3. Recent Advances and Concepts in the Search for Biological Correlates of hallucinogen-induced Altered States of Consciousness

Franz X. Vollenweider, M.D.

Introduction

Hallucinogens and related substances constitute a powerful experimental basis to investigate biological correlates of altered states of consciousness (ASC) (Hermle et al. 1988; Javitt and Zukin 1991; Vollenweider, 1994). In combination with functional brain imaging techniques and pharmacological methodologies, they are remarkable molecular probes to study the functional organization of the brain and to generate chemical hypotheses of ASC. The study of hallucinogens in humans is important because these substances affect a number of brain functions that typically characterize the human mind, including cognition, volition, ego, and self-consciousness. They can elicit a clinical syndrome that resembles in various aspects the first manifestation of schizophrenic disorders, but is different in other respects (Fischman, 1983; Gouzoulis et al. 1994; Vollenweider et al. 1997d). The various forms of ego-disorders are especially prominent features of psychedelic and naturally occurring psychoses. For example, they can produce a form of ego-dissolution that is experienced with heightened awareness, en-hanced introspection, sublime happiness, as well as a form that is experienced with anxiety and fragmentation. Hence, studies of the neuronal mechanisms of action of hallucinogens should provide not only novel insights into the pathophysiology of psychiatric disorders and their treatments, but in a more wider sense into the biology of consciousness as a whole, e.g. into the biology of ego structuring processes.

In the present discussion, I wish to summarize some of the recent advances in hallucinogen research that have resulted from human studies conducted in our group. In the first part, a human model of sensory gating deficits, the cortico-striato-thalamo-cortical (CSTC) loop model of psychosensory processing, is introduced to provide a perspective on how current scientific knowledge about hallucinogen drug action could be visualized within a synthetic framework to explain their subjective effects in humans. The CSTC model is based on the assumption that psychedelic and psychotic symptoms can be conceptualized by failure to inhibit or "gate" intrusive mental activity. Specifically, the CSTC loop model suggests that a deficient thalamic "filter" function leads to sensory overload of the cortex which in turn results in cognitive fragmentation and sensory flooding as seen in hallucinogen-induced states and naturally occurring psychoses (Vollenweider, 1994).

The theoretical conception of the "thalamic filter" theory is comparable to animal models of sensory gating deficits such as the prepulse inhibition paradigm (PPI), although the PPI paradigm does not explicitly refer to the thalamus as an anatomical structure responsible for filtering deficits. However, both the CSTC model and the PPI paradigm suggest that perturbations in cortico-striato-thalamic pathways are critical for the loss of inhibition processes and the pathogenesis of psychotic symptoms. This assumption is supported by increasing preclinical evidence demonstrating that hallucinogens specifically interfere with neurotransmitter systems within the limbic cortico-striatal-thalamic circuitry and produce PPI-deficits comparable to those seen in several neuropsychiatric disorders characterized by failure to inhibit irrelevant cognitive, motor or sensory information.

Positron emission tomography (PET) was used to test the hypothesis that hallucinogens may lead to a disruption of "filter" functions and produce a sensory overload of the frontal cortex. Moreover, a correlational analysis between hallucinogen-induced changes in neuronal activity and specific dimensions of ASC was carried out to elucidate the neuronal substrates of psychedelic states. Psychometric measures and PET investigations with specific receptor ligands were and are performed to investigate the effects of hallucinogens on brain functions before and after pretreatment with specific neuroreceptor antagonists. These studies provide a paradigm shift where interactions of different neurotransmitter systems are seen as the basis for the psychological effects of hallucinogens. The PPI paradigm is used as a second measure to characterize the putative effects of hallucinogens on inhibition processes in humans and functional interactions of neurotransmitter systems in ASC. Clearly, among the many topics that could be considered in this

context, I have to make some selection, and some of the subjects unavoidably will remain sketchy.

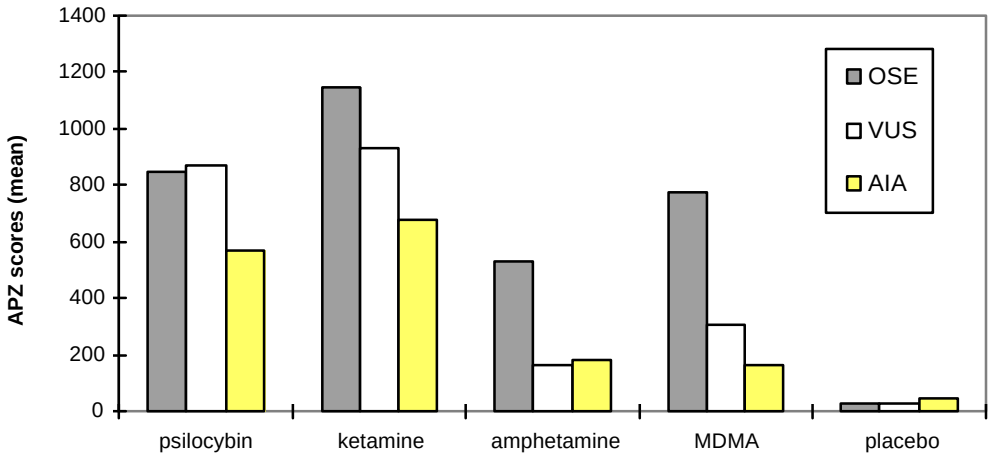

Figure 1. APZ Profiles in healthy volunteers (n = 20).

