

A systems model of altered consciousness: Integrating natural and drug-induced psychoses

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ABSTRACT: Increasing evidence from neuroimaging and behavioral studies suggests that functional disturbances within cortico-striato-thalamic pathways are critical to psychotic symptom formation in drug-induced and possibly also naturally occurring psychoses. Recent basic and clinical research with psychotomimetic drugs, such as the N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, ketamine, and the serotonin-2A (5-HT_{2A}) receptor agonist, psilocybin, suggest that the hallucinogenic effects of these drugs arise, at least in part, from their common capacity to disrupt thalamo-cortical gating of external and internal information to the cortex. Deficient gating of sensory and cognitive information is thought to result in an overloading inundation of information and subsequent cognitive fragmentation and psychosis. Cross-species studies of homologues gating functions, such as prepulse inhibition of the startle reflex, in animal and human models of psychosis corroborate this view and provide a translational testing mechanism for the exploration of novel pathophysiologic and therapeutic hypotheses relevant to psychotic disorders, such as the group of schizophrenias.

KEY WORDS: NMDA antagonist (ketamine), Serotonin-2A agonist (psilocybin), Model psychosis, Schizophrenia, Positron Emission Tomography (PET), Prepulse inhibition of the acoustic startle (PPI).

INTRODUCTION

This review summarizes recent experiments assessing commonalities between naturally occurring psychoses and the effects of both serotonergic hallucinogens such as psilocybin, and N-methyl-D-aspartate (NMDA) antagonists such as ketamine, in humans. Converging approaches to understanding the pharmacological effects of hallucinogens on brain functions have been utilized in these studies. The major approaches include the investigation of drug-induced changes of brain activation patterns as indexed by [18F]fluorodeoxyglucose (FDG) and the characterization of functional interactions among neurotransmitter systems by assessing drug-induced displacement of specific radiolabeled receptor ligands using positron emission tomography (PET). Furthermore, receptor mechanisms of hallucinogenic and related drugs are investigated by exploring the effects of specific receptor antagonists on drug-induced psychological alterations and on information processing functions such as sensorimotor gating as indexed by prepulse inhibition (PPI) of startle.

The premise of the present review is that schizophrenia cannot

be understood adequately by any single-transmitter model. First, it has long been recognized that a number of distinct etiologies are likely to be responsible for a group of disorders that have sufficiently overlapping symptomatology to be classified phenomenologically as schizophrenia. Second, even within one of these etiologically distinct subtypes of schizophrenia, multiple neurotransmitter systems are likely to be functionally abnormal and contribute to the symptomatology. This review attempts to summarize a systems model that should have heuristic value in the further explication of the complex interactions that are evident in the recent literature on the group of schizophrenias. The proposed model is based on the integration of information from studies of patients suffering from schizophrenia and studies of drug-induced human and animal models of psychoses.

Indoleamine hallucinogens, such as LSD or psilocybin, and dissociative anesthetics, such as phencyclidine (PCP) or ketamine, produce a number of psychotic symptoms, as well as both cognitive and behavioral deficits associated with schizophrenic psychoses [64,142,144]. Hence, exploring the mechanisms responsible for these actions of psychotomimetics may provide new insights into the neurobiology of the group of schizophrenias. Indeed, recent research into psychotomimetic drug actions has revitalized a number of alternative hypotheses to the classic dopamine hyperactivity model of schizophrenia. In particular, the serotonin hypothesis of schizophrenia was derived from early studies of the pharmacology of LSD and its structural relationship to serotonin (5-Hydroxytryptamine, 5-HT) [45,157]. More recently, this hypothesis has received renewed support: first by the finding that indoleamine hallucinogens (e.g., LSD or psilocybin) produce their psychotomimetic effects through excessive 5-HT_{2A} receptor activation [90,151]; second, by the finding of 5-HT₂ receptor abnormalities in the brains of schizophrenic patients [8,59,69,81]; and third, by the role of 5-HT₂ receptor antagonism in the effects of atypical neuroleptics such as clozapine and risperidone in patients and animal models of schizophrenia [84,96]. Similarly, the discovery that PCP and ketamine are antagonists at the NMDA subtype of glutamate receptors [6] added strong support to the glutamate deficiency hypothesis of schizophrenia [74]. The glutamate deficiency hypothesis is consistent with findings of decreased glutamate concentrations in the cerebrospinal fluid of schizophrenic patients [74], alterations in cortical and subcortical NMDA receptor densities [7,31,67,75], and reduced glutamate release in postmortem brains of schizophrenic patients [32,58,117].

One recently identified commonality that is critical to the

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development of this systems model is the hyper-frontality that is seen in both the initial stages of psychosis and in drug-induced psychoses in humans. For example, we have found that both serotonergic hallucinogens (e.g., psilocybin) and NMDA antagonists (e.g., ketamine) produce a marked activation of the prefrontal cortex (hyper-frontality) as well as other overlapping changes in cortical, striatal, and thalamic regions [149,150]. This commonality [145] suggests that some of the psychotic symptoms induced by these drugs may relate to a common final pathway or neurotransmitter system. This view is consistent with the "thalamic filter" hypothesis of psychoses, which posits that cortico-striatal pathways exert a modulatory influence on thalamic gating of sensory information to the cortex [23,142,143]. Theoretically, thalamic gating deficits should result in sensory overload with excessive processing of exteroceptive and interoceptive stimuli leading to a collapse of integrative cortical functions, and subsequently to cognitive fragmentation and psychosis. This view is also derived from animal model studies of the gating deficits in schizophrenia, which demonstrate that both serotonergic hallucinogens and NMDA antagonists disrupt prepulse inhibition (PPI) of the acoustic startle reflex, a measure of sensorimotor gating and information processing [46]. Extensive lesion and drug studies have shown that PPI is subject to considerable forebrain modulation from cortical, limbic, striatal, pallidal, and thalamic structures, including the cortico-striato-pallido-thalamic (CSPT) circuitry [135,137,138].

