Advances and Pathophysiological Models of Hallucinogenic Drug Actions in Humans: A Preamble to Schizophrenia Research

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Recent research into the pharmacological mechanism of hallucinogens (LSD, psilocybin) and dissociative anesthetics (PCP, ketamine) suggest that multiple neurotransmitter systems are involved in drug-induced and possibly also in naturally occurring psychoses. Specifically, animal models suggest that a dysbalance between serotonin, glutamate, and dopamine in the limbic cortico-striato-thalamic circuitry may be critical to psychotic symptom formation. To test this hypothesis, psychometric measures and metabolic PET investigations were performed (1) with FDG to elucidate the common neuronal substrates of different hallucinogens, (2) with specific receptor ligands before and after pretreatment with specific receptor antagonists to explore the putative interactions of hallucinogens with various neurotransmitter systems. Our data demonstrate that the neuronal substrate of normal and abnormal thought and behavior is associated with a distributed neuronal network and with multiple interactive neurotransmitter systems. The data also support the view that the hallucinogen challenge paradigm constitutes a powerful tool for elucidating the pathophysiology of neuropsychiatric disorders.

Introduction

Indoleamine hallucinogens such as LSD and psilocybin and dissociative anesthetics such as phencyclidine (PCP) and ketamine produce a psychosis-like syndrome in humans, which shares a number of features with naturally occurring psychoses such as schizophrenia (*Bowers* and *Freedman*, 1966; *Fischman*, 1983; *Hermle* et al., 1988; *Javitt* and *Zukin*, 1991; *Hermle* et al., 1992; *Vollenweider* et al., 1997e). Preclinical research into the biology of the LSD/psilocybin or PCP/ketamine model of psychosis has prompted the hypothesis that other neurotransmitter systems beside dopamine may be important in contributing to the pathophysiology of schizophrenic disorders. Specifically, animal models of psychopathology suggest that LSD and psilocybin produce their psychotomimetic effects through agonist actions at 5-HT2 receptors, while PCP and ketamine-induced psychosis is thought to be due to a blockade of glutamatergic NMDA receptors. Indeed, more recent human studies into the pathophysiology of the psilocybin and ketamine models of psychosis suggest that a role is played by the 5-HT2 and NMDA receptor systems in psychotic symptom formation (*Vollenweider* et al., 1997d; *Vollenweider* et al., 1997e). However, it would be overly simplistic to hypothesize that the pathophysiology of drug-induced states and schizophrenia is either dopaminergic, serotonergic, or glutamatergic in nature. A more plausible hypothesis would be that the dysregulation of or abnormal interrelationship between dopamine, serotonin, and glutamate contributes to the pathogenesis of drug-induced psychoses and schizophrenic disorders.

In the present study, I wish to summarize some of our recent results and advances in hallucinogen research, based on human studies. Different strategies for exploring the pharmacological effects of hallucinogens on brain functions have been developed by our group. The basic approaches are to investigate hallucinogen-induced metabolic changes with fluorodeoxyglucose (FDG) and to characterize functional interactions of neurotransmitter systems by assessing hallucinogen-induced displacement of specific radiolabeled receptor ligands using positron emission tomography (PET). To explore further the role of specific receptor systems in hallucinogen drug action, the blocking effects of specific receptor antagonists on hallucinogen-induced psychosis is investigated using psychometric measures and neuropsychological tests. A human model of sensory gating deficits, the cortico-striato-thalamo-cortical (CSTC) loop model, is introduced to provide a perspective as to how current scientific knowledge about hallucinogen drug action might be visualized within a synthetic framework to explain their subjective effects in humans. Specifically, the CSTC loop predicts that a disruption of the thalamic "filter" functions by ketamine or psilocybin may lead to a sensory overload of the cortex which in turn results in the cognitive fragmentation and sensory flooding seen in hallucinogen-induced mental states and naturally occurring psychoses (*Vollenweider*, 1992; *Vollenweider*, 1994). Moreover, the model suggests that a serotonergic-dopaminergic or glutamatergic-dopaminergic neurotransmitter dysbalance in the limbic cortico-striato-thalamic circuitry may be critical to psychotic symptom formation.

PET with FDG was used to test the hypothesis that psilocybin and ketamine may lead to a metabolic activation of the frontal cortex (hyperfrontality). Univariate and multivariate correlational analyses between hallucinogen-induced changes in cerebral glucose metabolism and specific dimensions of altered states of consciousness were computed to elucidate the neuronal substrates associated with psychotic symptom formation. Psychometric measures and PET investigations with specific receptor ligands were performed before and after pretreatment with specific neuroreceptor antagonists to explore the pharmacological profiles of hallucinogens. These

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studies represent a paradigm shift, seeing interactions of different neurotransmitter systems as the basis of the psychological effects of hallucinogens. Clearly, the study can only deal with a selection of the many topics that might be considered in this context, and some of the subjects are therefore inevidably sketchy.

The Role of Hallucinogens in the Generation of Chemical Hypotheses of Schizophrenia

The classical chemical hypothesis of schizophrenic disorders is the dopamine hypothesis. The dopamine hypothesis is based on the observation that sustained administration of the central nervous system stimulant amphetamine can produce a psychosis in normals that uniquely resembles the paranoid form of schizophrenia (*Angrist* and *Gershon*, 1970; *Griffith* et al., 1972; *Bell*, 1973). In addition, it was demonstrated that amphetamine, usually in doses which are nonpsychotogenic in normals, can provoke or lead to a renewed exacerbation of psychotic symptoms in schizophrenic patients (*Lieberman* et al., 1990). Moreover, the role of neuroleptics in the treatment of amphetamine-induced and naturally occurring psychosis is well established. Amphetamine is thought to produce its mood activating and psychotogenic effects by increasing presynaptic dopamine release and by inhibiting its reuptake (*Snyder*, 1973; *Sharp* et al., 1987). Drawbacks of the dopamine hypothesis, however, arise from the observation that dopamine antagonists mainly affect the positive symptoms of schizophrenia, while there is little effect on negative symptoms. This indicates that the perturbations found in the dopaminergic system in schizophrenia may not be the central defect and that other neurotransmitter systems such as serotonin, glutamate, or GABA may also be implicated in the pathophysiology of psychotic states (*Carlsson* and *Carlsson*, 1990; *Meltzer*, 1991).