Measurement of psychological dimensions of ASC

In the context of the present theme -relating psychological and biological effects of hallucinogens- the assessment and characterization of altered states of consciousness (ASC) is of fundamental importance. Among several rating scales, the APZ questionnaire, which has become the standard in Europe for measuring specific states of consciousness and which has been used on a routine basis by our group, is to be described. In short, the APZ questionnaire was developed based on a large prospective study done with 393 subjects tested with cannabinoids, dimethyltryptamine, psilocybin, mescaline, harmaline, nitrosoxide, hypnosis, autogenic training, and meditation techniques (Dittrich, 1994). It measures three primary and one secondary etiology-independent dimensions of ASC. The first dimension, designated as "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 experience of the sense of time is changed or completely vanished. 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, loss of autonomy and self-control variously associated with arousal, anxiety, and paranoid feelings of being endangered. The third subscale "visionary restructuralization"(VUS), refers to auditory and visual illusions, hallucinations, synaesthetic phenomena, as well as to changes in the meaning of various precepts.

The intercultural consistency of the APZ dimensions OSE, AIA and VUS has been rigorously tested in a subsequent study, the International Study on Altered States of Consciousness (ISASC), and the 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). The APZ rating scale is now available in an English version and it is important to emphasize the need for a quantitative instrument such as the APZ to exchange and integrate further research into the effects of hallucinogens on an international level.

So far, the APZ questionnaire has been used to characterize the psychological effects of hallucinogens, dissociative anesthetics, stimulants, and entactogens. For example, using the APZ questionnaire, we recently demonstrated in a double-blind placebo-controlled study that the psychological effects of MDMA in normals can be clearly differ-

entiated from those seen in comparable studies with

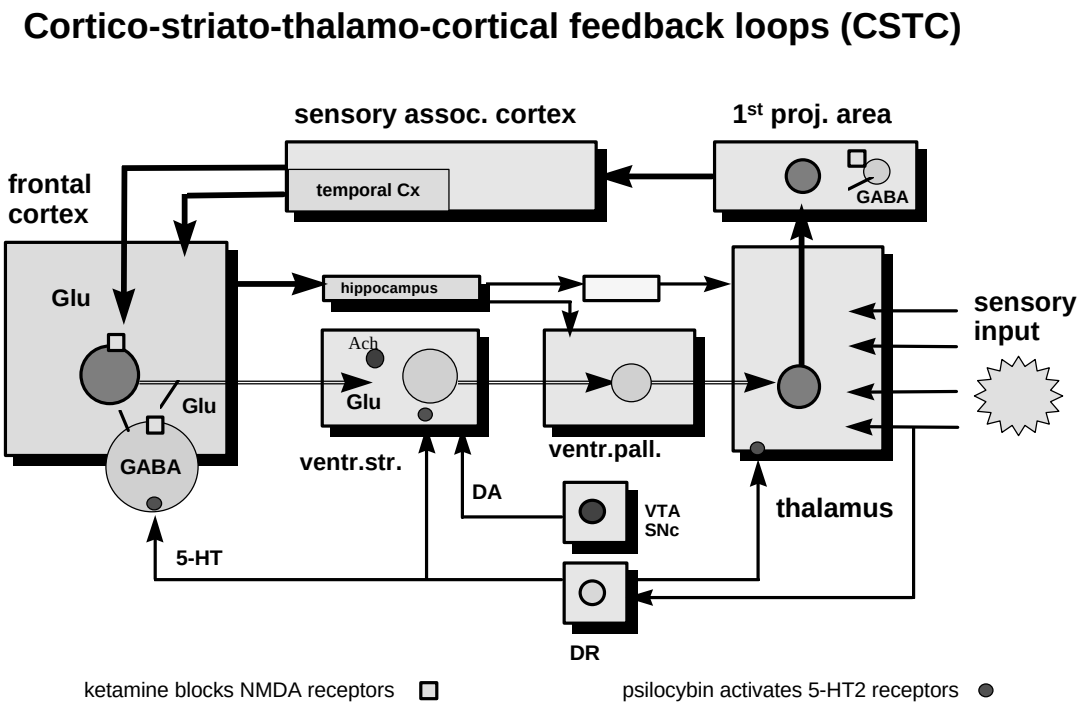

Figure 2. Cortico-striato-thalamo-cortical feedback loops.

ketamine, psilocybin, and amphetamine (Vollenweider et al. 1997e) (Figure 1).

As seen in figure 1, MDMA (1.7 mg/kg p.o.) produced a unique pattern of APZ scores. Although the OSE scores in MDMA subjects were approximately similar (80%) to those seen after psilocybin and ketamine, the VUS and AIA scores were only about 30-50% of the values seen in psilocybin and ketamine subjects (Vollenweider et al. 1997b; Vollenweider et al. 1997b). In contrast to psilocybin and ketamine subjects, loosening of ego-boundaries and perceptual changes produced by MDMA were generally not experienced as problematic or psychotic fusion, but instead as a positive or pleasurable state in which the distinction between self and nonself was reduced and a sense of enhanced empathy existed. Furthermore, MDMA subjects noted that this state allowed them to feel "more united with the world" and less "separated from others". Unlike psilocybin and ketamine, both of which produced comparable increases in hallucinations as indicated by the VUS scores, MDMA did not produce hallucinations, but instead what was typically described was an intensification of sensory perception ("colors were more intense," "objects appeared more detailed," sound was more clear, etc.), and visual illusions ("3D-vision of flat objects," micropsia and macropsia, etc.). Finally, with regard to psychostimulants, euphorigenic doses of d-amphetamine produced similar AIA scores, but lower OSE and VUS scores than those seen in the study with MDMA (Vollenweider et al. 1997a). Although additional studies using multiple doses are needed to confirm these conclusions, the present findings are suggestive of appreciable differences in the psychological profiles produced by MDMA relative to psilocybin, ketamine, or d-amphetamine.