PARALLELS BETWEEN PSILOCYBIN- AND KETAMINE-INDUCED ALTERED STATES OF CONSCIOUSNESS (ASC) AND SYMPTOMS OF SCHIZOPHRENIA

Psychotomimetic drugs have been shown to provide useful tools to study the neurobiology underlying the symptomatology of the group of schizophrenias. In this respect, standardized assessments of the common denominator of drug-induced Altered States of Consciousness (ASC) and endogenous psychoses are of fundamental importance. However, only recently have standardized assessments been used to characterize and to compare hallucinogen-induced states and naturally occurring psychoses. According to the seminal work of Dittrich and co-workers [35,37], the common denominators of drug- and non-drug-induced ASC consist of three main dimensions (factors), which can be assessed quantitatively by the APZ rating scale (*Aussergewöhnlicher Psychischer Zustand* = Altered States of Consciousness = ASC). The APZ scale reliably measures shifts in mood, thought disorder, and changes in the experience of the self/ego and of the environment in both drug- and non-drug-induced ASC [36]. The first dimension, OB ("oceanic boundlessness"), measures derealization and depersonalization phenomena associated with a positive basic mood ranging from heightened feelings to sublime happiness or grandiosity. The second dimension, AED ("dread of ego dissolution"), measures thought disorder, ego disintegration, loss of autonomy and self-control variously associated with arousal, anxiety, and paranoid feelings of being endangered. The third dimension, VR ("visionary restructuralization"), refers to auditory and visual illusions, hallucinations, synaesthesias, and changes in the meaning of various percepts. The cross-cultural consistency of the APZ dimensions, OB, AED, and VR, has been confirmed in an international study on ASC [37]. Furthermore, empirical studies demonstrate that the APZ dimensions are altered consistently in a manner that is independent of the particular treatment, disorder, or condition that precipitated the ASC.

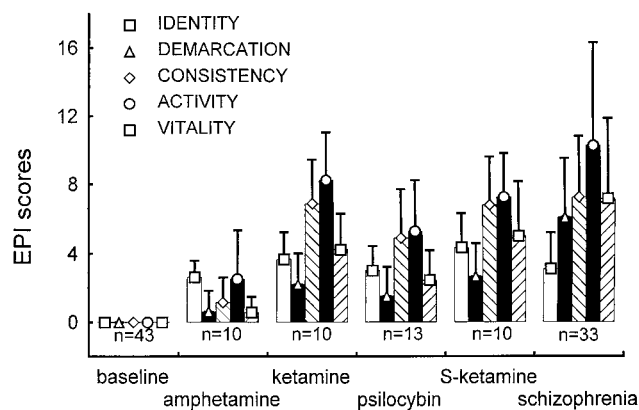


FIG. 1. Comparison of mean Ego-Pathology Scores (EPI) obtained in model psychoses and first episode schizophrenics. Mean $\pm$ SD, all $p < 0.01$.

In an extensive study with acute schizophrenic, schizoaffective, and schizophreniform psychotic patients, it was demonstrated that the OB dimension of the APZ correlates with factor 3 of the well-established Brief Psychiatric Rating Scale (BPRS), including most of the positive symptoms of schizophrenia, such as conceptual disorganization, grandiosity, and unusual thought content. Similarly, the AED dimension of the APZ correlates with factor 1 of the BPRS, which includes anxiety and depression [55]. These data corroborate and extend previous indications that the ASC induced by psychedelics have qualitative similarities with the earliest phases of schizophrenic psychoses [14,25,54,55,57,65].

Another commonality of psychotomimetic drug effects and schizophrenia involves ego disorders as assessed by the "Ego Pathology Inventory" (EPI) [110,154]. The "ego identity" scale of the EPI includes items for doubts, changes or loss of one's own identity in respect to "gestalt," physiognomy, gender, and biography. The "ego demarcation" scale refers to one's uncertainty or lack in differentiating between ego and nonego spheres concerning the thought process, affective state, and body experience. The "ego consistency" scale comprises the 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 ruin of mankind, or of the universe [113]. Direct comparisons of EPI scores of psilocybin- and ketamine-treated subjects with those obtained in first episode schizophrenics revealed that the dimensions "ego consistency" and "ego identity" were impaired similarly in both conditions. At the doses tested, the scores for "ego activity" and "ego demarcation" reached only about 1/2 to 2/3 of the values seen in schizophrenic patients (Fig. 1). Similarly, the dimension "ego vitality" was clearly less affected in ketamine and psilocybin subjects than in schizophrenic patients, suggesting that higher doses or chronic treatments would be necessary to impair the more basic and central nucleus of ego experience such as ego vitality [113]. Given the fact that the various forms of ego disorders have commonalities with the group of schizophrenias [42,65, 82], these findings suggest that psychotomimetic drugs can mimic some important aspects of schizophrenic psychoses, but that there

