Mescaline-Induced Psychopathological, Neuropsychological, and Neurometabolic Effects in Normal Subjects: Experimental Psychosis as a Tool for Psychiatric Research

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The psychological, neuropsychological, and neurometabolic effects of the hallucinogenic agent mescaline were investigated in 12 normal men who were volunteers. Mescaline produced an acute psychotic state 3½–4 hr after drug intake, as measured by the Brief Psychiatric Rating Scale (BPRS) and Paranoid Depression Scale (PDS). The Assessment of Altered States of Consciousness (APZ) questionnaire revealed specific effects of mescaline in the visual system. Neuropsychological effects were studied with a face/nonface ***decision task with known right-hemisphere advantage, in which mescaline induced a decrease of functioning of the right hemisphere. In functional brain imaging using single photon emission computed tomography (SPECT), mescaline produced a "hyperfrontal" pattern with an emphasis on the right hemisphere, which was correlated with mescaline-****induced psychotic psychopathology. Our findings question the validity of the concept of hypofrontality as an explanation for schizophrenic symptomatology. The study of psy-****choactive substances under controlled laboratory conditions has the methodological ad-****vantage of intraindividual control, and hence, minimal variability of data.*

Introduction

Hallucinogenic drugs produce qualitative and quantitative alterations of consciousness. In particular, the psychopathological effects of mescaline have been described by Beringer as early as 1927. In the 1950s and 1960s hallucinogens, such as 3,4,5- trimethoxy-phenethylamine (mescaline), lysergic acid diethylamide (LSD), PCP, etc. were widely used to produce changes of perception, thought and mood, which were thought to resemble schizophrenia to some extent (Hermle et al 1988). Advantages of the investigation of

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experimentally induced psychotic states include that they can be provoked in normal control subjects, who can be tested before, during, and after intake of the agent, providing the possibility of intraindividual comparisons. Moreover, in experimentally induced psychosis, primary pathological mechanisms can be more readily discerned from secondary reactions to, and coping mechanisms with, such pathology. Compared to samples of patients, the experimental approach leads to a much greater homogeneity of data, and hence to the possibility of more precise comparisons.

Although schizophrenia still is defined in purely psychopathological terms, research in this disorder concentrates on biological methods (in particular, neuropsychological and neurometabolical approaches), which to a large extent shaped current opinion on underlying pathology. 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. Research in experimental psychoses, however, came to a sudden end in 1966, when the use of hallucinogenic substances was severely restricted by law. Hence, 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 was restricted to spontaneously occurring (endogenous) psychotic states. 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.

Although we are aware of the dissimilarities of experimentally induced psychotic states and schizophrenia, several authors have questioned the arguments usually given to support such a "disparate" view. To begin with the strongest argument, auditory hallucinations, traditionally have been regarded as predominant in patients with (endogenous) schizophrenia, whereas disorders of visual perception are a predominant feature of organic, especially drug-induced psychoses. However, several authors have questioned the rare occurrence of visual hallucinations in schizophrenia as well a the scarcity of auditory hallucinations in experimental psychoses. They emphasized the similarity of perceptual disorders in incipient schizophrenia and drug-induced psychoses (Chapman 1966; Hoffer and Osmond 1966; Winters 1975).

The lack of insight in schizophrenia and the preserved insight in drug-induced psychotic states, often quoted as an argument in favor of differences, might represent nothing but a result of the experimental procedure: Persons who take drugs know about the causes of their psychological changes, whereas the patients suffering from endogeneous psychoses do not (cf. Fishman 1982). Lack of chronicity in experimental psychosis as well as lack of negative symptoms has also been stressed as a reason for differences between these states. However, this difference is easily accounted for by the differences in the duration of pathogenic factors: Whereas the effects of psychoactive drugs only last for hours, the supposedly present endogeneous process lasts for weeks and months.

Notwithstanding the differences, the similarities between substance-induced schizophrenic-like states and (endogeneous) schizophrenia quite possibly point to similar pathogenetic pathways. 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.

Our investigation relates to the following neuropsychological and neuroimaging findings in schizophrenia research:

1. 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. Many of them have found a dysfunction of the left hemisphere using divided visual field studies (Beaumont and Dimond 1973; Tomer et al 1982). A few authors have claimed a dysfunction of the right hemisphere (Schweitzer et al 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, respectively, 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).

2. 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 (Ingvar 1979; Brodie et al 1984). Researchers using positron-emission-tomography (PET) could partly replicate "hypofrontality" as a major finding in schizophrenia (Delisi 1986; Buchsbaum et al 1987). Others did not find evidence of hypofrontal patterns in schizophrenia (Sheppard 1983; Wiesel et al 1985; Gur 1987). Small sample sizes, the variability of the schizophrenic syndrome, and especially different testing conditions (e.g., eyes closed or open, patients with or without neuroleptic treatment, different image processing equipment, and a variety of tracer substances) may be responsible for these differences.

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. According to the concept of hypofrontality in schizophrenia we expected reduced perfusion of the frontal brain regions.

Method

Subjects

Twelve physically and mentally healthy men who volunteered (age: ranging from 27–47 years; mean:35.5 years) were included in an open study. Each volunteer gave written informed consent. Subjects were carefully selected 1 to 2 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 one or two experiences with tetrahydrocannabinol some years ago.

Each subject had been without any medication for at least 2 months prior to the study, and had not been subject to excessive caffeine intake and stressful life 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 higher.

Substances

Mescaline (3,4,5-trimethoxy-phenethylamine) was synthesized in the Institute of Pharmaceutics, University of Tübingen, Germany, and was 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 ethic committee at the University of Freiburg, Germany. Permission from the Federal Health Administration (BGA, Berlin) was obtained for the use of 6 g of mescaline sulfate.

Psychometric Scales

All subjects were examined by two experienced raters (one psychiatrist, one psychologist) using the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham 1976). In addition to Paranoid Depression Scale (PDS, von Zerssen 1986) was applied as a self-assessment inventory of paranoid and depressive symptoms to evaluate the psychological effects under baseline (1 hr before substance intake), and ½ hour, 1½ hr, 3½ hr, and 7 hr after ingestion of mescaline.