Certainly, several types of ASCs possibly may have etiology-specific dimensions, e.g. acoustic-hallucinatory phenomena, memory disturbances etc., besides those mentioned above. The identification of such specific dimensions will be pertinent to a more comprehensive description of ASC's. Moreover, since individual reaction differences on ASC-inducing agents are high, even when experimental conditions are kept constant, research into other

factors such as personality traits, genetic predispositions, environmental factors, etc., influencing the course of ASC is mandatory. Such studies were performed (Dittrich, 1994) or are in progress (Vollenweider et al., in preparation). Another important need, particularly for exploring pathophysiological commonalties of ASC and naturally occurring psychoses, is the systematic assessment of similarities and differences of psychotic symptoms seen in drug-induced ASC and psychiatric patients, using the same psychometric instruments, e.g. such as the APZ, HRS or IPP rating scales (Dittrich, 1994; Scharfetter 1995; Strassman, 1995).

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 a starting working hypothesis to analyze and integrate the effects of different chemical types of hallucinogens at a system level. The model conceptualizes psychedelic states as complex disturbances that arise from more elementary deficits of sensory information processing in cortico-striato-thalamo-cortical (CSTC) feedback loops. The model was not entirely new; 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 this hypothesis, insofar as serotonergic and GABAergic neurotransmission are also brought into the scheme (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 of 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 feedback via the thalamus to the anterior cingulate and the orbitofrontal cortex (Figure 2).

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 seen in drug-induced altered mental states and psychotic disorders. The filter capability of the thalamus is thought to be under the control of cortico-striato-thalamic (CST) feedback 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, excerts 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 model suggests that striatal activity is modulated by a number of subsidiary circuits, with their respectively 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 dopaminergic systems on the striatum is, however, thought to be counter-balanced by the glutamatergic excitatory input from cortico-striatal pathways. This assumption implies that an increase in dopaminergic tone, as well as a decrease in glutamatergic neurotransmission should theoretically lead to a reduction of the inhibitory influence of the striatum on the thalamus and result in an opening of the thalamic “filter” and, subsequently, in a sensory overload of the cerebral cortex, resulting in 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, namely the frontal cerebral cortex, cingulate cortex, hippocampus, striatum, nucleus accumbens, thalamus, and amygdala. Excessive activation of the postsynaptic elements of these serotonergic projection sites should also result in a reduction of the thalamic gating mechanism and, consequently, in a sensory overload of frontal cortex resulting in psychosis.

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, the reduction of glutamatergic functions, 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-$HT_{2A/2C/1A}$ agonist psilocybin, should lead to activation of the frontal cortex similar to that seen with ketamine (see figure 2).

- Factor I: frontomedial, frontolateral, cingulate ant. and post., parietal, and sensorimotor Cortex
- Factor II: occipitomedial and -lateral Cortex
- Factor III: temporomedial and lateral Cortex
- Factor IV: caudate nucleus, putamen
- Factor V: thalamus

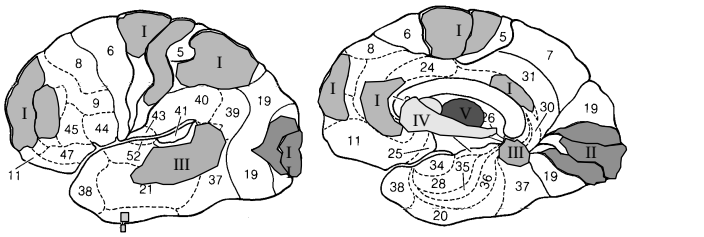

Figure 3. Five clusters of brain regions (factors 1-5) that can be interpreted as functional "units" or "modules." Each unit comprises a number of functionally highly intercorrelated brain regions. For example, the "fronto-parietal factor"(I)includes the frontomedial, frontolateral, anterior and posterior cingulate, parietal, and sensorimotor cortex. The integrity of this factor structure is not disrupted in ASC, but the activity of brain regions within such an unit alters with psychedelic states. The "fronto-parietal factor" appears to play a fundamental role as a "central supervision and execution system" insofar as this unit is involved in ego-structuring processes and self-representation by interpretation and integration of extra- and intrasensory information, planning and execution of motor functions.

The hyperfrontality hypothesis of ketamine- and psilocybin-induced mental states has been tested in healthy volunteers using positron emission tomography (PET) and the radioligand [^{18}F]fluoro-deoxyglucose (FDG). PET with FDG enables one to explore directly the interactive organization of the human brain, via the coupling of cerebral glucose metabolism and neuronal activity. In fact, the central hypothesis of a frontocortical activation in psychedelic states could be confirmed. Both ketamine and psilocybin led to a marked metabolic activation of the frontal cortex and a number of overlapping metabolic changes in other brain regions (Vollenweider et al. 1997c; Vollenweider et al. 1997d). To elucidate the relationship between regional metabolic activation of the brain and specific states of consciousness a correlational analysis was performed. One of the main findings of this computation was that ego dissolution and derealization phenomena correlated with the increase of metabolic activity in the frontal cortex including the anterior cingulate, and also with changes in the temporal cortex and basal ganglia. These findings demonstrated that not a single brain region, but distributed neuronal networks are involved in psychedelic and psychotic symptom formation.