The LSD/Psilocybin Model Psychosis: A Case for Serotonin

Besides stimulants, hallucinogens such as psilocybin (o-Phosphoryl-4-hydroxy-N,N-dimethyltryptamin) and LSD (d-lysergic acid diethylamide) have also been reported to produce a psychosis-like syndrome in man that resembles the first manifestation of schizophrenia in various ways (*Bowers* and *Freedman*, 1966; *Leuner*, 1981; *Gouzoulis* et al., 1994).

In particular, ego-disorders and changes in the perception of surroundings are prominent features of psychedelic and endogeneus psychotic states (*Fischman*, 1983). Due to the structural similarities between psilocybin, LSD and serotonin (5-hydroxytryptamine, 5-HT), early investigators hypothesized that the serotonergic system might play a critical role in the pathophysiology of schizophrenia (*Gaddum* and *Hammeed*, 1954; *Wooley* and *Shaw*, 1954). More recently, this hypothesis has received renewed support, first from a growing body of electrophysiological, behavioral and radioligand-binding studies suggesting that LSD and psilocybin exert their psychological effects through excessive 5-HT2 receptor activation (*Braff* and *Geyer*, 1980; *Meert* et al. 1989; *Buckholtz* et al., 1990; *Glennon*, 1990; *Burris* et al., 1991; *Sipes* and *Geyer*, 1994), second from the recent finding of 5-HT2 receptor abnormalities in postmortem schizophrenic brain (*Mita* et al., 1986; *Arora* and *Meltzer*, 1991; *Joyce* et al., 1993; *Laruelle* et al., 1993), and third from the discovery of 5-HT2 receptor antagonism of atypical neuroleptics such as clozapine and risperidone (*Nyberg* et al., 1993; *Meltzer* et al., 1994).

The PCP/Ketamine Model Psychosis: The Case for Glutamate

Aside from the classical stimulants and hallucinogens, other agents became available that were claimed to mimic the primary symptoms of schizophrenic psychoses. Phencyclidine (PCP) and its congener ketamine are two dissociative anesthetics that can uniquely produce a psychosis-like mental state in normals, including both positive and negative symptoms of schizophrenic disorders (*Luby* et al., 1959; *Domino* et al., 1965). Subjects under PCP or ketamine exhibit depersonalization and derealization phenomena, thought disorders, tangentiality, delusions of influence, gradiosity, and visual disturbances as well as apathy, anhedonia, and social withdrawal (*Collier*, 1972; *Ghoneim* et al., 1985; *Hansen* et al., 1989; *Øye* et al., 1992; *Krystal* et al., 1994; *Mathisen* et al., 1996; *Vollenweider* et al., 1997c). In 1983, long after the discovery of the psychotomimetic effects of PCP and ketamine, it was found that at subanesthetic doses, racemic ketamine, primarily blocks the PCP binding site of the N-methyl-D-aspartate (NMDA)-sensitive glutamate receptor (*Anis* et al., 1983), providing a strong case for a "glutamate deficiency" hypothesis in schizophrenia (*Kim* et al., 1980). The assumption that PCP and ketamine-induced psychosis may be primarily due to a blockade of the NMDA receptor complex was corroborated by the recent finding that the relative psychotomimetic potency of subanesthetic doses of the pure (S) and (R) ketamine enantiomeres parallels their relative affinity at the NMDA receptor complex (*Øye* et al., 1992; *Mathisen* et al., 1995), and their relative potency to block NMDA-mediated neurotransmission in animal studies (*Zeilhofer* et al., 1992). In particular, it was found that (S) ketamine has a four to five fold greater affinity to bind to the PCP binding site of the NMDA receptor in human brain than (R) ketamine, and that at these concentrations (R) ketamine also interacts weakly with the sigma receptor sites, where (S) ketamine binds only negligibly (*Øye* et al., 1991). The "glutamate deficiency" hypothesis of schizophrenia is further supported by the discovery of decreased glutamate concentration in the cerebrospinal fluid of schizophrenic patients (*Kim* et al., 1980), alterations in cortical and subcortical NMDA receptor densities (*Deakin* et al., 1989; *Kornhuber* et al., 1989; *Simpson* et al., 1992; *Ishimaru* et al., 1994), and reduced glutamate release in postmortem schizophrenic brain preparations (*Sherman* et al., 1991). Moreover, other NMDA antagonists such as MK-801 can also elicit PCP-like symptoms in healthy volunteers (*Reimherr* et al., 1986; *Troupin* et al., 1986). Finally, a single dose of PCP can worsen previously presented schizophrenic symptoms in stabilized patients without producing additional psychotomimetic effects (*Ban* et al., 1961; *Luby* et al., 1962).

Characteristics of Ketamine and Psilocybin-induced ASC

In the context of the present theme – relating the psychological to the biological effects of hallucinogens – the assessment and characterization of altered states of consciousness (ASC) is of fundamental importance. In this respect, I would now like to give a brief description of the APZ questionnaire, which has become the standard in Europe for measuring specific states of consciousness and which has been used on a routine

base by our group (*Dittrich*, 1994). In short, the APZ questionnaire measures three primary dimensions and one secondary etiology-independent dimension of ASC. The first dimension, designated "oceanic boundlessness" (OSE), measures derealization phenomena and ego-dissolution which are associated with enhanced sensory awareness and a positive basic mood ranging from heightened feelings to sublime happiness and exaltation. Ego-dissolution can include or start with a mere loosening of ego-boundaries, but may end up in a feeling of merging with the cosmos, where the sense of time is changed or completely vanishes. This state might be comparable to a mystical experience, if fully developed. The second dimension, "dread of ego-dissolution" (AIA) measures thought disorder, ego-disintegration, and loss of autonomy and self-control, variously associated with arousal, anxiety, and paranoid feelings of being endangered. The third dimension, "visionary restructuralization" (VUS) refers to auditory and visual illusions, hallucinations, and synesthetic phenomena, as well as to changes in the meaning of various percepts. The intercultural consistency of the APZ dimensions OSE, AIA, and VUS has been confirmed in an international study on ASC (*Dittrich* et al., 1985). Furthermore, the APZ dimensions have been shown to be altered consistently in a manner that is independent of the particular treatment, disorder, or condition that led to the ASC (*Dittrich* et al., 1985; *Dittrich*, 1994).

So far, the APZ questionnaire has been used by our group to characterize the psychological effects of hallucinogens (*Vollenweider* et al., 1997e), dissociative anesthetics (*Vollenweider* et al., 1997c; *Vollenweider* et al., 1997d), stimulants (*Vollenweider* et al., 1997b), and entactogens (*Vollenweider* et al., 1998f). The subjective effects of psilocybin and ketamine will be briefly summarized here (see also Fig. **1** and **2**).