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

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 (see Figure 1).

In each trial, a fixation cross was shown first for 650 msec, followed by the face/nonface stimulus, showing a face and a nonface simultaneously in the right and left visual field. Exposure time was 60 msec. This was followed by the presentation of a mask (pattern

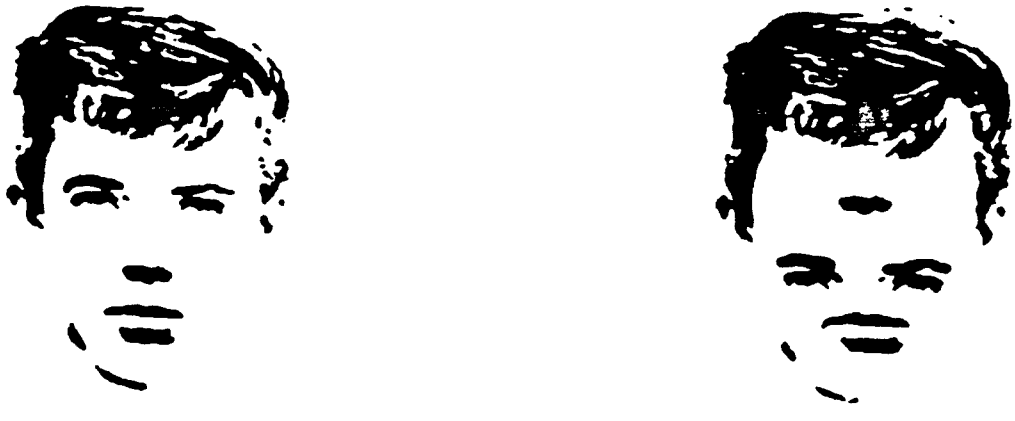

Figure 1. Face/nonface stimulus material used in the experiment.

SF 1-3 superior frontal cortex
FB fontal basal cortex
C 1-2 central cortex
IF inferior frontal cortex
SP superior parietal cortex
MF [illegible]
IP inferior parietal cortex
SO superior occipital cortex
ST superior temporal cortex
IT inferior temporal cortex
IO inferior occipital cortex
BG anterior basal ganglia
TH thalamus
HI hippocampus
CB cerebellum

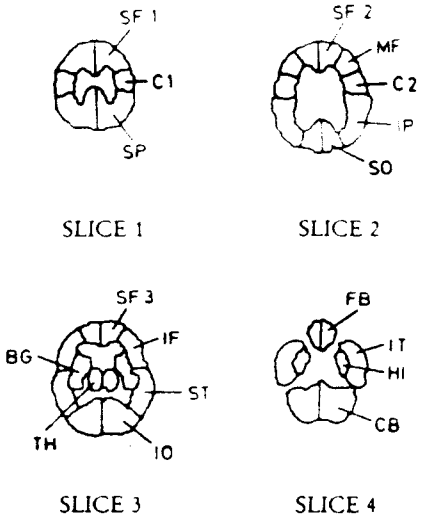

Figure 2. Position of 4 transversal SPECT slices. Each SPECT slice is 22-mm thick. Slice 1 starts 82 mm, slice 2-60 mm, slice 3-38 mm, and slice 4-16 mm above the canthomeatal line.

of random lines and dots) for 6 sec. 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 ^{99m}Tc-hexamethylpropyleneamineoxime (HMPAO) displays regional cerebral bloodflow (rCBF) directly (Sharp et al 1986). SPECT was performed with a single head rotating scintillation camera (Siemens ZLC-Digitrac Orbiter) and a dedicated computer system. As a lipophilic agent, HMPAO crosses the blood–brain barrier by passive diffusion and is retained intracellularly as a hydrophilic complex for several hr. Because of its long retention in brain tissue, HMPAO allows rCBF studies with the wide-spread rotating gamma camera system.

Brain metabolism for each subject was investigated using ^{99m}Tc-HMPAO SPECT 4½ hr after mescaline intake. SPECT was performed 15 min after an intravenous injection of 740 MBq ^{99m}Tc-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 Podreka 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 four adjacent 22-mm thick cross sections (see Figure 2).

For evaluation of relative 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

Fasting subjects arrived at hospital 7:30 AM and were studied one at a time. After baseline measurements had been obtained, mescaline was given orally with some liquid at 8:30 AM. 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 exper-

imental session (10 hr) and the duration of the drug effects (approximately 12–15 hr), respectively, subjects were under permanent supervision by either the psychologist or a psychiatrist.

In a separate experiment (Fünfgeld et al, in preparation) carried out later, the same procedure was performed without mescaline in a gender-matched 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- and observer rating, Pearson correlation between these two measures was used. The APZ questionnaire was analyzed by means of two-tailed Student's *t*-test. Neurometabolic data were evaluated as follows: The original 18 regions of interest in each hemisphere were collapsed to build up more global areas as indicated in the caption of Figure 5. This procedure led to the definition of "anterior versus posterior cortical," and "subcortical"—presumably limbic—areas, each separately for the left and right hemisphere. This procedure was adopted in order to avoid artifacts due to an overestimation of the precision of the scanning technology. One ANOVA for repeated measures for these combined areas was calculated with the within-subjects factors "anterior/posterior" (ANT POST), "left/right hemisphere" (LH RH), and "with/without mescaline" (MESC). A second ANOVA for repeated measures with the within subjects factors "cortical/subcortical" regions and "left/right" hemisphere was performed. Because neuropsychological data had been collected from two independent samples, a repeated measures ANOVA with the group factor "with/without mescaline" and the within-subjects factors "visual field" and "repeated trials" was performed. Variance of the factor "repetition" was decomposed for linear, quadratic, and cubic trends. Two-tailed significance levels of 0.05 were adopted.