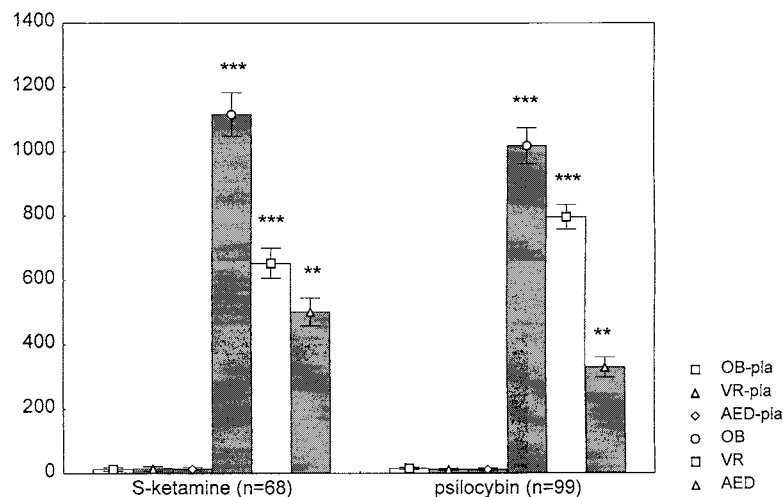


FIG. 2. Comparison of mean values of APZ-OAV scores obtained in placebo (pla) and S-ketamine (0.012 mg/kg/min, i.v.) and psilocybin (15–20 mg, po) conditions. OB, Oceanic Boundlessness; AED, Anxious Ego-Dissolution; VR, Visionary Restructuralization. Mean $\pm$ SE; *** $p < 0.001$, ** $p < 0.01$.

are also differences, particularly in the quality and quantity of ego disorders, at the doses tested.

In a series of studies using both the APZ and EPI rating scales, we found that administration of either a serotonergic hallucinogen (e.g., psilocybin) or an NMDA antagonist (e.g., ketamine) elicited a psychosis-like syndrome in normal volunteers that was characterized by ego disturbances, illusions and hallucinations, thought disorders, paranoid ideations, and changes in mood and affect (Figs. 2 and 3) [145,149–151].

Both psilocybin and ketamine produced a number of psychotic symptoms that resembled the positive symptoms seen in incipient stages of acute schizophrenic episodes. For example, the hallucinatory disintegration and the loss of self-control over thought process and intentionality observed in psilocybin- and ketamine-induced psychoses are highly reminiscent of acute schizophrenic decompensation [15,61,72,91,108,111]. Also, the finding of heightened awareness associated with euphoria reported by psilocybin- and ketamine-treated subjects is consistent with the view that the earliest affective changes in schizophrenic patients are often pleasurable or exhilarating [14,25,54,65]. Furthermore, the fact that these drug-induced states are characterized by visual hallucinations is consistent with evidence that visual hallucinations occur significantly more often in acute than in chronic schizophrenic patients [43,54,55,92]. Similar findings were reported in comparable studies in healthy volunteers with psilocybin or the phenalkylamine hallucinogen mescaline [63,114].

Psilocybin- and ketamine-induced emotional disturbances and disorganization of thought appeared to be secondary to and influenced by serialization 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 was transient and occurred only in some of the subjects. Typically, psilocybin and ketamine subjects—in contrast to patients with schizophrenia—recognized serialization and depersonalization phenomena as being abnormal experiences that were attributable to having ingested a drug. Inter-individual differences in these responses might have been due to variations in dosage and/or personality structure [34,41,139].

Despite the number of similarities between the psilocybin and ketamine models of psychoses, substantial differences are also apparent in the limited human studies, in keeping with the more extensive animal literature and the different primary mechanisms of actions of these drugs. Specifically, while both psilocybin and ketamine appear to produce phenomena resembling the positive symptoms common to the schizophrenias, only ketamine appears to also mimic the negative symptoms associated with the schizophrenias. For example, it appears that both S-ketamine and racemic ketamine produced more pronounced anxiety, thought disturbances, and ego disintegration than psilocybin. Moreover, in contrast to psilocybin, both S-ketamine and racemic ketamine transiently produced apathy, emotional withdrawal, and feelings of indifference that resembled in many ways the negative symptoms of schizophrenia. This finding is consistent with the view that ketamine and PCP induce thought disturbances and cognitive impairments in healthy subjects that mimic those seen in schizophrenia, including deficits in working memory, attention, abstract reasoning, decision making, and planning [77–79,88,148]. Thus, it has been argued frequently that the NMDA antagonists, including ketamine and PCP, partially mimic the negative and disorganized symptoms of schizophrenia as well as the positive symptoms [29,87,145] (Table 1).

A Neuronal Basis of ASC: The CSTC Model of Information Processing

Recent theories about the neuronal basis of ASC posit that deficits in early information processing may underlie the diversity of psychotic symptoms and cognitive disturbances observed in both drug-induced model psychoses [142,144] and naturally occurring psychoses [17,47]. In particular, it is thought that a fundamental feature of information-processing dysfunction in both hallucinogen-induced states and schizophrenia-spectrum disorders is the inability of these subjects to screen out, inhibit, filter, or gate extraneous stimuli and to attend selectively to salient features of the environment. Gating deficits may cause these subjects to become overloaded with excessive exteroceptive and interoceptive