Psilocybin (15–20 mg), (S) ketamine (0.014–0.02 mg/kg/min), and racemic ketamine (0.02–0.03 mg/kg/min) administration in healthy volunteers elicited a psychosis-like syndrome including ego-dissolution, illusions and hallucinations, thought disorders, paranoid ideations, and changes in mood and affect. In many ways, the ketamine and psilocybin-induced clinical syndrome resembles acute schizophrenic experiences, but is different in other respects. For example, the hallucinatory disintegration and loss of self-control over thought processes and intentionality observed in psilocybin and ketamine subjects are highly reminiscent of acute schizophrenic decompensation (*Rümmele* and *Gnirss*, 1961; *Keeler*, 1965; *Bowers* and *Freedman*, 1966; *Martindale* and *Fischer*, 1977; *Heimann*, 1986; *Scharfetter*, 1987). Furthermore, the finding of heightened awareness associated with euphoria and/or visual hallucinations in psilocybin and ketamine psychosis is in line with the notion that the earliest affective changes in schizophrenic patients are often pleasurable or exhilarating (*Chapman*, 1966; *Bowers*, 1968; *Hermle* et al., 1992; *Gouzoulis* et al., 1994) and that visual hallucinations occur significantly more often in acute than in chronic schizophrenic patients (*McCabe* et al., 1972; *Freedman* and *Chapman*, 1973; *Gouzoulis* et al., 1994). Emotional disturbances and disorganization of thought appeared to be secondary to and influenced by derealization and depersonalization phenomena, especially when subjects were no longer able to distinguish internal processes from external ones. At the doses tested, this difficulty in reality appraisal and impairment of ego functioning was transient and occurred only in some of the subjects. Typically, psilocybin subjects – unlike schizophrenics – could recognize derealization and depersonalization phenomena as abnormal experiences and attribute them to the drug. Interindividual differences in these responses might have been due either to variations in dosage or personality trait (*Fischer* et al., 1970; *Thatcher* et al., 1970). At the dose tested, S and racemic ketamine generally produced more pronounced anxiety, thought disorder, and ego-disintegration than psilocybin as measured by the AIA and AMDP scales (AMDP data not shown). In contrast to psilocybin, both S and racemic ketamine produced apathy, emotional withdrawal, and feelings of indifference. This finding is consistent with the view that NMDA antagonists such as ketamine and PCP can also mimic some negative symptoms of schizophrenia (*Corssen* et al., 1968; *Collier*, 1972; *Krystal* et al., 1994).

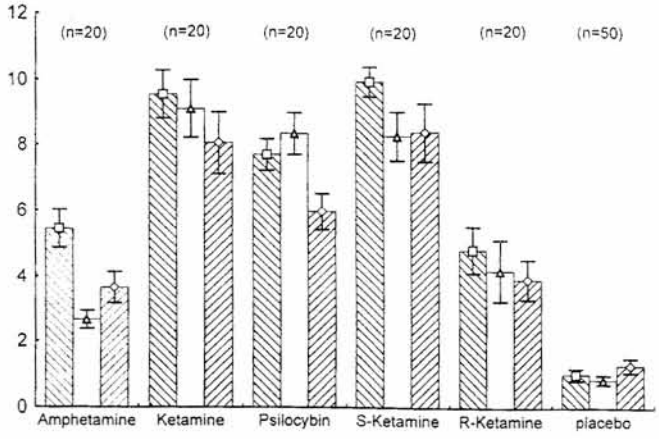


Fig. 1 Mean values of APZ scores in various drug conditions. For dosage of drugs see text. (Mean ± SE).
□ OSE △ VUS ◇ AIA

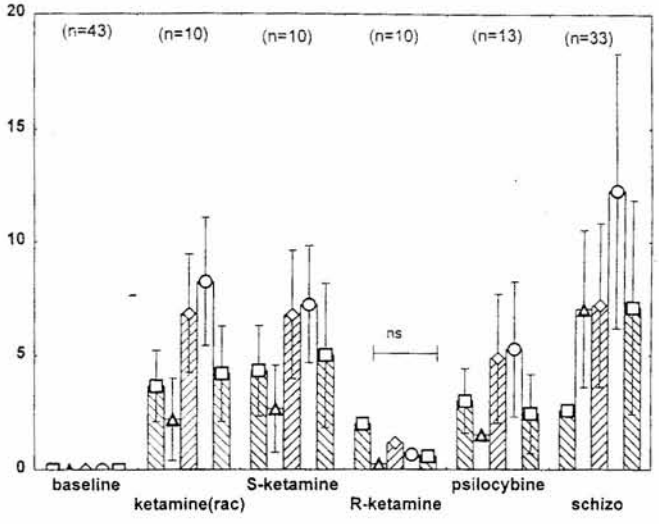


Fig. 2 Mean EPI values obtained in model psychoses and first-episode schizophrenics. (mean ± SD, all but R-ketamine: $p < 0.01$).
□ Identity △ Demarcation ◇ Consistency ○ Activity □ Vitality

Another psychometric scale that has proved useful for assessing specific dimension of ego disorders is the "Ego Pathology Inventory" (EPI), developed by *Scharfetter* (*Scharfetter*, 1981; *Weber* and *Scharfetter*, 1984). The EPI was divided empirically into five features used to describe ego pathology and related behavior: ego identity, demarcation, consistency, activity, and vitality (*Scharfetter*, 1981; *Weber* and *Scharfetter*, 1984). The "ego identity" scale includes items of doubts, changes, or loss of one's own identity in respect to "gestalt", physiognomy, gender, geneologic origin and biography. The "ego demarcation" scale refers to one's uncertainty or lack of differentiation between ego and non-ego spheres concerning the thought process, affective state, and body experience. The "ego consistency" scale comprises dissolution, splitting, and destruction in experiencing a coherent self, body, thought process, chain of feelings, and a structured external world. The "ego activity" scale refers to the deficit in one's own ability, potency, or power for self-determined acting, thinking, feeling, and perceiving. The "ego vitality" scale includes the experience or fear of one's own death, of the fading away of liveliness, of the demise of mankind or of the universe. Both the construct and the discriminatory validity of the EPI inventory have been validated recently in schizophrenics and controls by an extensive empirical study using confirmatory factor analysis (*Scharfetter*, 1995).