Nevertheless, the hyperfrontality finding 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 is in line with the thalamic filter theory, suggesting 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, the hyperfrontality is of particular interest because it appears to parallel similar findings in acutely ill schizophrenic and non-schizophrenic psychotic patients, but contrasts with the hypofrontality finding seen in chronic schizophrenics. Third, the common hyperfrontality finding also supports the idea that the psychedelics used in these studies may mediated their effects through a common neurotransmitter system. As 5-HT_2 and NMDA receptors have been located on GABAergic neurons in the frontal cortex, GABAergic neurons in cortico-striatal pathways may provide a common anatomical substrate involved in the genesis of ketamine- and psilocybin-induced hyperfrontality and psychosis. On the other hand, both psilocybin and ketamine have been reported to activate either directly or indirectly the dopaminergic system. As activation of dopaminergic pathways could theoretically lead to disruption of the information flow in CST-loops, the possibility remains that dopamine also contributes to the pathophysiology of hyperfrontality and acute psychotic symptom formations (Kehr, 1977; Meltzer et al. 1978; Meltzer et al. 1981; Hiramatsu et al. 1989). Certainly, such hypotheses 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 between cortical activity and psychological dimensions of ASC of our psilocybin and ketamine studies clearly indicated that complex neuronal networks are involved in the formation of ASC. This implies that a multivariate analysis of metabolic and psychological data and relatively large sample size, e.g. 50 -100 subjects, is mandatory to identify the common neuroanatomical substrates of ASC with accurate precision. 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 the psychological dimensions of ASC (Vollenweider et al. 1997; 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 subjects was computed. Surprisingly, this computation revealed that the "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 Figure 3). According to their content, the factors were labeled "fronto-parietal cortex," "temporal cortex," "occipital cortex," "striatum" (which included the nucleus caudate and putamen), and "thalamus." Subsequent comparison of the factor score values of the drug and placebo condition revealed, however, that subjects during hallucinatory states had significantly higher scores on the "frontal-parietal" and "striatal" network, and lower scores on the "occipital cortex" than in resting states. This finding indicates that neuronal activity within these modules (factors) and the more global relationship between these units (factors) is markedly different in ASC than in the normal waking state.

Moreover, multiple regression analysis between psychological scores (APZ scores) and factor score values (normalized metabolic activity) revealed first that the dimension OSE (oceanic boundlessness) relates to changes in metabolic activity in the frontal-parietal, temporal, and occipital cortex. Second, that VUS (visionary restructuralization including hallucinatory phenomena) is associated with metabolic alterations of a fronto-parietal, temporal, striatal, and occipital network, and third that anxious ego-disintegration (AIA) is primarily associated with metabolic changes in the thalamus, as shown by the following regression equations:

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*

*F1 is the fronto-parietal factor, F2 is the occipital factor, F3 is the temporal factor, F4 is the striatal factor, and F5 is the thalamic factor; *denotes significance at the level of $p < 0.05$.*

The present results suggest that hallucinogens in combination with functional brain imaging techniques (PET, SPECT, fMRI etc.) 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 the more fragmented and anxious ego-dissolution AIA. The present data also indicate that the CSTC model used here provides a satisfactory starting point to approach the functional organization of the brain in ASC. It should be noted, however, that the present correlations, which are based on an aggregation of 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 tomo-

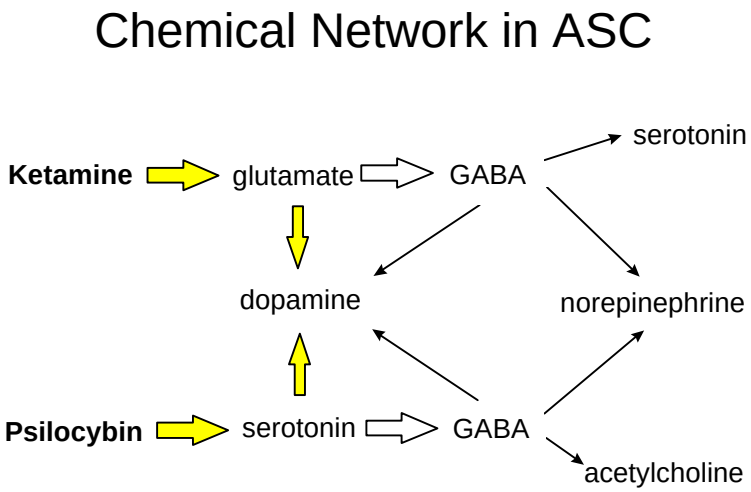

Figure 4. Chemical Network in Altered States of Consciousness (see text).

graphy for localizing the electric activity in the brain, which is called LORETA (low resolution electromagnetic tomography) (Pasqual-Marqui et al. 1994). LORETA allows locating differences in the distribution of electrically active neuronal populations with the 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). It is proposed that the combination of LORETA and PET will bring further insight into the functional organization of the brain in ASC.