Results

Neuropsychological and Psychopathological Measures

Ingestion of 0.5 g mescaline resulted in psychotomimetic effects as well as in pronounced changes of hemisphere balance. With repeated testing RH-performance (t_0–t_3) in the left visual field (LVF) deteriorated steadily as psychopathology increased (measured by BPRS and PDS; see Table 1). The ANOVA of neuropsychological performance was carried out over the trials t_0–t_3 (at t_3, the mescaline effect was as its maximum). The asymmetry patterns of subjects under mescaline as compared to control subjects without mescaline yielded a nonsignificant group effect [$F(1,22) = 0.13$; $p = 0.725$], indicating no difference in laterality of general performance. Decomposition of the repeated measures produced no significant linear, quadratic, and cubic trends over both groups. There was, however, a significant two-way interaction of "subject-group × quadratic trend of repetition" [$F(1,22) = 6.03 = p = 0.022$], indicating that differences between both groups in overall performance can be approximated by a quadratic function.

At t_3 LH-performance in the right visual field (RVF) improved to a level of performance even exceeding that seen prior to the mescaline intake (t_0). At t_4 (430 min after mescaline

Table 1. BPRS-Ratings (mean and SD) before and after Mescaline Intake in Male Volunteers

Time	Total score (mean ± SD)	ANER (mean ± SD)	ANDP (mean ± SD)	THOT (mean ± SD)	ACTV (mean ± SD)	HOST (mean ± SD)
t_0	19.6 ± 1.4	4.3 ± 0.7	4.8 ± 1.0	4.14 ± 0.3	3.4 ± 0.7	3.0 ± 0.0
t_1	27.0 ± 6.0	5.3 ± 1.4	8.5 ± 2.4	4.68 ± 1.0	5.1 ± 2.1	3.5 ± 1.0
t_2	32.1 ± 9.3	6.5 ± 3.1	7.5 ± 3.3	7.4 ± 4.7	6.9 ± 3.1	3.7 ± 0.8
t_3	33.5 ± 10.2	6.1 ± 1.4	6.5 ± 2.6	10.1 ± 5.6	6.8 ± 3.2	4.0 ± 1.4
χ^2	20.30	8.65	9.47	20.47	12.92	3.87
p	0.0001	0.034	0.023	0.0001	0.004	0.275

Results of Friedman rank ANOVAs comparing t_0–t_3 (df = 3).
ANER: anergia, ANDP: anxiety and depression, THOT: thought disorder, ACTV: activation, HOST: hostility.

intake) hemifield asymmetry was back to baseline. Data from the control experiment with an age-matched and gender-matched group without mescaline clearly demonstrate no decrease of LVF performance (see Figure 3).

The BPRS total score (see Table 1) changed significantly during the experiment (t_0–t_3; measured by Friedman rank ANOVA; df = 3; $\chi^2 = 20.30$, $p < 0.001$). The increase was most prominent in the subscales thought disorder (THOT; $p = 0.0001$) and activation (ACTV; $p = 0.004$). Furthermore, significant changes were found in the subscales of anergia (ANER; $p = 0.034$) and anxiety/depression (ANDP; $p = 0.023$). The self-rating score "Delusions" (PDS-P) was also significantly changed (Friedman rank ANOVA; df = 3; $\chi^2 = 8.82$, $p = 0.032$). The self-rating "Delusions" (PDS-P) and the observer rating in the BPRS scale "Thought Disorder" (THOT) correlated significantly at t_2 (Pearson correlation, 2-tailed: $r = 0.84$; $p = 0.001$) and t_3 ($r = 0.78$; $p = 0.002$) (see Table 2).

APZ-data on subjective drug experience under mescaline were compared with APZ-data from a different placebo-controlled study on 3,4-methylenedioxyethamphetamine (MDE) (cf. Hermle et al 1992). The difference between mescaline and MDE in the dimensions AIA (df = 20; $p = 0.005$) and VUS were highly significant (df = 15; $p = 0.000$). The difference in the APZ-dimension OSE was not statistically significant (see Table 3) (see Figure 4).

Neurometabolical Measures

Figure 5 presents SPECT data of all 18 single regions of interest as described in Figure 2. Statistical procedures have been performed on combined regions in order to evaluate anterior versus posterior, as well as limbic metabolic activity. Figure 6 summarizes the mescaline-induced changes. Statistical results are shown in Table 4.

The interaction ANT POST × L R is significant and points to different rCBF indices in anterior versus posterior cortical regions. As illustrated in Figure 7, 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 regions, whereas posterior cortical regions show a reduction of 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, whereas there is no difference in posterior cortical regions. In cortical and limbic regions