Comparison of the ego-pathology (EP) scores (mean values) in psilocybin and ketamine subjects with EP scores obtained in first episode schizophrenic patients revealed that the "ego-consistency" (forming a coherent frame of reference) and "ego-identity" features were impaired similarly in both conditions (Fig. **2**). Scores for the "ego-activity" feature (one's self-determined acting, thinking, feeling and perceiving) and scores for "ego-demarcation" were only about $^1/_2$ to $^2/_3$ of the values seen in schizophrenic patients. Similarly, the "ego-vitality" was clearly less affected in ketamine and psilocybin subjects than in schizophrenic patients (*Scharfetter*, 1995). Taken together, the present findings support the notion that serotonergic agonists such as psilocybin and NMDA antagonists such as ketamine can mimic some major aspects of schizophrenic psychoses (*Claridge*, 1978; *Leuner*, 1981; *Fischman*, 1983), but there were also differences, particularly in the quality and quantity of ego-disorders at least at the doses tested (*Hollister* and *Hartmann*, 1962; *Thatcher* et al., 1971; *Parashos*, 1976).

The CSTC Model of Sensory Information Processing and ASC

Based on the available neuroanatomical evidence and pharmacological findings of psychedelic drug actions, we proposed a cortico-subcortical model of psychosensory information processing that can be used as an initial working hypothesis to analyze and integrate the effects of different chemical types of hallucinogens at a system level. The model proposes that psychedelic states can be conceptualized as complex disturbances arising from more elementary deficits of sensory information processing in cortico-striato-thalamo-cortical (CSTC) feedback loops. The model was not entirely new, since it incorporates the idea that psychotic symptoms might relate to a dopaminergic and/or dopaminergic-glutamatergic neurotransmitter dysbalance in mesolimbic and/or mesolimbic-corticostriatal pathways, but it enlarges on this hypothesis by bringing serotonergic and GABAergic neurotransmission into the scheme as well (*Vollenweider*, 1992; *Vollenweider*, 1994).

In short, five CSTC loops have been identified and each loop, functioning in parallel, is thought to mediate a different set of functions: the motor, the oculomotor, the prefrontal, the association and the limbic loop. The limbic loop is involved in memory, learning and self-nonself discrimination by linking cortical categorized exteroceptive perception and internal stimuli of the value system. The limbic loop originates in the medial and lateral temporal lobe and hippocampal formation, projects to the ventral striatum including the nucleus accumbens, the ventromedial portions of the caudate nucleus and putamen. Projections from these nuclei then converge on the ventral pallidum and feed back via the thalamus to the anterior cingulate and the orbitofrontal cortex (Fig. **3**).

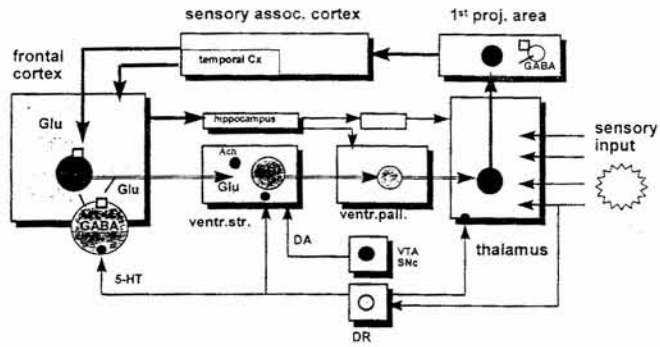


Fig. 3 The limbic cortico-striato-thalamic (CST) feedback loop is involved in memory, learning, and self-nonself discrimination via linkage of cortical categorized exteroceptive perception and internal stimuli of the value system. It is postulated that the filter function of the thalamus, which is under the control of the CSTC feedback/reentry loops, protects the cortex from exteroceptive sensory information overload, as well as from internal arousal. The model predicts that sensory overload of the cortex and psychosis may result from thalamic gating deficits, which may be caused by ketamine either via a blockage of NMDA-mediated glutamatergic (Glu) cortico-striatal and/or via an increase in mesolimbic dopaminergic (DA) neurotransmission. Excessive stimulation of 5-HT2 receptors - e.g., by psilocybin - may lead to a similar neurotransmitter imbalance in CSTC loops, which will again result in an opening of the thalamic filter and a sensory overload of the cortex, psychosis, and arousal.
▨ Ketamine blocks NMDA receptors
● psilocybin activates 5-HT2 receptors

The model includes the view that the thalamus acts a filter or gating mechanism for the extero- and interoceptive information flow to the cerebral cortex and that deficits in thalamic gating may lead to a sensory overload of the cortex, which in turn may ultimately cause the sensory flooding, cognitive fragmentation and ego-dissolution observed in drug-induced altered mental states and psychotic disorders. The filter capability of the thalamus is thought to be under the control of corticos-striato-thalamic (CST) feed back loops. Specifically, it is hypothesized that the striatum, comprising the dorsal and the ventral striatum (including the nucleus accumbens) and the corresponding dorsal and ventral pallidum, exerts an

inhibitory function on the thalamus. Inhibition of the thalamus should theoretically result in a decrease of sensory input to the cortex and in a reduction of arousal, protecting the cerebral cortex from sensory overload and breakdown of its integrative capacity. The striatal activity is thought to be modulated by a number of subsidiary circuits, or neurotransmitter systems. The mesostriatal and mesolimbic projections provide an inhibitory dopaminergic input to the striatum including the nucleus accumbens. Under physiological conditions, the inhibitory influence of the dopaminergic systems on the striatum is, however, thought to be counterbalanced by the glutamatergic excitatory input resulting from corticostriatal pathways. This assumption implies that an increase in dopaminergic tone as well as a decrease in glutamatergic neurotransmission should theoretically lead to a reduction in the inhibitory influence of the striatum on the thalamus and result in a opening of the thalamic "filter" and, subsequently, in a sensory overload of the cerebral cortex and psychotic symptom formation. Finally, the reticular formation, which is activated by input from all sensory modalities, gives rise to serotonergic projections to the components of the CST loops, the frontal cerebral cortex, cingulate cortex, hippocampus, striatum, nucleus accumbens, thalamus, and amygdala. Excessive activation of the postsynaptic elements of the serotonergic projection sites should also result in an impairment of the thalamic gating mechanism and, consequently, in a sensory overload of frontal cortex and psychosis.