Further explorations into the role of serotonin and dopamine in ASC

The CSTC model suggests that serotonergic pathways modulating cortico-striatal-thalamic loops of sensory and cognitive information processing are critical to hallucinogenic drug action, as well as for the treatment and pathogenesis of schizophrenia (Carlsson and Carlsson 1990; Vollenweider et al. 1997d). Indeed, both indoleamine (psilocybin, LSD) and phenylalkylamine (mescaline, DOI) hallucinogens, which produce schizophrenia-like syndromes in humans, primarily bind to 5-HT_1, 5-HT_2, 5-HT_5 and 5-HT_7 receptors in various animal tissue preparations (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-HT_2 receptors: first, because the potency of hallucinogens correlates with 5-HT_2 receptor binding affinity in animals (Titeler et al. 1988); and second, because the behavioral effects of hallucinogens in animals can be blocked by 5-HT_2 antagonists (Sanders-Bush et al. 1988; Meert et al. 1989; Wing et al. 1990; Schreiber et al. 1995). Furthermore, the affinity of LSD for D_2 receptors (Watts et al. 1995) and other influences of hallucinogens on dopamine (DA) functions (Smith et al. 1975; Haubrich and Wang 1977) suggest some contribution of DA systems to hallucinogen effects. The role of the serotonin and dopamine systems in

the generation of hallucinogen-induced ASC has never been systematically tested in human studies. With respect to understanding and development of novel pharmacological treatments of psychoses, human studies are, however, essential, particularly since more recent data indicate that some animal models of hallucinogenic drug action may not reflect hallucinogenic properties in man (Koerner and Appel 1982).

To test the hypotheses that 5-HT_2 and/or DA D_2 receptors contribute to hallucinogen action in humans, we studied the influences of pretreatment with the preferential 5-HT_{2A} antagonist ketanserin (Hoyer and Schoeffter 1991), the D2 antagonist haloperidol (Burt et al. 1976), or the mixed 5-HT_2/D_2 antagonist risperidone (Leysen et al. 1996) on the psychological and cognitive effects of psilocybin in normal subjects, using a placebo-controlled, within-subject design (Vollenweider et al. 1996). The APZ rating scale and a neuropsychological test were used to assess the subjective effect of psilocybin and putative working memory deficits. As seen in figure 5, the subjective effects of psilocybin were blocked dose-dependently by the serotonin 5-HT_{2A} antagonist ketanserin or the atypical antipsychotic risperidone, but were increased by the dopamine antagonist and typical antipsychotic haloperidol. These data are consistent with animal studies and provide the first evidence in humans that psilocybin-induced ASC's are primarily due to serotonin 5-HT_{2A} 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 the OSE score including positively experienced derealization and depersonalization phenomena, but markedly increased cognitive deficits and anxious ego-dissolution as measured by the AIA score, it appears that psilocybin also has a complex indirect influence on dopaminergic systems (Figure 4, 5). Nevertheless, our results show that 5-$HT_{2A/C}$ 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. 1997d) similar to that seen in acutely ill schizophrenic patients, supports the hypothesis that excessive serotonergic activity may be a critical factor in psychedelic and naturally occurring psychoses, at least in a subset of schizophrenic patients, and that specific 5-HT_{2A} antagonists may be useful in normalizing such imbalances (Meltzer, 1991). With respect to hallucinogen-assisted psychotherapy, specific 5-HT_{2A} antagonists may also prove valuable to antagonize prolonged or unwanted side effects of indole hallucinogens.

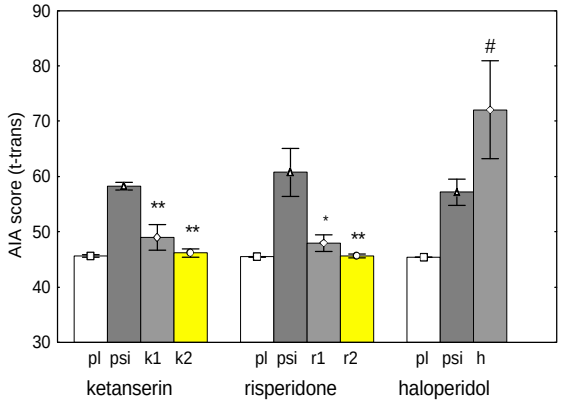

Figure 5. Placebo (pl) and psilocybin (psi) effects on AIA scores. Pretreatment with the selective 5-HT_{2A} receptor antagonists ketanserin (k1, k2) and risperidone (r1, r2) significantly blocks psilocybin-induced increased AIA scores, while haloperidol (h) markedly increased the cognitive deficits and anxious ego-dissolution score.

Whether psilocybin increases dopaminergic activity through 5-HT_2 receptor stimulation alone or in combination with 5-HT_1 receptors or via another receptor system needs to be further investigated and is the main scope of an ongoing PET study on serotonin-dopamine interactions (Vollenweider et al. 1997g). The clarification of this issue is important, since more recent studies suggest that atypical neuroleptics mediate their antipsychotic effects through 5-HT_2 and D_2 antagonism (Meltzer and Gudelsky 1992).

The sensorimotor gating model and ASC

Another important research concept that allows one to explore the neuropharmacology of hallucinogens and cognitive and sensorimotor gating or "filtering" deficits in ASC is the prepulse inhibition paradigm of the startle response (PPI) (for review see (Swerdlow et al. 1992; Geyer and Markou 1995). The PPI paradigm is based on the observation that a startle response to an intensive stimulus is inhibited or gated when the startling cue is preceeded 30-500 msec earlier by a weak prepulse. Theoretically, and as similarly proposed by the CSTC loop model, impairments in inhibition processes lead to sensory overload, attentional deficits, and cognitive fragmentation. PPI has been used as an operational