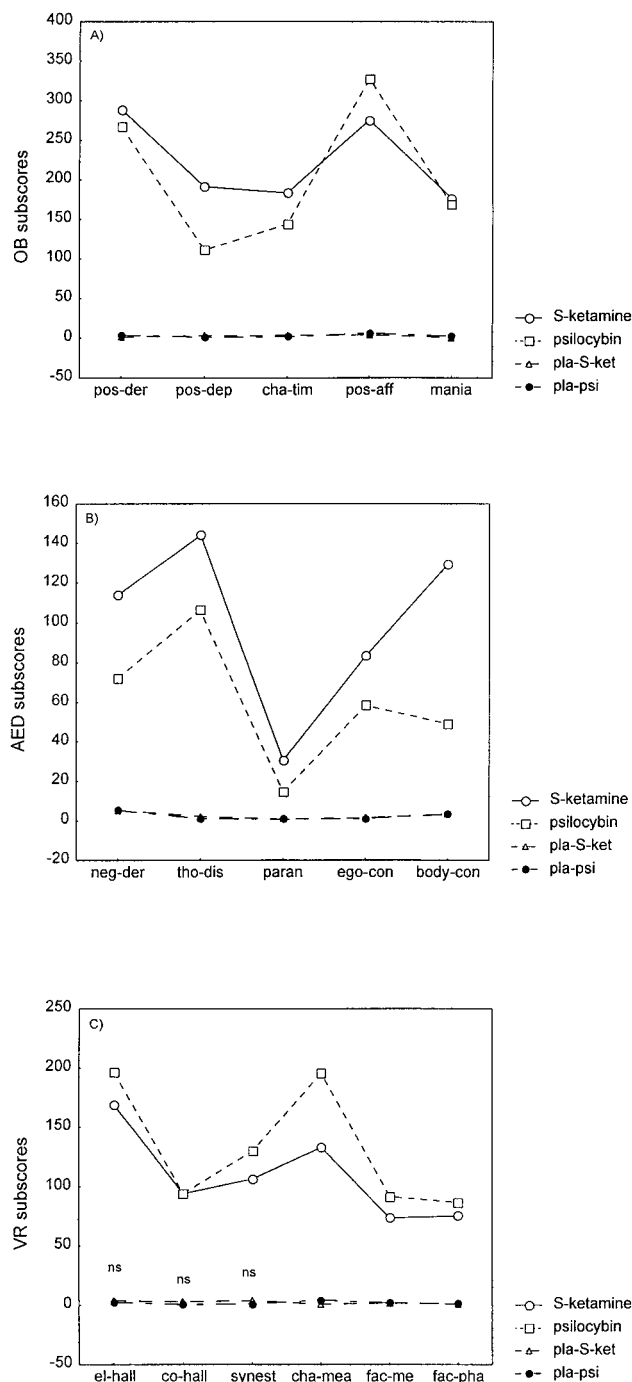


FIG. 3. Effects of S-ketamine and psilocybin on APZ-OAV subscales: (A) OB subscales are: positively experienced derealisation (pos-der) and depersonalization (pos-dep), changed sense of time (cha-tim), positive affect (pos-aff), and mania-like experience (mania). Note that psilocybin produced significantly higher scores for pos-aff and lower scores for pos-der and cha-tim than S-ketamine. (B) AED subscales are: negatively experienced derealisation (neg-der), thought disorder (tho-dis), paranoia (paran), loss of ego (ego-con), and body control (body-con). Note that S-ketamine produced significantly higher scores for tho-dis, ego-con, and body con. (C) VR subscales are: elementary (el-hall) and complex hallucinations (co-hall), synesthesias (synest), changed meaning of percepts (cha-mea), facilitated memory (fac-mem), and phantasies (fac-pha). Mean $\pm$ SE, all $p < 0.01$.

stimuli, which, in turn, could lead to a breakdown of cognitive integrity and difficulty in distinguishing self from nonself [13,70,71,94,110,144]. Impaired sensorimotor gating and loosening of ego boundaries could lead to positive symptoms such as delusions, hallucinations, thought disturbances, persecution, and the loss of a coherent ego experience. In addition, various negative symptoms, such as emotional and social withdrawal, could result from and be understood as efforts to protect from input overload.

Based on the available neuroanatomical evidence and pharmacological findings of hallucinogenic drug actions, we propose that a cortico-subcortical model of psychosensory information processing can be used as an initial working hypothesis to analyze and integrate the effects of different chemical types of hallucinogens at a systems level. The model advances that drug-induced ASC can be conceptualized as complex disturbances that arise from more elementary deficits of sensory information processing in cortico-striato-thalamo-cortical (CSTC) feedback loops [23,142,144]. The model is based on evidence that sensorimotor gating functions are modulated by multiple interacting neurotransmitter systems, including dopaminergic, glutamatergic, serotonergic, GABAergic, and cholinergic systems within cortical, limbic, striatal, and brain-stem structures [134,135].

In short, the model is based upon five segregated CSTC loops functioning in parallel: the motor, oculomotor, prefrontal, association, and limbic loops. 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 and 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 (Fig. 4) [3].

The CSTC model posits that the *thalamus*, with its various nuclei, plays a key role in controlling or gating extero- and interoceptive information to the cortex and is thereby fundamentally involved in the regulation of the level of awareness and attention [53,127,129]. Experimental evidence indicates that the thalamic transfer of information to the cortex is highest during waking and, especially, states requiring high levels of attention (and thus consciousness) [28]. Conversely, information transfer by the thalamus is demonstrably low during drowsiness or sleep [27]. By extending this concept, we suggest that nonphysiological disruptions beyond the normal range of thalamic gating of sensory and cognitive information result in an overloading inundation of the cortex. This inundation of information, in turn, may ultimately cause the sensory flooding, cognitive fragmentation, and ego dissolution seen in both drug-induced ASC and naturally occurring psychoses.

The gating capacity of the thalamus is thought to be under the control of several pathways and neurotransmitter systems. *Cortico-striato-thalamic* (CST) pathways projecting to the dorsomedial (MD) and reticular nuclei of the thalamus are suggested to control the thalamic transfer of information to the cortex [27]. Specifically, it is hypothesized that the GABAergic input from striatum and pallidum exerts an inhibitory influence on these thalamic neurons. Inhibition of the thalamus should result in a decrease of sensory input to the cortex and in a reduction of arousal, protecting the cortex from sensory overload and breakdown of its integrative capacity. The striatal activity is modulated by a number of subsidiary circuits and neurotransmitter systems. The mesostriatal dopaminergic projections provide an inhibitory input to the striatum. In parallel, the mesostriatal serotonergic pathway projects