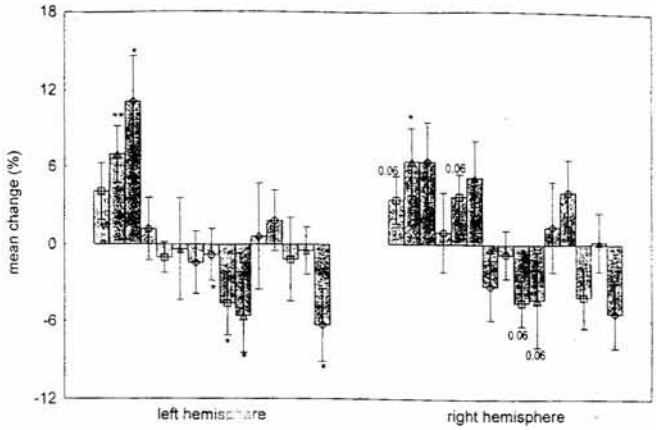


Fig. 4 Mean changes in relative glucose metabolism (absolute values/global) from baseline to ketamine condition. Note the concomitant frontal increase and occipital decrease in metabolism (hyperfrontality). FRM = frontomedial cortex, FRL = frontolateral cortex, CGA = cingulate anterior, CGP = cingulate posterior, PAR = parietal cortex, SMS = somatosensory cortex, MOT = motor cortex, TEL = temporolateral cortex, TEM = temporomedial cortex, OCM = occipitomedial cortex, OCL = occipitolateral cortex, CAU = caudate nucleus, PUT = putamen, THA = thalamus, and CER = cerebellum. (n = 10, mean ± SE)

□ FRM	□ PAR	□ TEM	□ PUT
△ FRL	△ SMS	△ OCM	△ THA
◇ GCA	◇ MOT	◇ OCL	◇ CER
○ GCP	○ TEL	○ CAU	

First Results Testing the CSTC Model

Although the CSTC model is an oversimplification, it provides a set of testable hypotheses, specifically, according to the CSTC model we have hypothesized that the reduction in glutamatergic functions, brought about for example by the NMDA antagonist ketamine, should lead to a sensory overload and metabolic activation of the cerebral cortex, presumably of the frontal cortex (hyperfrontality). If the CSTC model is valid, stimulation of the serotonergic system, for example by the mixed 5-HT2/1 agonist psilocybin, should lead to activation of the frontal cortex similar to that seen with ketamine (see also Fig. **3**). The hyperfrontality hypothesis of ketamine and psilocybin-induced mental states has been tested in healthy volunteers using positron emission tomography (PET) and the radioligand [18F]fluorodeoxyglucose (FDG). PET and FDG permit the direct exploration of the interactive organization of the human brain, via the coupling of cerebral glucose metabolism and neuronal activity. In fact, it was possible to confirm the central hypothesis of frontocortical activation in psychedelic states. Both ketamine and psilocybin led to a marked metabolic activation of the frontal cortex including the anterior cingulate (25–35% increase in absolute glucose metabolism), and a number of overlapping metabolic changes in other brain regions (for details see *Vollenweider* et al., 1997d; *Vollenweider* et al., 1997e). As seen in Fig. **4** and **5**, the finding of hyperfrontality in both ketamine and psilocybin subjects was corroborated by significantly increased relative metabolic rates of glucose (absolute value/global) in the frontal cortex, but also by the finding of significantly increased fronto-occipital ratios (frontal values/occipital values: 11–14%)

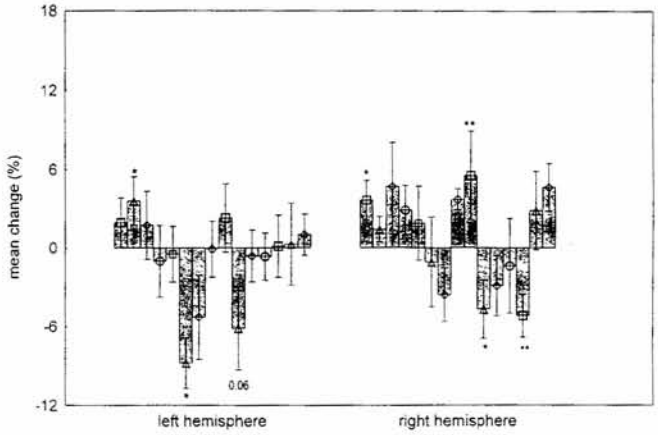


Fig. 5 Mean changes in relative glucose metabolism (absolute values/global) from baseline to psilocybin condition. Note the similarity of frontal increase and occipital decrease in relative metabolism in the psilocybin and ketamine model psychosis. (n = 10, mean ± SE, Wilcoxon's p: *< 0.05)

□ FRM	□ PAR	□ TEM	□ PUT
△ FRL	△ SMS	△ OCM	△ THA
◇ GCA	◇ MOT	◇ OCL	◇ CER
○ GCP	○ TEL	○ CAU	

To elucidate the relationship between regional metabolic activation of ihe brain and specific states of consciousness, a correlational analysis was performed. Ego-dissolution and derealization phenomena correlated with the increase in metabolic activity in the frontal cortex including the anterior cingulate, but also with changes in the temporal cortex and basal ganglia. These findings demonstrate that distributed neuronal networks rather than one single briaft region are involved in psychedelic and psychotic symptom formation.

Nevertheless, the hyperfrontality observed in these studies is potentially important. First, the marked stimulation of the frontal cortex, the anterior cingulate, the temporomedial cortex, and the thalamus seen in both psilocybin and ketamine subjects corroborate the thalamic filter theory, which suggested that a disruption of the limbic cortico-striato-thalamic (CST-) loop should theoretically lead to a sensory overload of the frontal cortex and its limbic relay stations. This interpretation is also supported by the recent finding that ketamine administration in haloperidol-stabilized schizophrenics resulted in an increase of cerebral blood flow in the thalamus, frontomedial, and anterior cingulate cortex, concomitant with the exacerbation of psychotic symptoms (*Lahti* et al., 1995).