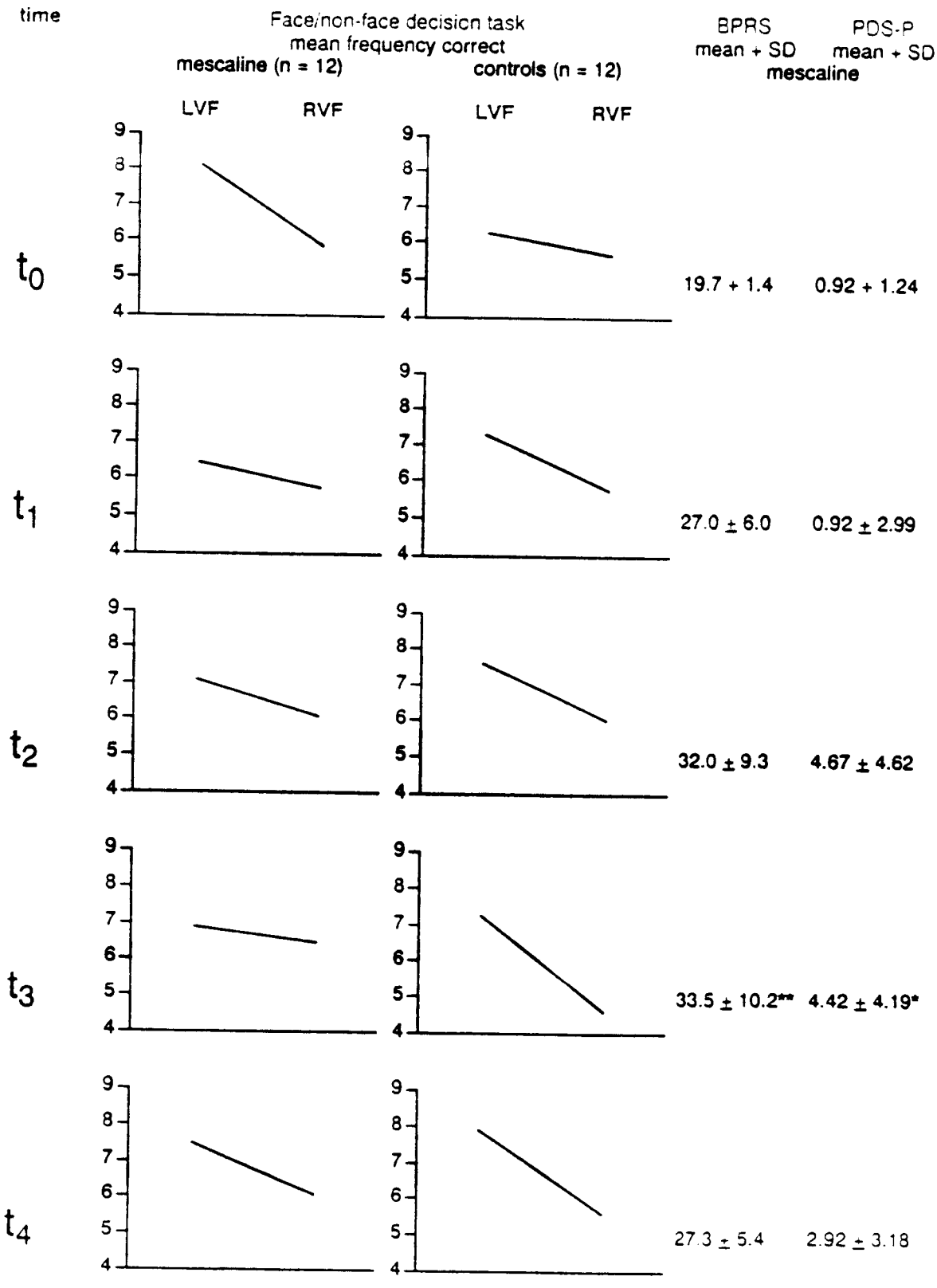

Figure 3. Effects of mescaline in healthy male volunteers (n = 12), compared with a control group matched for age and sex without mescaline. Changes of tachistoscopic hemifield advantages. Total scores of BPRS, PDS-P (delusional ideas) are shown for baseline (t_0) and times t_1–t_4. Under mescaline, 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 of LVF performance was noticed.

Table 2. PDS-Self-Ratings (mean and SD) before and after Mescaline Intake in 12 Male Volunteers

	PDS-P (mean ± SD)	PDS-D (mean ± SD)	PDS-Kv (mean ± SD)
t_0	0.92 ± 1.24	3.58 ± 3.96	10.90 ± 6.48
t_1	3.25 ± 2.99	6.16 ± 5.28	10.75 ± 6.51
t_2	4.67 ± 4.62	7.00 ± 4.69	8.75 ± 7.28
t_3	4.42 ± 4.19	7.16 ± 5.30	10.00 ± 6.94
χ^2	8.825	6.700	3.350
p	0.031	0.082	0.340

Results of Friedman rank ANOVAs comparing t_0–t_3 (df = 3).
PDS-P: delusions, PDS-D: depression, PDS-Kv: denial of illness.

there are tendencies of higher HMPAO uptake in the RH, which are also independent of mescaline intake.

Exploratory post hoc correlations between mescaline-induced changes in psychopathology (correct responses at t_3 minus correct responses at t_0, i.e., within-subject comparison) and mescaline induced changes in SPECT data (difference between RIs for each of the 18 ROIs per hemisphere in the mescaline group and the control group) and respective significance levels were calculated. Only 3 of these 36 correlations turned out to be significant: left SF3 ($r = 0.6274$; $p = 0.039$), left C1 ($r = -0.6674$; $p = 0.028$), and right ST ($r = 0.6433$; $p = 0.033$). If the necessary adjustment of the significance level for the number of significance tests (Bonferoni-adjustment) were carried out, none of these correlations would remain significant. Hence, we refrain from any further interpretation.

Discussion

This study is on the psychological, neuropsychological, and neurometabolic effects of mescaline in normal male volunteers.

As can be seen from the BPRS- and the PSD-P data, mescaline produced an acute psychotic state at t_3, that is, 3½ to 4 hr after drug intake. This is in line with well established findings about the course of mescaline intoxication (Beringer 1927; Guttmann and Maclay 1963). Significant psychotic effects were further revealed by the APZ questionnaire, an instrument that is unsurpassed with respect to its validity and reliability. The psychotic effects were mainly concerned with the dissolution of ego-boundaries, visual hallucinations, and dimensions of "oceanic boundlessness," often mixed with anxious passivity

Table 3. APZ-Scores (mean and 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

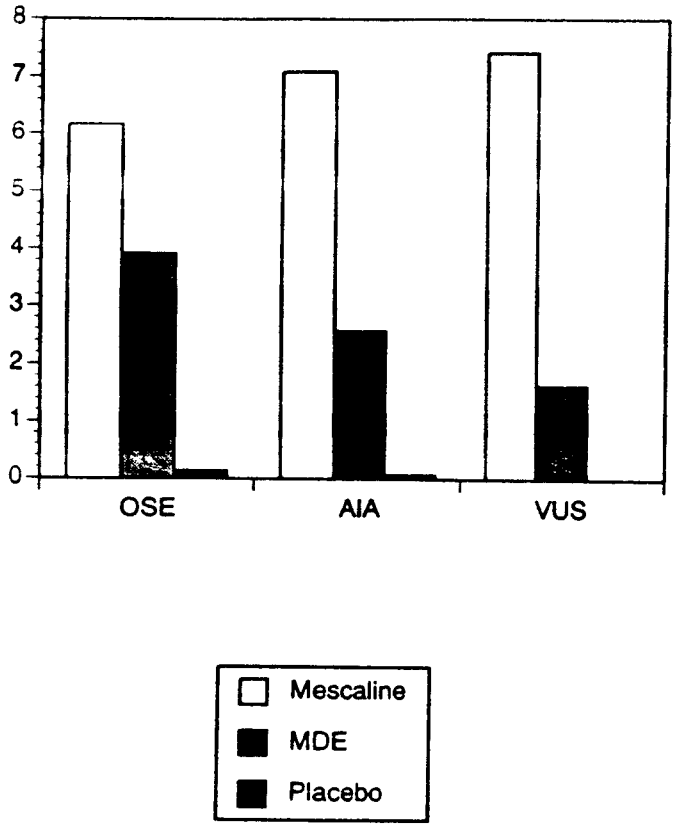

Figure 4. Dimensions of the APZ questionnaire under mescaline, MDE, and placebo (see Table 3).