measure of cognitive and sensorimotor gating in both human and animal studies. PPI deficits have been found in patients with schizophrenia, obsessive compulsive disorder (OCD), Huntington's disease, and psychosis-prone normals compared to normals, reflecting failure to gate sensory, cognitive, or motor information (Geyer et al. 1990; Swerdlow et al. 1994; Swerdlow et al. 1995). More importantly, the PPI deficits seen in these psychiatric patients can be mimicked in rats treated with hallucinogenic 5-HT agonists (psilocybin, DOI, etc.) or NMDA antagonists (ketamine, PCP, or MK 801), giving support to the idea that the sensory flooding seen in ASC and psychotic patients may have a common underlying neurobiological basis (Mansbach and Geyer 1989; Sipes and Geyer 1994) (see above). In fact, the similarity of PPI deficits in animal studies and schizophrenic patients, in combination with other findings, has revitalized interest in hallucinogens in the 1990s and prompted a concerted search into the neurotransmitter systems involved in modulating PPI in rodents (for review see Geyer and Markou 1995).

Studies into the PPI-disruptive effects of hallucinogens and related drugs contributed to the development of specific hypotheses about the primary locus that may be responsible for the psychological effects of hallucinogens in humans. For example, animal studies subsequently demonstrated that the PPI-disruptive effects of both hallucinogenic 5-HT_2 agonists, such as DOI (Sipes and Geyer 1995a; Sipes and Geyer 1997a) and serotonin (5-HT) releasing compounds, such as MDMA ("Ecstasy"), could be blocked with selective 5-HT_{2A} antagonists (Padich et al. 1996). These findings gave substantial support to the idea that indole- and phenylethylamine hallucinogens, but presumably also “entactogens” such as MDMA may mediate their psychological effects in humans through action at a common site, 5-HT_{2A} receptors, although other subtypes of serotonin receptors are also implicated in the modulation of PPI (Sipes and Geyer 1994; Sipes and Geyer 1995; Sipes and Geyer 1996).

The hypothesis that indoleamine hallucinogens such as psilocybin mediate their psychedelic effects primarily via 5-HT_2 receptor activation has been confirmed more recently in a human study (see above, (Vollenweider et al. 1996)). However, whether and how indoleamine hallucinogens and entactogens affect PPI in humans, has not yet been tested. Moreover, it is unclear whether the 5-HT_2 receptor system contributes to the psychological effects of entactogens in humans, since entactogens, unlike hallucinogens, do not produce hallucinations or psychotic symptoms in man.

To explore and compare the putative effects of a typical indoleamine hallucinogen and entactogen on PPI, we have begun to investigate the effects of psilocybin, a 5-HT_2 agonist, and MDMA, a 5-HT releaser, on PPI of acoustic startle in normal laboratory rats versus healthy human volunteers (a collaboration with Mark Geyer, UCSD) (Vollenweider et al. 1997e). To illustrate the need of such comparison studies, the major results of the MDMA study shall briefly be given here. Based on previous studies in rats and mice, the hypothesis was that MDMA would disrupt PPI in both rats and humans.

Surprisingly, our preliminary data indicate that MDMA produces opposite effects on PPI in animals and humans: (1) MDMA decreased PPI of acoustic startle in a dose-related fashion in rats, as expected from previous studies; and (2) a typical recreational dose of MDMA (1.7 mg/kg) increased PPI measured under comparable conditions. The multiple doses of MDMA used in rats ranged from the same 1.7 mg/kg dose used in humans to one order of magnitude higher, in keeping with the typical differences in effective doses between these species. The dose of MDMA used in the human study was shown to have substantial psychological effects in the same subjects, characterized by an easily controlled affective state with feelings of relaxation, heightened mood, euphoria, increased sensory awareness, and elevated psychomotor drive, as detailed elsewhere (Vollenweider et al. 1997f).

The time between administration and testing was selected to be at or near the time of peak effects observed in rats and humans, given the respective routes of administration (subcutaneous injection vs oral). Thus, despite attempts to maximize the comparability of the tests in rats and humans, MDMA produced opposite behavioral effects in rats versus humans, using a measure of sensorimotor gating that is thought to have a high degree of cross-species homology (Geyer and Markou 1995). In the absence of mechanistic studies, no firm conclusions can be drawn regarding the mediation of the observed MDMA effects in humans. Hence, considerably more research will be required to determine whether this disparity between drug effects in rats and humans reflects a species-specific difference in the mechanism of action of MDMA or in the behavioral expression of a similar pharmacological effect, or both. Furthermore, these findings demonstrate the importance of conducting

mechanistic studies of pharmacological agents in healthy humans as well as in experimental animals.

Outlook

In conclusion, the present data indicate that human hallucinogen research with PET and PPI offers a powerful research strategy for studying brain function and neurotransmitter interactions in ASC. The data indicate that neuronal substrates of normal and abnormal thought and behavior are associated with an interactive neuronal network of multiple neurotransmitter systems. The data also corroborate the view that the hallucinogen challenge paradigm not only constitutes a powerful tool to bridge the gap between the mental and the physical, but will also enhance our understanding of the pathophysiology of neuropsychiatric disorders.