Second, this hyperfrontality is of particular interest because it appears to parallel similar SPECT and PET findings in acutely ill schizophrenics, but to contrast with the hypofrontality found in chronic schizophrenics. For example, a hyperfrontal pattern of CBF (*Ebmeier* et al., 1993; *Parellada* et al., 1994) or an increased frontal to parietal ratio of metabolism was found under resting conditions and associated with positive psychotic symptoms in acute unmedicated first episode schizophrenics (*Cleghorn* et al., 1989; *Kaplan* et al., 1993; *Catafau* et al., 1994). Similarly, a hyperfrontal metabolic pattern (*Ebmeier* et al., 1993) and a positive correlation between the increase in cerebral blood flow in the right anterior cingulate cortex and a "disorganization" syndrome was found in chronic schizophrenic patients during acute psychotic episodes (*Liddle* et al., 1992; *Ebmeier* et al., 1993). Moreover, a hyperfrontal pattern of tracer uptake was also reported in acutely ill non-schizophrenic psychotic patients (*Ebmeier* et al., 1995). A predominantly right metabolic hyperfrontality associated with derealization and depersonalization phenomena was found in the mescaline model of psychosis (*Hermle* et al., 1993). The finding of hyperfrontality in model psychoses and naturally occurring psychoses therefore strongly suggests that hyperfrontality, rather than hypofrontality is a pathophysiological manifestation of acute psychotic symptom formation. Furthermore, these data clearly indicate that hallucinogens provide a valuable research strategy for exploring possible functional disturbances related to psychiatric disorders.

Third, the finding of hyperfrontality also supports the idea that the psychedelics used in these studies may mediate their effects through a final pathway or a common neurotransmitter system, downstream to their primary locus of action. For example, both 5-HT2 and NMDA receptors have been located on GABAergic neurons in the frontal cortex (*Olney* et al., 1991; *Aghajanian*, 1994). Hence, GABAergic neurons in cortico-striatal pathways may well provide a common anatomical substrate that is implicated in the genesis of ketamine- and psilocybin-induced hyperfrontality and psychosis. On the other hand, it is well documented that both psilocybin and ketamine can activate either directly or indirectly the dopaminergic systems. As activation of the dopaminergic pathways might theoretically lead to a disruption of the information flow in CST-loops, the possibility remains that dopamine may also be a candidate contributing to the pathophysiology of hyperfrontality and acute psychotic symptom formation (*Kehr*, 1977; *Meltzer* et al., 1978; *Meltzer* et al., 1981; *Hiramatsu* et al., 1989). Certainly, hypotheses such as these need substantial prospectively acquired corroborative evidence and carefully designed mechanistic studies (see below).

Patterns of Cortical Activity in Altered States of Consciousness

The correlational analysis of cortical activity and the psychological dimensions of ASC in our psilocybin and ketamine studies clearly indicate that complex neuronal networks are involved in the formation of ASC. This implies that a multivariate analysis of metabolic and psychological data and a relative large sample size (e.g. 50 – 100 subjects) are imperative if the common neuroanatomical substrates of ASC are to be identified accurately. Therefore, a number of additional placebo-controlled FDG/PET experiments with S ketamine, R ketamine, and amphetamine were performed in normal subjects to explore further the relationship between hallucinogen-induced patterns of cortical activity and psychological dimensions of ASC (*Vollenweider* et al., 1997c; *Vollenweider* et al., 1997b). To identify the interactive organization of the brain in resting states and ASC, normalized metabolic PET data from placebo and corresponding drug conditions were subjected to a factor analysis and factor scores for each individual subject were computed (n = 106) (*Vollenweider*, 1997a). Surprisingly, this computation revealed that "cortical-subcortical organization" (based on a five-factor solution) during ASC was very similar to that seen under placebo condition, indicating that the functional integrity of interrelated brain regions (factors), which might be interpreted as functional "units" or "modules", is not disrupted in ASC (see Fig. **3**). According to their content, the factors were labeled "fronto-parietal cortex", "temporal cortex", "occipital cortex", "striatum" (which included the caudate nucleus and putamen), and "thalamus". Subsequent comparison of the factor scores under drug or placebo condition revealed, however, that subjects had significantly higher scores on the "frontal-parietal" and "striatal" network, and lower scores on the "occipital cortex" during hallucinatory states than in resting states. This finding indicates that neuronal activity within these modules (factors) and within the more global relationship between these units (factors) differs markedly during ASC and normal waking state.

Moreover, multiple regression analysis of psychological scores (APZ scores) and factor score values (normalized metabolic activity) revealed three facts. First, the feature OSE (oceanic boundlessness) relates to changes in metabolic activity in the frontal-parietal, temporal, and occipital cortex; second, VUS (visionary restructuralization, including hallucinatory phenomena) is associated with metabolic alterations in the fronto-parietal, temporal, striatal, and occipital network and, third, anxious ego-dissolution (AIA) is primarily associated with metabolic changes in the thalamus (Table **1**). It is noteworthy that the observed association between anxious

Table 1 The relationship between the APZ scores OSE, VUS; and AIA, the EPI score "ego identity impairment" and normalized metabolic activity in the five functional brain modules (factors) identified by factor analysis. Factors which significantly contribute to the computation are indicated by asterisks: * = $p < 0.05$

OSE	= 0.32 F1*	− 0.20 F2*	+ 0.11 F3	+ 0.20 F4*	+ 0.05 F5
VUS	= 0.20 F1*	− 0.27 F2*	+ 0.17 F3*	+ 0.32 F4*	+ 0.10 F5
AIA	= 0.00 F1	+ 0.09 F2	+ 0.01 F3	+ 0.17 F4	+ 0.28 F5*
identity	= 0.04 F1	− 0.04 F2	+ 0.05 F3	+ 0.10 F4	+ 0.20 F5*

F1 (fronto-parietal factor), F2 (occipital factor), F3 (temporal factor), F4 (striatal factor), F5 (thalamic factor)

ego-dissolution and increased relative metabolic activity in the thalamus is underscored further by the finding of a positive correlation between ego-identity impairment and the thalamic factor.