experiences. Compared to results from a study on MDE (Hermle et al 1992), mescaline produced significantly more pronounced effects than MDE. Whereas this general effect could be caused by the particular doses used in the studies, the differential scores of the two substances in the three APZ scales reveal genuine differences on the psychological effects of the substances. In particular, mescaline is comparatively more effective in producing visual changes than MDE. It also induced more anxiety and passivity experiences.

Neuropsychological effects were studied with a face/nonface decision task with known RH advantage. Mescaline induced a decrease of functioning of the RH, and a slight increase of functioning of the LH. However, the mescaline-induced reversal of the normal hemifield asymmetry for the RH specific task did not reach statistical significance ($p = 0.074$). In a separate experiment carried out later (Fünfgeld et al in preparation) we were able to show that the differences in our neuropsychological measures were neither due to time-of-day or practice effects.

The significant two-way interaction of "subject-group × quadratic trend of repetition" may be caused by two reasons: Firstly, controls without mescaline build up an asymmetry pattern with an increasing LVF-advantage over repeated trials, with more or less stable RVF-performance. The repeated presentation of the face/nonface decision task can lead to the formation of what Kinsbourne (1970) called a "set," in the sense that in the ongoing trials facial material is more likely to be expected. The second reason for this interaction is obviously the degrading LVF-performance of the subjects under mescaline, which could be described counteracting the formation of such an expectancy set.

Functional brain imaging using ^{99m}Tc-HMPAO SPECT showed an increase of rCBF under mescaline in both anterior regions as well as an even more pronounced increase

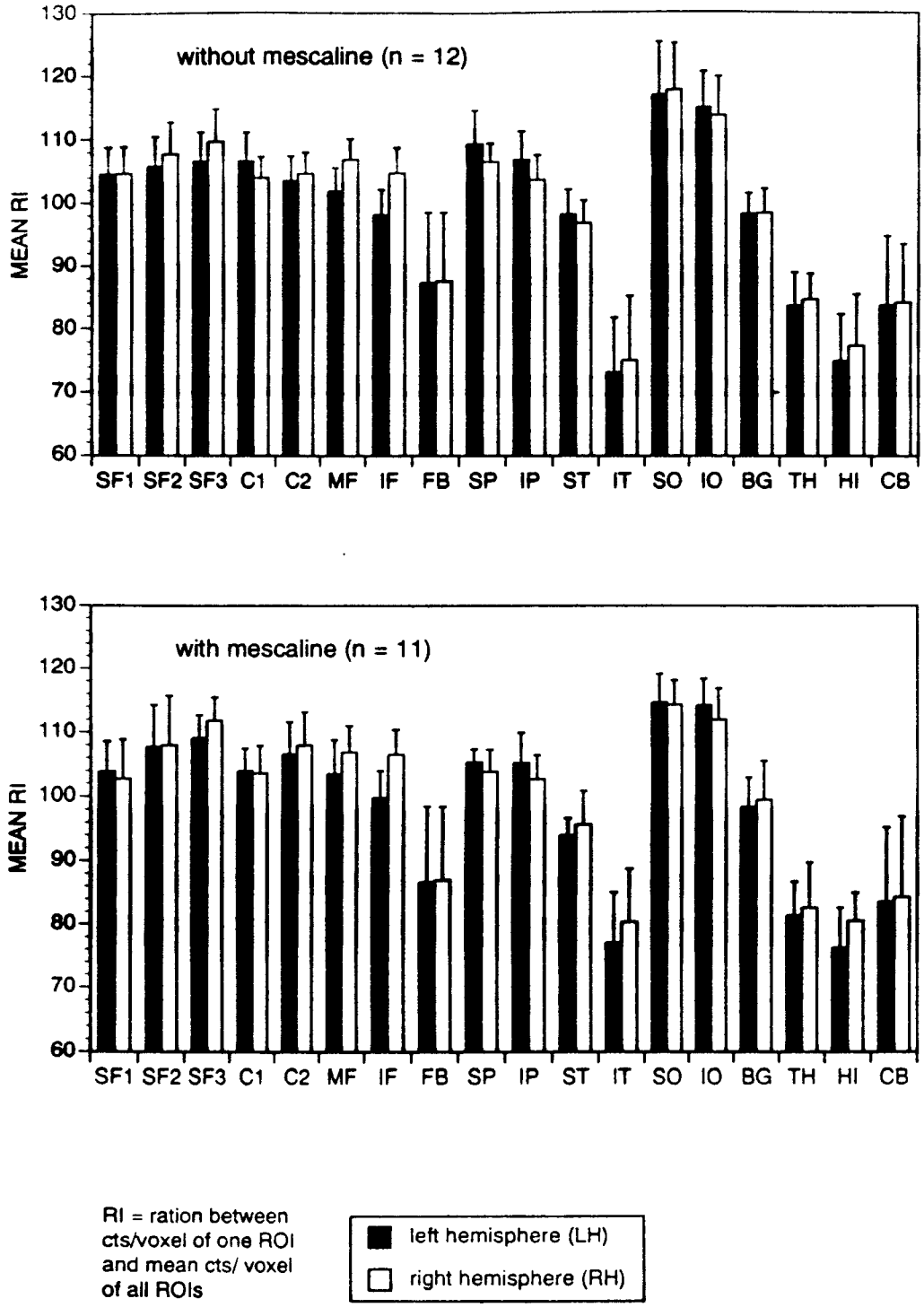

Figure 5. ^{99m}Tc-HMPAO uptake in 36 single ROIs with and without mescaline.