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References

Beart PM, McDonald D. (1982): 5-hydroxytrypt-aminergic-dopaminergic interactions in the ventral tegmental area of rat brain. *J Pharm Pharmacol* 34:591-593

Burt DR, Creese I, Snyder SH. (1976): Properties of [3H]Haloperidol and [3H]Dopamine binding associated with dopamine receptors in calf brain membranes. *Mol Pharmacol* 12:800-812

Carlsson M, Carlsson A. (1990): Schizophrenia: A subcortical neurotransmitter imbalance syn-drome? *Schizophrenia Bull* 16:425-432

Creese I, Burt DR, Snyder SH. (1975): The dopamine receptor: differential binding of d-LSD and related agents to agonist and antagonist states. *Life Sci* 17:1715-1720

Dittrich A, von Arx S, Staub S. (1985): International study on altered states of consciousness (ISASC). Summary of the results. *Germ J Psych* 9:319-339

Dittrich A. (1994): Psychological aspects of altered states of consciousness of the LSD type: measurements of their basic dimensions and prediction of individual differences. In Pletscher A, Ladewig D (eds), 50 years of LSD. Current status and perspectives of hallucinogens. New York, Parthenon Publishing, pp.101-118.

Fischman LG. (1983): Dreams, hallucinogenic drug states, and schizophrenia: a psychological and biological comparison. *Schizophrenia Bull* 9:73-94

Geyer MA, Swerdlow NR, Mansbach RS, Braff DL. (1990): Startle response models of sensorimotor gating and habituation deficits in schizophrenia. *Brain Res Bull* 25:485-498

Geyer MA, Markou A. (1995): Animal models of psychiatric disorders. In Bloom FE, Kupfer DJ (eds), The fourth generation of progress. New York, Raven Press, pp.787-798.

Gouzoulis E, Hermle L, Sass H. (1994): (Psychedelic experiences at the onset of productive episodes of endogenous psychoses). *Nervenarzt* 65:198-201

Haubrich DR, Wang PFL. (1977): N,N-dimethyltryptamine lowers rat brain acetyl-choline and dopamine. *Brain Res* 131:158-161

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

Hiramatsu M, Cho AK, Nabeshima T. (1989): Comparison of the behavioral and biochemical effects of the NMDA receptor antagonists, MK-801 and phencyclidine. *Eur J Pharmacol* 166:359-366

Hoyer D, Schoeffter P. (1991): 5-HT receptors: Subtypes and second messengers. J Receptor Res 11:197-214

Javitt DC, Zukin SR. (1991): Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry* 148:1301-1308

Kehr W. (1977): Effect of lysuride and other ergot derivatives on monoaminergic mechanism in rat brain. *Eur J Pharmacol* 41:261-273

Koerner J, Appel JB. (1982): Psilocybin as a discriminative stimulus: lack of specificity in an animal behavior model for 'hallucinogens'. *Psychopharmacology* (Berlin) 76:130-135

Lahti AC, Holcomb HH, Medoff DR, Tamminga CA. (1995): Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *NeuroReport* 6:869-872

Leonard BE. (1994): Serotonin receptors--where are they going? *Int Clin Psychopharmacol* 9 Suppl 1:7-17

Leysen JE, Janssen PA, Gommeren W, Wynants J, Pauwels PJ, Janssen PAJ. (1996): In vitro and in vivo receptor binding and effects on monoamine turnover in rat brain regions of the novel antipsychotics risperidone and ocaperidone. *Mol Pharmacol* 41:494-508

Mansbach RS, Geyer MA. (1989): Effect of phencyclidine and phencyclidine biologs on

sensorimotor gating in the rat. *Neuropsychopharm* 2:299-308

Meert TF, de Haes P, Janssen PA. (1989): Risperidone (R 64 766), a potent and complete LSD antagonist in drug discrimination by rats. *Psychopharmacology* (Berlin) 97:206-212

Meltzer HY, Fessler RG, Simonovic M, Fang VS. (1978): Stimulation of rat prolactin secretion by indolealkylamine hallucinogens. *Psychopharmacology* (Berlin) 56:255-259

Meltzer HY, Sturgeon RD, Simonovic M, et al. (1981): Phencyclidine as an indirect dopamine agonist. In Domino EF (ed), PCP (Phencyclidine): Historical and Current Perspectives. Ann Arbor, NPP Books, pp.207-242. Meltzer HY. (1991): The mechanism of action of *novel antipsychotic drugs. Schizophrenia* Bull 17:263-287

Meltzer HY, Gudelsky GA. (1992): Dopaminergic and serotonergic effects of clozapine -Implications for a unique profile. *Arzneim Forsch* 42:268-272

Padich RA, McCloskey TC, Kehne JH. (1996): 5-HT modulation of auditory and visual sensorimotor gating:II. effects of the 5-HT_2A antagonist MDL 100,907 on disruption of sound and light prepulse inhibition produced by 5-HT agonists in Wistar rats. *Psychopharmacology* (Berlin) 124:107-116

Pasqual-Marqui RD, Michel CM, Lehmann D. (1994): Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *Int J Psychophysiol* 18:49-65

Peroutka SJ. (1994): 5-hydroxytryptamine receptor interactions of D-lysergic acid diethylamide. In Pletscher A, Ladewig D (eds), 50 Years of LSD. New York, The Parthenon Publishing Group, pp.19-26.

Sanders-Bush E, Burries KD, Knoth K. (1988): Lysergic acid diethylamide and 2,5-dimethoxy-4-methylamphetamine are partial agonists at serotonin receptors linked to phosphoinositide hydrolysis. *J Pharmacol Exp Ther* 246:924-928

Scharfetter C. (1995) The self-experience of schizophrenics. Empirical studies of the ego/self in schizophrenia, borderline disorders and depression. Zürich, University of Zürich.