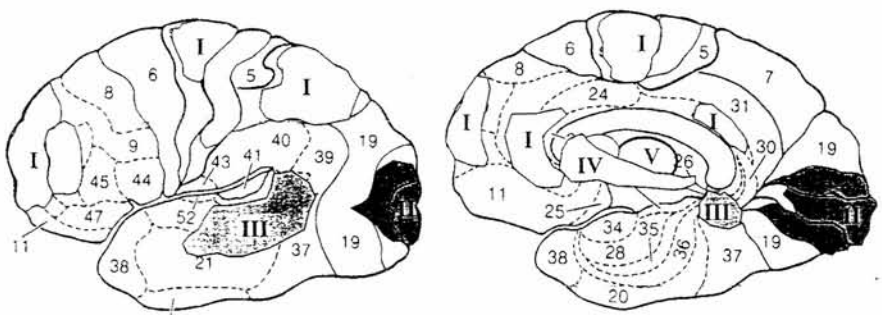
The present results suggest that, in combination with functional brain imaging techniques (PET, SPECT, fMRI etc.) hallucinogens are promising research tools for exploring the biological correlates of ego-structuring processes. It appears that the more positively experienced form of ego-dissolution, OSE, can functionally and metabolically be differentiated from AIA, the more fragmented and anxious form of ego-dissolution. The present data also indicate that the CSTC model used here provides a satisfactory starting point from which to approach the functional organization of the brain in ASC. It should be noted, however, that the present correlations, which are based on aggregated observations over time (APZ ratings, metabolism) and space (brain regions), though probably correct in the order of magnitude, might be inadequate at a finer level of resolution. To explore further the circuitry dynamics of the CSTC model during ASC, we have started making use of a new three-dimensional EEG-based functional brain tomography technique for localizing electrical activity in the brain, known as LORETA (low resolution electromagnetic tomography) (*Pasqual-Marqui* et al., 1994). LORETA allows differences in the distribution of electrically active neuronal populations to be located, and has the additional advantage of the high time resolution of the EEG. A first aim of an ongoing study is to explore the course of the functional relationship between the thalamus and cortical regions (particularly the frontal cortex) during MDMA or psilocybin administration in healthy volunteers (*Vollenweider, Gamma* and *Frei*, in preparation). The hypothesis is that the combination of LORETA and PET will bring further insight into the functional organization of the brain in ASC.

Further Explorations of the Role of Serotonin and Dopamine in ASC

The role of 5-HT2 A receptors in psilocybin psychosis

The CSTC model suggests that serotonergic pathways modulating cortico-striatal-thalamic loops of sensory and cognitive information processing play a critical role in hallucinogenic drug action (*Vollenweider*, 1992; *Vollenweider*, 1994), as well as in the treatment and pathogenesis of schizophrenia (*Meltzer*, 1991). Indeed, animal studies reveal that both indoleamine (psilocybin, LSD) and phenylalkylamine (mescaline, DOI) hallucinogens bind with high affinity to 5-HT1, 5-HT2, 5-HT5 and 5-HT7 receptors (*Peroutka*, 1994). Furthermore, it has been suggested that the common effects of these two classes of hallucinogens may be mediated by agonist actions at 5-HT2 receptors: first, because the potency of hallucinogens correlates with 5-HT2 receptor-binding affinity in animals (*Titeler* et al., 1988); and second, because the behavioral effects of hallucinogens in animals can be blocked by 5-HT2 antagonists (*Sanders-Bush* et al., 1988; *Meert* et al., 1989; *Wing* et al., 1990; *Sipes* and *Geyer*, 1994; *Schreiber* et al., 1995; *Sipes* and *Geyer*, 1997). However, the moderate affinity of LSD for D2 receptors (*Pieri* et al., 1974) and other influences of hallucinogens on dopamine (DA) functions (*Smith* et al., 1975; *Haubrich* and *Wang*, 1977) also suggest that DA systems contribute to a certain extent to hallucinogen effects. The role of the serotonin and dopamine systems in the generation of hallucinogen-induced ASC has never been tested in human studies. For the understanding and development of novel pharmacological treatments of psychoses, however, human studies are unavoidable, particularly since more recent data indicate that same animal models of hallucinogenic drug action may not reflect hallucinogenic properties in man (*Koerner* and *Appel*, 1982).

To test the hypotheses that 5-HT2 and/or DA D2 receptors contribute to hallucinogen action in humans, we studied the influences of pretreatment with the preferential 5-HT2 A antagonist ketanserin (*Hoyer* and *Schoeffter*, 1991), the D2



Key figure for the five cortical-subcortical area factors
factor I: frontomedial, frontolateral, cingulate ant. & post. Parietal, and sensorimotor cortex
factor II: occipitomedial and occipitolateral cortex
factor III: temporomedial and temporolateral cortex
factor IV: caudate nucleus, putamen
factor V: thalamus

Fig. 6 Anatomic localization of the five cortical-subcortical area factors identified by factor analysis from 14 cortical/subcortical regions of interest. Each factor represents a functional "unit" or "module" of highly intercorrelated brain regions. Descriptive names of the brain regions involved in each factor are given in the figure.

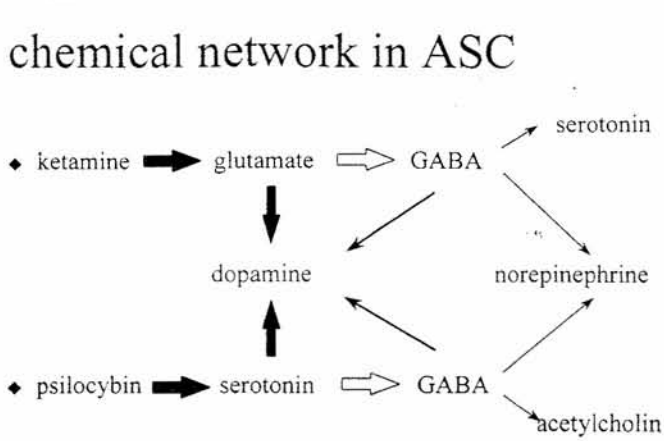


Fig. 7 Putative neurotransmitter interactions in ASC.

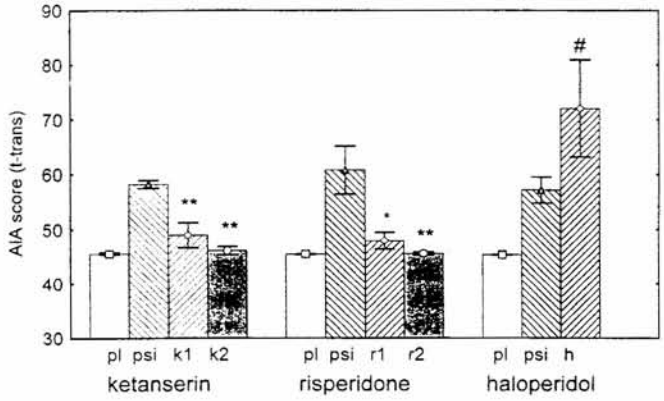


Fig. 8 Effects of ketanserin (k1 = 20 mg, k2 = 40 mg p.o.), risperidone (r1 = 0.5 mg, r2 = 1.0 mg p.o.), and haloperidol (h = 1.5 mg i.v.) on psilocybin-induced AIA scores. P1 = placebo, psi = psilocybin (0.26 mg/kg). * = $p < 0.05$; ** = $p < 0.01$.