TABLE 1
COMPARISON OF EFFECTS OF SEROTONERGIC HALLUCINOGENS, NMDA ANTAGONISTS, AND SYMPTOMS IN SCHIZOPHRENIAS

	Psilocybin ¹	Ketamine ¹	Schizophrenias
Receptor level			
Primary locus of action	5HT _{2A/1A} GABA, DA _{2/1}	NMDA 5-HT _{2A} , GABA, DA _{2/1}	Unknown
Downstream effects on Psychopathology	mGluR	mGluR	
Positive symptoms			
Hallucinations/Illusions	++	+	++
Delusions	+	+	++
Thought disorder	+	++	++
Negative symptoms			
Blunted affect	0-+	+ - ++	++
Withdrawal	+	+ - ++	++
Depersonalization	+ - ++	++	++
Derealization	+	++	++
Neuropsychology			
Attention disturbance	+ - ++	+	++
Distractibility	+	++	++
Working memory	+	++	++
Associative deficits	+	+ - ++	++
Planning/mental	++	?	++
Flexibility			
Cortical activity			
Frontal (PET)	++ (acute)	++ (acute) -- (chronic) ²	++ (acute) -- (chronic)

¹ Both psilocybin and ketamine secondarily increase striatal DA release.

² Chronic administration of NMDA antagonists in rats decreases frontal cortical activity (summarized after [78,79,87,88,112,113,145,148,150–153]).

from the dorsal raphe to the striatum [107], providing an independent modulatory influence on this circuit. Under physiological conditions, the inhibitory influences of the dopaminergic and serotonergic systems on the striatum are thought to be counterbalanced by the excitatory glutamatergic input derived from corticostriatal pathways [23]. This relationship implies that, either an increase in dopaminergic tone (e.g., by amphetamine), an increase in serotonergic activation (e.g., by psilocybin), or a decrease in glutamatergic transmission (e.g., by ketamine) should reduce the inhibitory influence of the striatum on the thalamus and open the thalamic “filter.” Thus, any of these changes would lead to a sensory overload of the cerebral cortex and, ultimately, psychosis. By extrapolation, genetic, biochemical, or developmental abnormalities leading to functional changes similar to these pharmacologically induced effects could produce multiple distinct etiologies leading to phenomenologically similar psychotic syndromes.

Reverberating activity in the limbic CSTC feedback loop, including the MD thalamus, has been associated with focusing, maintaining, and shifting attention/intention in sustained delay-related behavior [93]. Transient inhibition of the MD thalamus by GABAergic input from the striatum appears to be necessary to initiate new patterns of behavior [60]. Several hypotheses have been offered to describe the specific function of the reticular thalamus in the modulation of attention. For example, it has been hypothesized that the reticular thalamus may control the “search-light” of attention [30,118,119]), increase the signal-to-noise ratio of the thalamocortical transfer [85], or control the quality rather than the quantity of information forwarded to the cortex [126]. A more recent hypothesis suggests that reticular thalamic neurons may modulate high frequency patterns of thalamocortical oscillations (about 40 Hz rhythms), thus facilitating the flow of relevant

information through the thalamus [106,128,155]. As pointed out by Smythies [125], this speculation suggests that the reticular thalamus might be involved in the overall organization of “binding” (bringing the train of input into a coherent experience) rather than with selective attention *per se*.

With regard to the ASC produced via the serotonergic agonist actions of hallucinogens such as psilocybin or LSD, it is important to recognize that the thalamus receives not only GABAergic input from the ventral pallidum, but also serotonergic input from the midbrain raphe nuclei and noradrenergic input from the locus coeruleus [9,10,130]. These monoaminergic projection systems comprise important parts of the reticular formation (RF), a meshwork of nuclei located in the brainstem. The RF is crucial for bringing the brain into a state conducive for consciousness [28, 102] by setting the general level of wakefulness and facilitating the transfer of information through the thalamus [122]. The RF, which is activated by input from all sensory modalities, includes extensive and diffuse serotonergic projections to components of the CST loops: the ascending ventral pathway terminates in the prefrontal and cingulate cortices, hippocampus, striatum, nucleus accumbens, and amygdala, the dorsal pathway projects to the thalamus. Excessive activation of the postsynaptic elements of the serotonergic projection sites (e.g., by psilocybin) should also result in a reduction of thalamic gating and, consequently, in a sensory overload of frontal cortex and psychosis.

Empirical Approaches to Neuronal Correlates of Drug-induced ASC

Although the CSTC model is an oversimplification, it provides a set of testable hypotheses. Specifically, according to the CSTC

