow a consistent, unified interpretation. This may be due to the fact that the interpretation of rCBF data is itself controversial. It is unknown, for example, how cerebral blood flow correlates with neuronal activity in normal controls as well as under pathological circumstances.

Further intestigations with functional MRI will help to clarify the relationship between agents acting on neuropsychological performance and brian metabolism. The above described experimental method can be combined in intraindividual comparisons using visual, auditory, and cognitive stimulation paradigms.

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