antagonist haloperidol (*Burt* et al., 1976), or the mixed 5-HT2/D2 antagonist risperidone (*Leysen* et al., 1996) on the psychological and cognitive effects of psilocybin in normal subjects (*Vollenweider* et al., 1996). The APZ rating scale was used to assess the subjective effects of psilocybin. We found that the effects of psilocybin an the OSE, VUS and AIA scores were blocked in a dose-dependent way by ketanserin or the atypical antipsychotic risperidone. Unlike ketanserin and risperidone, the dopamine antagonist haloperidol had only weak effects on psilocybin-induced psychosis. Haloperidol moderately reduced the OSE score (50%), but had virtually no effects on the VUS score (< 5%). Moreover, haloperidol markedly increased the psilocybin-induced AIA score (Fig. **8**). These data are consistent with animal studies and provide first evidence in humans that psilocybin-induced psychosis is primarily due to serotonin 5-HT2 A receptor activation. Given the evidence that psilocybin does not act directly upon DA receptors (*Creese* et al., 1975) and the fact that haloperidol partially ameliorated psilocybin-induced euphoria, derealization and depersonalization phenomena (OSE), it appears that psilocybin also has a complex indirect influence an dopaminergic systems. In fact, there is considerable preclinical evidence for a modulatory influence of the ascending serotonergic pathways from the raphe on the mesolimbic and mesostriatal dopamine systems (*Joyce*, 1993; *Kapur* and *Remington*, 1993; *Zazpe* et al., 1994). Whether serotonin increases or decreases striatal dopaminergic activity is, however, controversial. Nevertheless, our results show that 5-HT2 A/C receptor activation can lead to psychotic symptoms that do not depend on DA systems. This finding, together with our previous observation that psilocybin stimulates frontocortical glucose metabolism in normals (*Vollenweider* et al., 1997e) in a way similar to that seen in acutely ill schizophrenic patients, supports the hypothesis that excessive serotonergic activity may be a critical factor in schizophrenic psychoses, or at least in a subset of schizophrenic patients, and that specific 5-HT2 A antagonists may be useful in normalizing such imbalances (*Meltzer*, 1991).

Modulation of dopamine activity by serotonin

The putative serotonin-dopamine interaction in psilocybin psychosis is an issue that needs further investigation. To explore the dynamic interaction of different neurotransmitter systems, we use a research strategy in which a hallucinogen is administered and alterations in receptor binding parameters (Bmax, Kd, BP) are measured in a neurotransmitter system that is functionally coupled to the primary mechanism of action of the challenge drug.

In respect to serotonin/dopamine interaction, PET was used to examine the effect of psilocybin on the in vivo binding of [11C]raclopride to D2-dopamine receptors in the striatum of healthy volunteers (*Vollenweider* et al., 1997 g). [11C]raclopride receptor binding potential (BP) was significantly reduced in human caudate (19%) and putamen (20%) during the peak effect of psilocybin, indicating an increase in endogenous dopamine release.

Whether psilocybin increases striatal dopamine release through 5-HT2 receptor stimulation alone or in combination with 5-HT1 receptors cannot be inferred from the present data. Moreover, the hypothesis that psilocybin increases dopamine release via 5-HT2 activation appears to be at odds with a number of animal studies suggesting that 5-HT2 receptor antagonism, rather than 5-HT2 receptor stimulation, enhances striatal dopamine release (*Kapur* and *Remington*, 1993). For example, altanserin, a 5-HT2 antagonist, has been shown to increase striatal dopamine release in baboons (*Dewey* et al., 1995). However, there is substantial evidence from recent rat studies indicating that, under certain conditions, such as states of high serotonergic activity or during conditions of elevated dopamine efflux, stimulation of 5-HT2 receptors can facilitate striatal dopamine release (*Schmidt* et al., 1992; *Schmidt* et al., 1993; *Gudelsky* and *Nash*, 1996; *West* and *Galloway*, 1996). Since psilocybin also acts upon 5-HT1 A receptors (*Buckholtz* et al., 1990; *McKenna* et al., 1990) and stimulation of 5-HT1 A autoreceptors is expected to enhance dopaminergic tone (*Benloucif* and *Galloway*, 1991; *Neal-Beeliveau* et al., 1993), one might speculate that psilocybin increases striatal dopamine release through a concomitant stimulation of both 5-HT1 A and 5-HT2 A receptors. This hypothesis is in line with the finding that the serotonin releaser and reuptake inhibitor fenfluramine (*Dewey* et al., 1995) as well as the selective 5-HT reuptake inhibitor citalopram stimulate striatal DA release in humans as assessed by PET and [11C]raclopride (*Tiihonen* et al., 1996).

Certainly, considerably more research will be required to determine whether psilocybin enhances dopamine release via stimulation 5-HT2 or 5-HT1 receptors, or both. What is of particular interest for this study is that indications exist that abnormalities in the number of 5-HT1 A and 5-HT2 A receptors have been found in the frontal cortex, nucleus accumbens, striatum, and hippocampi in schizophrenic patients (*Mita* et al. 1986; *Arora* and *Meltzer*, 1991; *Joyce* et al. 1993; *Laruelle* et al. 1993; *Meltzer*, 1994). These data therefore also support further evaluation of the contribution of the 5-HT system to the pathophysiology of schizophrenia (*Meltzer*, 1991).

Conclusions

The present data indicate that hallucinogen research in humans offers a powerful research strategy for the investigation of human brain functions and neurotransmitter systems in ASC. The data demonstrate that the neuronal substrate of normal and abnormal thought and behavior is associated with a distributed neuronal network and with multiple interactive neurotransmitter systems. The data also support the view that the hallucinogen challenge paradigm not only constitutes a powerful tool for bridging the gap between the mental and the physical, but will also enhance our understanding of the pathophysiology of neuropsychiatric disorders.

Acknowledgements

The author would especially like to thank Prof. Dr. D. Hell and Prof. Dr. C. Scharfetter Psychiatric University Hospital Zürich, for continuing support and Dr. M.F.I. Vollenweider-Scherpenhuyzen, Institute of Anesthesiology, University Hospital of Zürich, for critical comments on the manuscript. This study was supported in part by the SNF (32-040900).

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