Cortico-striato-thalamo-cortical feedback

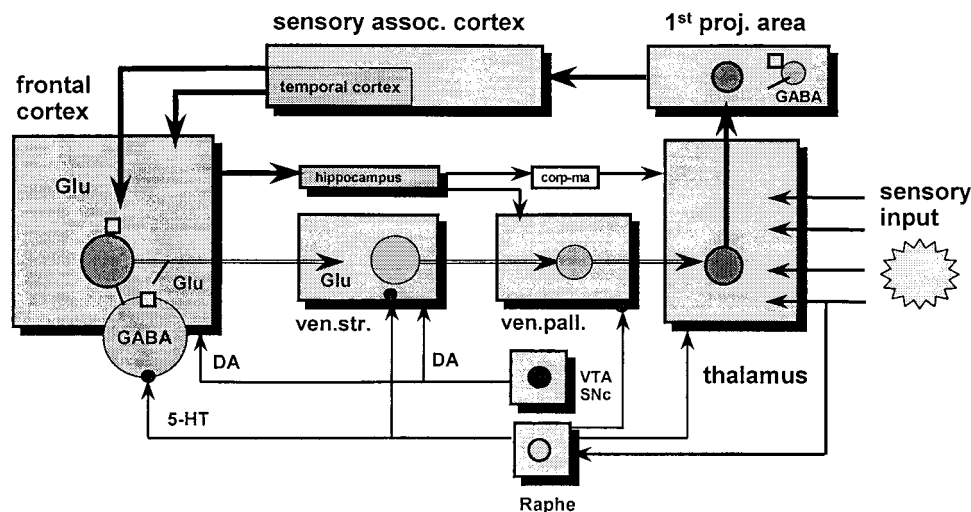


FIG. 4. The limbic cortico-striato-thalamic (CST) feedback loops are involved in memory, learning, and self-nonsel discrimination by linkage of cortically categorized exteroceptive perception with internal stimuli of the value system. The filter function of the thalamus, which is under the control of the CSTC feedback/re-entry loops, is postulated to protect the cortex from exteroceptive sensory information overload, as well as from internal over-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 by blockade of NMDA-mediated glutamatergic (Glu) cortico-striatal and/or by increasing 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 again results in an opening of the thalamic filter, sensory overload of the cortex, and psychosis. (Legend: ven.str., ventral striatum; ven.pall., ventral pallidum; VTA, ventral tegmental area; SNC, substantia nigra pars compacta; corp.ma, corpus mamillaria; 5-HT, serotonin).

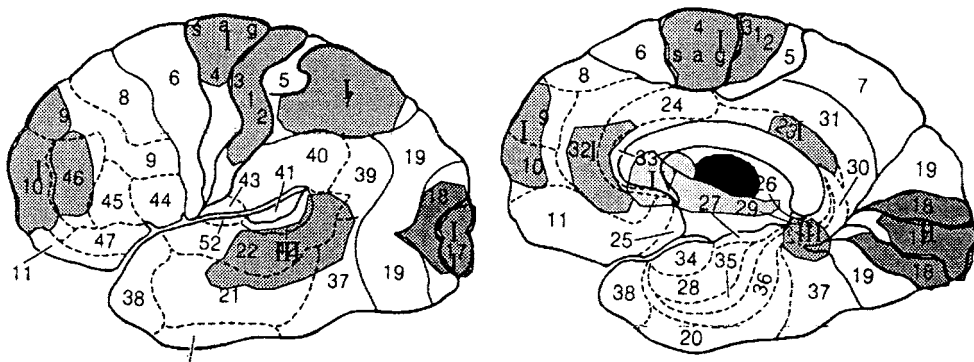
model, we have hypothesized that a reduction of NMDA-mediated neurotransmission, e.g., by ketamine, or a stimulation of postsynaptic sites of serotonergic projections, e.g., by psilocybin, should lead to a sensory overload of the cortex, and presumably to an activation of the prefrontal cortex (“hyper-frontality”). Indeed, in a comparative study using PET and the radioligand FDG, we found that both ketamine and psilocybin produced a marked activation of metabolism in the fronto-medial and -lateral cortices including the anterior cingulate, as well as a number of overlapping changes in the basal ganglia, thalamus, and other cortical regions in healthy human volunteers (for an overview [149,150]). Moreover, this hyper-frontality was associated with mania-like symptoms, ego dissolution, derealization, and thought disturbances [145,149,150] and was corroborated by comparable PET or SPECT studies using ketamine, psilocybin, or mescaline [19,56,62].

To further identify the common neuroanatomical substrates of drug-induced ASC, a number of additional placebo-controlled FDG-PET experiments with S-ketamine, R-ketamine, and amphetamine were performed and pooled with previous studies in normal subjects [144]. Factor analysis of normalized PET data ($n = 106$) revealed that the overall cortical-subcortical organization based on a five-factor solution during drug-induced ASC was very similar to that seen under placebo ($n = 46$), indicating that the functional integrity of interrelated brain regions within these factors, which might be interpreted as functional “units” or “modules,” was not disrupted in ASC (see Fig. 5). According to their content, these 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 of drug and placebo conditions revealed, however, that subjects had significantly higher scores on the “frontal-parietal” and “striatal” network and lower scores on the “occipital cortex” in these ASCs than in resting states. These findings indicate first that the fundamental structure of the functionally defined neuronal systems remains intact during ASC. Nevertheless, the neuronal activity within these functional modules and the global relationships between these modules differs markedly between drug-induced ASCs and the normal waking state.

Multiple regression analysis of psychological scores (APZ scores) and factor scores (normalized metabolic activity) revealed, firstly, that the dimension OB (oceanic boundlessness including derealization, depersonalization, heightened mood, and grandiosity) relates to changes in metabolic activity in the frontal-parietal cortex, occipital cortex, and striatum. Secondly, VR (visionary restructuralization including hallucinatory phenomena) is associated with activity changes in the same network as the OB dimension, but additionally relates to temporal activity. Thirdly, AED (anxious ego dissolution) is primarily associated with metabolic changes in the thalamus (see Equations 1–4). The observed association between AED and increased relative metabolic activity in the thalamus is underscored by the finding of a positive correlation between ego-identity impairment and the thalamic factor.

- ◆ 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



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FIG. 5. Anatomical 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.

$$OB = 0.32 F_1^* - 0.20 F_2^* + 0.11 F_3 + 0.20 F_4^* + 0.05 F_5 \quad (1)$$

$$VR = 0.20 F_1^* - 0.27 F_2^* + 0.17 F_3^* + 0.32 F_4^* + 0.10 F_5 \quad (2)$$

$$AED = 0.00 F_1 + 0.09 F_2 + 0.01 F_3 + 0.17 F_4 + 0.28 F_5^* \quad (3)$$

$$EPI-EI = 0.04 F_1 + 0.04 F_2 + 0.05 F_3 + 0.10 F_4 + 0.20 F_5^* \quad (4)$$

The relationship between the APZ scores OB, VR, and AED, and the EPI score ego-identity impairment (EPI-EI) and normalized metabolic activity in the five functional brain modules (factors) identified by factor analysis. F1 is fronto-parietal factor, F2 occipital factor, F3 temporal factor, F4 striatal factor, and F5 thalamic factor. Factors that significantly contribute to the computation are indicated by asterisks; $*p < 0.05$.