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 psychotic psychopathology. No statistically significant influence of mescaline intake on the subcortical (limbic) system was found.

From a general point of view, this study has systematic and methodological implications for research in experimental and endogeneous psychoses. Our brain imaging data seem to conflict, in part, with results from other groups on schizophrenic patients. First results

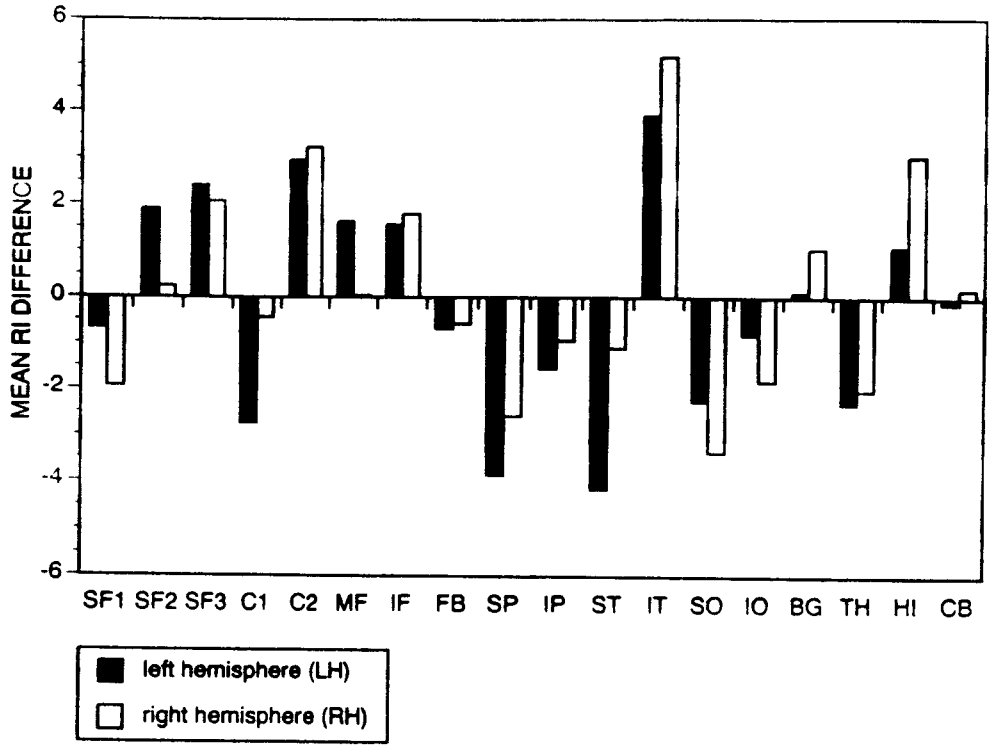

Figure 6. ^{99m}Tc-HMPAO uptake in 36 single ROIs; mescaline-induced changes (data "with mescaline" minus "without mescaline").

of brain imaging studies using xenon scintigraphy and PET in schizophrenic patients drew the attention to "hypofrontality" in schizophrenia (Ingvar and Franzen 1974; Farkas et al 1984). Taking into account the large variety of existing functional brain imaging partly confirming and partly refusing 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 earlier investigations of brain imaging are due to a number of factors inherent to different methods as well as the heterogeneity of psychotic syndromes (DeLisi 1986, Kling et al 1986; Gur et al 1987). Moreover, whether a "hypofrontal or hyperfrontal pattern" in functional imaging studies is present, depends on accidental methodological procedure, such as eyes open or closed (Leenders 1989).

Table 4. Cortical and Limbic rCBF Patterns with and without Mescaline

Parameter	Cortical regions	
Effects	F (1,10)	Signif
LR	3.98	0.074
ANT POST × LR	7.19	0.023[a]
MESC × ANT POST	5.25	0.045[a]
MESC × ANT POST × LR	5.27	0.045[a]
	Limbic regions	
Effects		
RL	4.34	0.064

n = 11; the data of one volunteer was lost for technical reasons.
ANT POST: anterior-posterior-effect; LR: left-right-effect; MESC: mescaline;
[a] $p < 0.05$