Schreiber R, Brocco M, Audinot V, Gobert A, Veiga S, Millan MJ. (1995): (1-(2,5-dimethoxy-4 iodophenyl)-2-aminopropane)-induced head-twitches in the rat are mediated by 5-hydroxytryptamine (5-HT) 2A receptors: modulation by novel 5-HT2A/2C antagonists, D1 antagonists and 5-HT1A agonists. *J Pharmacol Exp Ther* 273:101-112

Sipes TA, Geyer MA. (1994): Multiple serotonin receptor subtypes modulate prpuls inhibition of the starle respons in rats. *Neuropharmacology* 33:441-448

Sipes TA, Geyer MA. (1995a): DOI disruption of prepulse inhibition of startle in the rat is mediated by 5-HT2a and not by 5-HT2C receptors. *Behavioural Pharmacology* 6:839-842

Sipes TA, Geyer MA. (1995b): 8-OH-DPAT disruption of prepulse inhibition in rats; reversal with (+)WAY 100,135 and localization of site of action. *Psychopharmacology* 117:41-48

Sipes TE, Geyer MA. (1996): Functional behavioral homology between rat 5-HT1B and guinea pig 5-HT1D receptors in the modulation of prepulse inhibition of startle. *Psychopharmacology* 125:231-237

Sipes TE, Geyer MA. DOI disrupts prepulse inhibition of startle in rats via 5-HT2A receptors in the ventral pallidum. [In Press] *Brain Res* (1997):

Smith RC, Boggan WO, Freedman DX. (1975): Effects of single and multiple dose LSD on engogenous levels of brain tyrosine and catecholamine. *Psychopharmacologia* 42:271-276

Strassman RJ. (1995): Hallucinogenic drugs in psychiatric research and treatment. *J Nerv Ment Dis* 183:127-138

Swerdlow NR, Caine SB, Braff DL, Geyer MA. (1992): The neural substrates of sensorimotor gating of the starle reflex: a review of the recent findigs and their implications. Journal of *Psychopharmacology* 6:176-190

Swerdlow NR, Braff DL, Taaid N, Geyer MA. (1994): Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. *Arch Gen Psychiatry* 51:139-154

Swerdlow NR, Filion D, Geyer MA, Braff DL. (1995): "Normal" personality correlates of sensorimotor cognitive, and visuospatial gating. *Biol Psychiatry* 37:286-299

Titeler M, Lyon RA, Glennon RA. (1988): Radioligand binding evidence implicates the brain 5-HT2 receptor as a site of action for LSD and phenylisopropylamine hallucinogens. *Psychopharmacology* (Berlin) 1988; 94:213-216

Vollenweider FX. (1992): Die Anwendung von Psychotomimetika in der Schizophrenie-

forschung unter besonderer Berücksichtigung der Ketamin/PCP-Modell-Psychose. *SUCHT* 38:389-409

Vollenweider FX. (1994): Evidence for a cortical-subcortical dysbalance of sensory information processing during altered states of consciousness using PET and FDG. In Pletscher A, Ladewig D (eds), 50 Years of LSD: State of the Art and Perspectives of Hallucinogens. Symposium of the Swiss Academie of Medical Sciences, October 21-22, 1993, Lugano-Agno, Switzerland. London, Parthenon Publishing, pp. 67-86.

Vollenweider FX, Gamma A, Baer T, et al. (1996) Ketanserin, a 5-HT2 antagonist, but not haloperidol, effectively blocks psilocybin-induced model psychosis in healthy volunteers. [Abstract] WPA-Abstractbook: 116

Vollenweider FX, Antonini A, Leenders KL, Mathys K. (1997a) Effects of high amphetamine doses on mood and cerebral glucose metabolism in normals using positron emission tomography (PET). [submitted] *Psychiatry Research: Neuroimaging.*

Vollenweider FX, Antonini A, Leenders KL, Oye I, Hell D, Angst J. (1997b): Differential Psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers measured by FDG-PET. *Eur Neuropsychopharmacol* 7:25-38

Vollenweider FX, Leenders KL, Scharfetter C, Antonini A, Maguire P, Missimer J, Angst J. (1997c): Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [F-18]-fluorodeoxyglocose (FDG). *Eur Neuropsychopharmacol* 7:9-24

Vollenweider FX, Leenders KL, Scharfetter C, Maguire P, Stadelmann O, Angst J. (1997d): Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharm* 16:357-372

Vollenweider FX, Liechti M, Gamma A, Hell D, Geyer M. (1997e) Effects of MDMA ("ecstasy") on sensorimotor gating, attention, and mood in healthy volunteers. [Abstract] The State of the Art in Psychiaty/Abstracts 1997: 28

Vollenweider FX, Liechti M, Gamma A, Huber T. (1997f): Psychological and cardiovascular effects and short-term sequale of MDMA ("Ecstasy") on MDMA-naive healthy volunteers. [submitted] *Neuropsychopharm*.

Vollenweider FX, Vontobel P, Hell D, Leenders KL (1997g) Evidence for 5-HT2 mediated increase of basal ganglia dopamine release in human model psychosis - a PET study with [11C]raclopride [Abstract] The State of the Art in Psychiaty/Abstracts 1997: 39.

Watts VJ, C.P. Lawler CP, Fox DR, K.A. Neve KA, D.E. Nichols DE, Mailman RB (1995): LSD and structural analogs: pharmacological evaluation at D_1 dopamine receptors. *Psychopharmacology*, 118: 401-409.

Wing LL, Tapson GS, Geyer MA. (1990): 5HT-2 mediation of acute behavioral effects of hallucinogens in rats. *Psychopharmacology* (Berlin) 100:417-425