These results show that the positively experienced form of ego dissolution, OB, can be clearly differentiated in terms of neuro-metabolic activity from the more fragmented and anxious ego dissolution AED. The OB dimension, which relates to the altered perception of time and space as well as the pleasurable experience of dissolution of ego boundaries, which can culminate in transcendental or "mystical" states, substantially loads on the fronto-parietal factor. Indeed, according to current views, in conjunction with parietal and limbic areas, the frontal cortex is critical for the construction and maintenance of a coherent self. In its executive faculty, the frontal cortex, including the anterior cingulate, has an active role in structuring time, directing attention to relevant extero- or interoceptive stimuli, and initiating and expressing appropriate behaviors [44,99,104]. The parietal cortex is important for

determining the relationship of the self to extrapersonal space, based on visuo-spatial input from the dorsal stream [98,105]. It is noteworthy that the fronto-parietal factor also includes somatosensory and motor cortical areas, which contribute essential information to the formation of body image and physical representation of the self. As an interrelated network, the areas of the fronto-parietal factor are sometimes called "Central Neural Authority" [66] to express the idea that they constitute a functional system crucially involved in ego-structuring processes and the formation of a coherent self that is defined in time and space. Based on these theoretical concepts, it appears plausible that overstimulation of the Central Neural Authority may lead to profound alterations of self-experience and space/time perception, as reflected by the increased OB scores in hallucinogen-induced ASC. Empirically, anxious ego dissolution (AED) and ego-identity impairment appear to depend mainly on thalamic activity. This finding is in line with the view that dysfunction of the thalamic filter could lead to sensory overload, cognitive fragmentation, and psychosis, as is postulated by the CSTC model.

IMPLICATIONS FOR SCHIZOPHRENIA RESEARCH

The Role of Cortico-striato-thalamic (CST) Pathways in Schizophrenia

First, the common activation of the frontal cortex, anterior cingulate, temporomedial cortex, and thalamus seen in subjects treated with psilocybin or ketamine accords with the thalamic filter

theory suggesting that a disruption of the CST loop should lead to a sensory overload of the frontal cortex and its limbic relay stations. A strikingly similar pattern of correlations between hyper-perfusion in the frontal, anterior cingulate, parietal, and temporal cortices with formal thought disorder and grandiosity was recently found in drug-naïve acutely schizophrenic patients [109]. Interestingly, after neuroleptic treatment and reduction of positive symptoms, this study found that persisting negative symptoms correlated with frontal, cingulate, basal, and thalamic hypo-perfusion. These findings underscore the view that positive and negative symptoms of schizophrenia or specific sub-syndromes may be related differentially to aberrant patterns of cerebral activity including limbic CST circuits rather than deficits in a single location [83,115]. In fact, a number of brain-imaging studies implicate the temporal cortex, basal ganglia, and thalamus in schizophrenia. Hyper-temporality [33,115], increased [20,156] and reduced [21, 116,120] metabolism in the basal ganglia [38,39], and abnormalities in thalamic activity [4,5,22,120,121] have all been reported in patients with schizophrenia.

Hyper-frontality as an Index of Acute Psychoses

Second, hallucinogen-induced hyper-frontality is of particular interest because it appears to parallel similar findings in acutely ill schizophrenic and nonschizophrenic psychotic patients [24,26,40, 109]. The finding that some psychotic symptoms are correlated with the activation of the prefrontal and/or cingulate anterior cortex in some studies in acute or drug-naïve first-episode schizophrenics [83,109] suggests that hyper-frontality rather than hypo-frontality (as seen in chronic schizophrenia) is a pathophysiological manifestation of certain acute psychotic symptoms. This view is corroborated by the observation that ketamine produced a similar activation of the prefrontal and cingulate cortices concomitant with an exacerbation of psychosis in chronic schizophrenic patients [80]. Furthermore, pretreatment with the atypical antipsychotic clozapine reduced S-ketamine-induced prefrontal and thalamic activation and associated psychotic symptoms in normal volunteers (Vollenweider, in preparation, 2001). In light of such evidence, it would be expected that drugs that reduce or prevent excessive prefrontal activation might be useful for treating positive and cognitive symptoms of schizophrenia.

Convergence of Effects of Psychedelic Hallucinogens and NMDA Antagonists

Third, the hyper-frontality common to the psilocybin and ketamine models of psychoses also supports the idea that psychedelic hallucinogens and psychotomimetic NMDA antagonists may mediate some of their effects through a common final pathway or neurotransmitter system, downstream to their primary locus of action. In particular, the similarity of the effects of psilocybin and ketamine on ego, cognition, and perception underscore recent animal and human findings suggesting a convergence in their behavioral effects despite the differences in their primary mechanisms of action. For example, electrophysiological studies have produced new evidence that both psychedelic hallucinogens and NMDA antagonists activate the serotonergic system and enhance glutamatergic transmission via non-NMDA receptors in the frontal cortex [2,100]. Of particular relevance to sensory overload theories of schizophrenia, animal model studies have demonstrated that both psychedelic hallucinogens and NMDA antagonists produce deficits in sensorimotor gating functions that mimic those seen in schizophrenic and schizotypal patients [18].