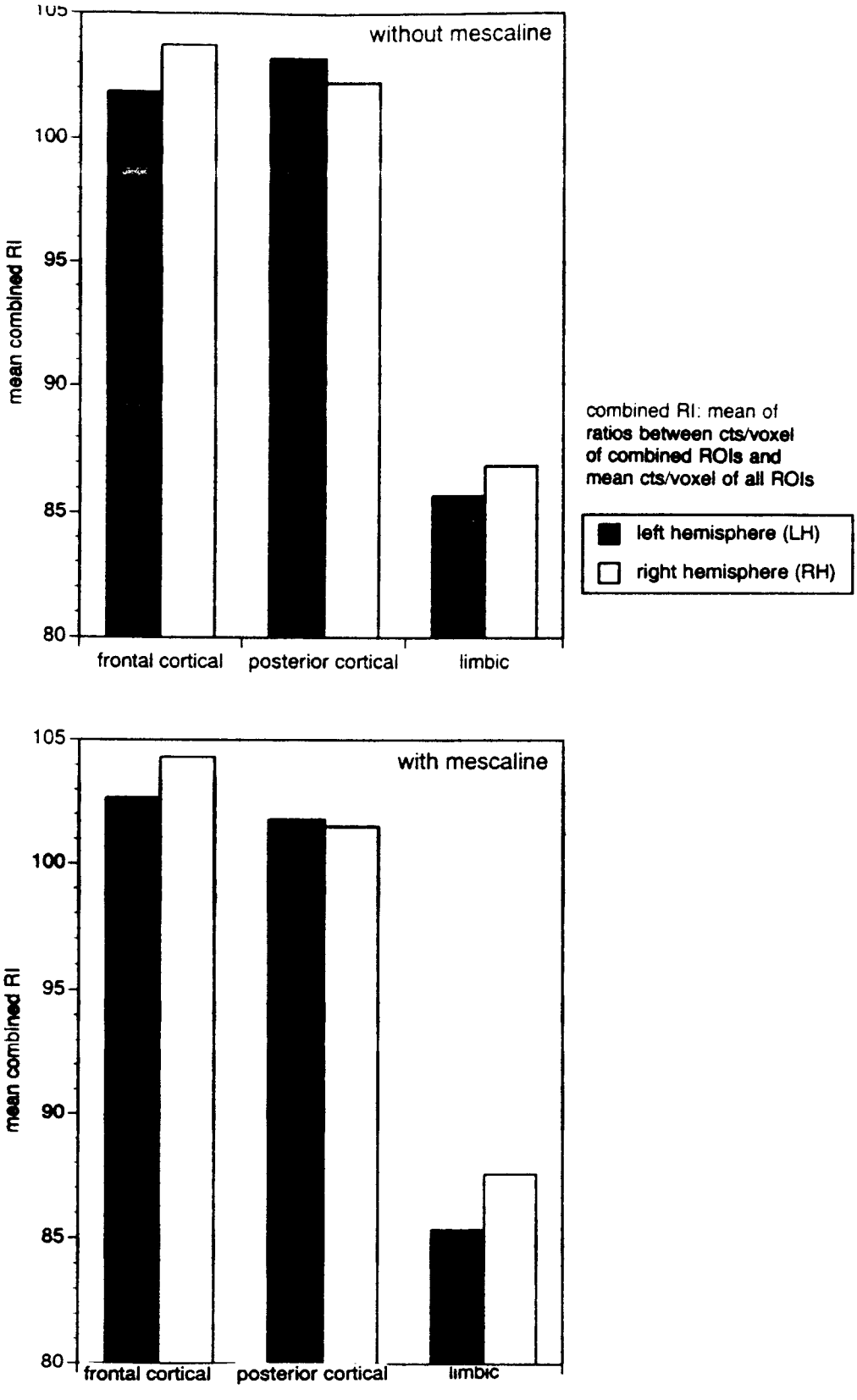

Figure 7. ^{99m}Tc-HMPAO uptake in cortical and limbic ROIs with and without mescaline cortical: frontal and posterior regions of the cortex: frontal = superior-frontal (SF 1-3), central (C 1-2), medio-frontal (MF), inferior-frontal (IF), fronto-basal (FB). Posterior = superior/inferior parietal (SP, IP), superior/inferior temporal (ST, IT), superior/inferior occipital (SO, IO). Limbic: = basal ganglia (BG), thalamus (TH), and hippocampus (HI).

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.

The neuropsychological findings of the present study, that is, the decrease of right hemisphere performance in the face/nonface decision task, parallel 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 findings discussed previously of a deficit of the right hemisphere or in both hemispheres in acute psychosis, which, therefore, cannot be interpreted as caused by a purely left-hemisphere dysfunction.

From a methodological point of view, it is important to keep in mind that the effects of hallucinogens are highly dependent on the setting in which they are taken. The technical, scientific setting interrupted the experience of the subjective drug effects several times and prevented further elaborations of psychotic contents. Possibly due to this fact, the subjective experiences are less pronounced the more technically sophisticated the study design. Our subjects, for example, reported the peak of their subjective reactions to mescaline during the SPECT investigation, which, contrary to psychopathological and neuropsychological testing, required confinement to horizontal posture without body movements.

With respect to the functional brain-imaging method, it is important that in the present study relative rCBF patterns were measured intraindividually. A subject thus serves as his own control, minimizing the variability of the data. Such an approach might ultimately help to shed some light on the relationship between objective "functional" brain images and subjective experience.

In conclusion, the experimental study of the effects of psychoactive substances in normal control subjects has methodological advantages as compared with the studies of patients, especially with respect to standardization and control. Our study is a step towards symptom-oriented research. According to the vulnerability model, research has to go beyond diagnostic categories such as "organic" and/or "endogenous." Using the broad array of psychological as well as biological techniques, experimentally induced psychotic syndromes seem to provide us with a valuable tool for psychiatric research.

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References

Beaumont JG, Diamond SJ (1973): Brain disconnection and schizophrenia. *Br J Psychiatry* 123:661–662.

Beringer K (1927): Der Meskalinrausch. Seine Geschichte und Erscheinungsweise. *Monographie Neurol Psychiatry* H 49.

Brodie JD, Christman DR, Corona JF (1984): Patterns of metabolic activity in the treatment of schizophrenia. *Ann Neurol* 15 (suppl): 166–169.

Buchsbaum MS, DeLisi LE, Holcomb HH, Hazlett E, Cooper-Langston K, Kessler R (1987):

Positron emission tomography studies of basal ganglia and somatosensory cortex neuroleptic drug effects: differences between normal controls and schizophrenic patients. *Biol Psychiatry* 22:479–494.

Chapman J (1966): The early symptoms of schizophrenia. *Br J Psychiatry* 112:225–251.

Cutting J (1985): *The Psychology of Schizophrenia*. Edinburgh, London, Melbourne, New York: Churchill Livingstone.

Cutting J (1990): *The Right Cerebral Hemisphere and Psychiatric Disorders*. Oxford: Oxford University Press.

DeLisi LE (1986): The use of positron emission tomography (PET) to image regional brain metabolism in schizophrenia and other psychiatric disorders: a review. In Nasrallah NA, Weinberger DR (eds), *The Neurology of Schizophrenia. Handbook of Schizophrenia*, vol I, Amsterdam, New York, Oxford: Elsevier.

Dittrich A, Arx S von, Staub S (1985): In collaboration with Cochrane R, Cordero M, Davenport D, et al. International Study on Altered States of Consciousness (ISASC). Summary of the results. *German J Psychol* 9(4):319–339.

Fahrenberg J, Selg H, Hampel R (1984): *Das Freiburger Persönlichkeitsinventar FPI-R*. Hogrefe: Göttingen.

Farkas T, Wolf AP, Jaeger J, Brodie JD, Christman DRM, Fowler JS (1984): Regional brain glucose metabolism in chronic schizophrenia: a positron emission transaxial tomographic study. *Arch Gen Psychiatry* 41:293–300.