In both animals and humans, the two most widely studied behavioral measures of sensorimotor gating dysfunctions in

schizophrenia are habituation and prepulse inhibition (PPI) of the startle response. Symptomatic schizophrenia patients and unmedicated schizotypal patients exhibit deficits in both startle habituation and PPI, operational measures of the filtering or gating deficits suggested to be central to schizophrenic symptomatology [16]. Indeed, the most striking correlate of deficient PPI in schizophrenia is a measure of thought disorder derived from the Rorschach test [103a]. Similarly, in rats, both psychedelic hallucinogens and NMDA antagonists produce deficits in both habituation [49,52] and PPI [50]. Consistent with the classic dopamine hypothesis of schizophrenia, both direct and indirect dopamine agonists also disrupt PPI robustly in rodents, via mechanisms that are sensitive to antipsychotics having antagonist actions at D2 dopamine receptors [51,89,136]. The effects of serotonergic hallucinogens on sensorimotor gating in rats are clearly due to their agonist actions at 5-HT_{2A} receptors [123], and are mediated at least in part by actions within the ventral pallidum, a component of the CSPT-loop [124]. Antipsychotics having appreciable affinity for 5-HT_{2A} receptors, primarily those deemed "atypical," are effective in preventing the disruptions of PPI produced by serotonergic hallucinogens [48,123]). Thus, these findings support the view that antagonist actions at 5-HT_{2A} receptors may contribute importantly to the unique clinical efficacy of atypical antipsychotics such as clozapine in the treatment of the schizophrenias [95,97].

In contrast to virtually all the behavioral effects of dopaminergic psychostimulants, the gating deficits produced by psychotomimetic NMDA antagonists such as PCP and ketamine have proven to be generally insensitive to blockade by typical antipsychotics that have preferential actions at D2 dopamine receptors (also [51,73]). Nevertheless, the PPI-disruptive effects of NMDA antagonists in rats are blocked by atypical antipsychotics such as clozapine or olanzapine [11,131,132]. These findings parallel observations in normal human volunteers indicating that the psychological effects of ketamine are insensitive to typical antipsychotics but are reversed by atypical antipsychotics [86]. In addition, the novel putative antipsychotic, M100907, which is a selective antagonist at 5-HT_{2A} receptors, is also effective in blocking the PPI-disruptive effects of NMDA antagonists in rats [141]. By contrast, M100907 is ineffective in blocking the PPI-disruptive effects of the dopamine agonist apomorphine [48]. Studies in rats have indicated that the NMDA antagonists produce these gating deficits by actions within particular parts of the CSPT circuitry, including the frontal cortex and hippocampus [12]. In contrast to the effects of dopamine agonists on PPI [133], NMDA antagonists, like serotonergic hallucinogens [124], appear to be ineffective when administered directly into the dopamine-rich nucleus accumbens [12]. Thus, the serotonergic hallucinogens and glutamatergic psychotomimetics produce schizophrenia-like deficits in behavioral measures of gating such as PPI and habituation of startle, and do so by actions localized to different parts of the CSPT circuitry. Despite their different primary mechanisms and sites of action, however, two common denominators of the effects of these classes of drugs is that they alter the dynamics of the integrated CSPT circuitry such that normal information processing is distorted by deficits in fundamental forms of sensorimotor gating.

Consistent with animal studies such as those summarized above, we have recently demonstrated that the effects of psilocybin in humans can be blocked completely by 5-HT₂ antagonists, suggesting that the classic psychedelic hallucinogens, the indoleamines (e.g., LSD) and phenylethylamines (e.g., mescaline), produce their central effects through a common action upon 5-HT₂ receptors [140,151]. The findings that NMDA antagonists also activate the serotonin system [68,101] and that 5-HT₂ antagonists

modify the stimulatory effects of NMDA antagonists on behavior in animal models [76] suggest that some of the effects of NMDA antagonists in humans also relate to 5-HT₂ receptor stimulation. This view is particularly supported by the finding that the highly selective 5-HT_{2A} antagonist and putative novel antipsychotic M100907 is effective in reversing NMDA antagonist-induced PPI deficits [141], a measure of sensorimotor gating in animal models of schizophrenia. Similarly, human studies indicate that the mixed 5-HT₂/D₂ antagonists and atypical antipsychotic sertindole and clozapine, respectively, ameliorate S-ketamine-induced PPI deficits and metabolic hyper-frontality and psychosis in healthy human volunteers [146,147]. However, the similarity of 5-HT₂ agonist and NMDA antagonist effects on the serotonergic system must be interpreted with caution. NMDA antagonists may disinhibit serotonergic activity via NMDA receptors located on cortical GABAergic neurons [1,103], while 5-HT₂ agonists act directly upon 5-HT₂ receptors located on both GABAergic neurons and pyramidal cells in the frontal cortex [2,100].

Thus, converging evidence from psychological and imaging studies in humans and neurobiological studies in animals indicates that similar neural systems are altered by serotonergic hallucinogens and psychotomimetic NMDA antagonists, despite the differences in the primary sites of action of these classes of drugs. Furthermore, these same systems appear to exhibit abnormalities in incipient stages of naturally occurring psychoses. When examined from the perspective of interacting neural systems, striking similarities in the consequences of exposure to psychedelic or psychotomimetic drugs are evident in both clinical and preclinical studies of brain mechanisms and treatments used in the treatment of schizophrenia.

CONCLUSIONS

The present review discussed evidence suggesting that serotonergic hallucinogens and NMDA antagonists produce psychological changes that resemble to a considerable degree the symptoms characteristic of incipient stages of schizophrenic psychoses. These commonalities in drug- and non-drug-induced psychoses are mirrored in similar alterations in patterns of neurometabolic activity observed in acutely ill schizophrenic patients or in healthy humans after administration of either classical hallucinogens or psychotomimetic NMDA antagonists. Despite the similar effects of serotonergic hallucinogens and NMDA antagonists, both animal and human studies confirm that these drug actions are mediated by different primary mechanisms of actions. A systems view of the consequences of these primary drug actions reveals that the common characteristics of these alterations of consciousness can be understood in the context of multiple interacting neurotransmitters including the serotonergic, dopaminergic, GABAergic, and glutamatergic systems within frontal, limbic, striatal, thalamic, and brainstem structures.

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