Fischman LG (1982): Dreams, hallucinogenic drug states and schizophrenia: A psychological and biological comparison. *Schizophr Bull* 9:73–94.

Flor-Henry P (1969): Psychosis and temporal lobe epilepsy: A controlled investigation. *Epilepsia* 10:363–395.

Gruzelier JH (1984): Funktionelle Hemisphärenasymmetrien bei Schizophrenen. In Hopf A, Beckmann H (Hrsg) *Forschungen zur biologischen Psychiatrie*. Springer, Berlin Heidelberg New York: Springer Valag, pp 3–17.

Gur RE, Resnick SM, Alavi A, et al (1987): Regional brain function in schizophrenia. *Arch Gen Psychiatry* 44:119–125/126–129.

Guttmann E, Maclay WS (1936): Mescaline and depersonalization. *J Neurol Psychopathol* 83:193–212.

Hermle L, Oepen G, Spitzer M (1988): Zur Bedeutung der Modellpsychosen. *Fortsch Neurol Psychiat* 56:48–58.

Hermle L, Spitzer M, Kovar KA, Borchard D, Gouzoulis E (1992): Psychological effects of 3,4-methylenedioxyethamphetamine (MDE, "Eve") in normal subjects: Are entactogenes a new class of psychoactive agents? *Neuropsychopharmacology* (in press).

Hoffer A, Osmond H (1966): Some psychological consequences of perceptual disorder and schizophrenia. *Int J Neuropsychiatry* 2:1–19.

Ingvar DH (1979): "Hyperfrontal" distribution of the cerebral grey matter flow in resting wakefulness, on the functional anatomy of the conscious state. *Acta Neurol Scand* 60:12–25.

Ingvar DH, Franzen G (1974): Distribution of cerebral activity in chronic schizophrenia. *Lancet* 2:1484–1486.

Kinsbourne M (1970): The cerebral basis of lateral asymmetries in attention. *Acta Psychologica* 33:193–201.

Kling AS, Metter EJ, Riege WH, Kuhl DE (1986): Comparison of PET measurement of local brain glucose metabolism and CAT Measurement of brain atrophy in chronic schizophrenia and depression. *Am J Psychiatry* 143:175–180.

Leenders KL (1989): PET in der Biologischen Psychiatrie. In Saletu B (ed), *Biolgische Psychiatrie*. Stuttgart New York: Thieme, pp 69–76.

Magaro PA, Page J (1983): Brain disconnection, schizophrenia and paranoia. *J Ment Nerv Dis* 171:133–140.

Musalek M, Podreka I, Suess E, et al (1988): Neurophysiological aspects of auditory hallucinations. *Psychopathology* 21:275–280.

Nasrallah HA (1986): Cerebral hemisphere asymmetries and interhemispheric integration in schizophrenia. In Nasrallah HA, Weinberger DR (eds). *Handbook of Schizophrenia*. vol 1. The neurology of schizophrenia. Science Publishers, Amsterdam, Oxford, New York, Elsevier. pp 157–174.

Oepen G, Fünfgeld M, Höll T, Zimmermann P, Landis T, Regard M (1988): Schizophrenia—an emotional hypersensitivity of the right cerebral hemisphere. *Int J Psychophysiol* 5:261–264.

Oldfield RC (1971): The assessment and analysis of handedness. The Edinburgh inventory. *Neuropsychologia* 9:97–113.

Overall JE, Gorham DR (1976): Brief Psychiatric Rating Scale. In W ECDEU *Assessment Manual For Psychopharmacology*, rev. ed. Rockville, MD: pp 157–169.

Podreka I, Suess E, Goldenberger G, et al (1987): Initial experience with Tc-99m-hexamethylpropylene-amine oxime (Tc-99m-HMPAO) brain SPECT. *J Nucl Med* 27:1657–1666.

Regard M, Landis T (1986): Affective and cognitive decisions on faces in normals. In Ellis HD, Jeeves MA, Newcombe F, Young A (eds), *Aspects of Face Processing*. Dordrecht: Martin Nijhoff, pp 363–369.

Schweitzer L, Becker E, Welsh E (1978): Abnormalities of cerebral lateralization in schizophrenia patients. *Arch Gen Psychiatry* 35:982–985.

Sharp PF, Smith FW, Gemmell HG, et al (1986): Technetium-99-m-HMPAO stereoisomers as potential agents for imaging regional cerebral blood flow: human volunteer studies. *J Nucl Med* 27:171–177.

Sheppard G, Gruzelier J, Manchanda R, et al (1983): 15-O-positron emission tomographic scanning in predominantly never-treated acute schizophrenic patients. *Lancet* II:1448–1452.

Tomer R, Mintz M, Myslobodsky MS (1982): Left hemisphere hyperactivity in schizophrenia: Abnormality inherent to psychosis or to neuroleptic side-effects? *Psychopharmacology* 77:168–170.

Venables PH (1984): Cerebral mechanisms, autonomic responsiveness and attention in schizophrenia. In Spaulding WD, Cole JK (eds), *Theories in schizophrenia and psychosis*. Lincoln: University of Nebraska Press, Nebraska Symposium on Motivation, vol 31, 1983. 47–91.

West ED (1984): Right hemisphere dysfunction and schizophrenia. *Lancet* 11:344.

Wiesel FA, Blomquist G, Greitz T, et al (1985): Regional brain metabolism in schizophrenic patients before and during neuroleptic treatment. *J Cereb Blood Flow Metab* 5(suppl 1):181–182.

Winters WD (1975): The continuum of CNS excitatory and hallucinosis. In Siegel RK, West LJ (eds); *Hallucinations*. New York: pp 53–70.

Zerssen D von (1986): Clinical Self-Rating-Scales (CSRS) of the Munich Psychiatric Information System (PSYCHIS Mönchen). In Sartorius N, Ban TA (eds); Berlin: Springer pp 270–303.

Zubin J, Spring B (1977): Vulnerability—a new view of schizophrenia. *J Abnorm Psychol* 86:103–126.