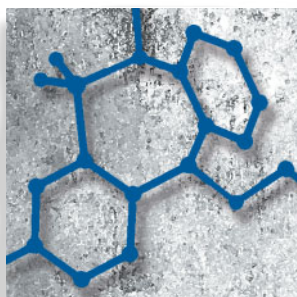


# Pharmacological aspects

## *Brain mechanisms of hallucinogens and entactogens*

*Franz X. Vollenweider, MD*



*This review focuses on recent brain imaging and behavioral studies of sensory gating functions, which assess similarities between the effects of classic hallucinogens (eg, psilocybin), dissociative anesthetics (eg, ketamine), and entactogens (eg, 3,4-methylenedioxymethamphetamine [MDMA]) in humans. Serotonergic hallucinogens and psychotomimetic anesthetics produce overlapping psychotic syndromes associated with a marked activation of the prefrontal cortex (hyperfrontality) and other overlapping changes in temporoparietal, striatal, and thalamic regions, suggesting that both classes of drugs act upon a common final pathway. Together with the observation that both hallucinogens and N-methyl-D-aspartate (NMDA) antagonists disrupt sensory gating in rats by acting on 5-hydroxytryptamine (serotonin) 5-HT<sub>2</sub> receptors located in cortico-striato-thalamic circuitry, these findings suggest that disruption of cortico-subcortical processing leading to sensory overload of the cortex is a communality of these psychoses. In contrast to hallucinogens, the entactogen MDMA produces an emotional state of positive mood, concomitant with an activation of prefrontolimbic/paralimbic structures and a deactivation of amygdala and thalamus.*

**H**allucinogens are a group of chemically heterogeneous compounds, all with the ability to induce altered states of consciousness (ASC) characterized by profound alterations in mood, thought processes, perception, and experience of the self and environment otherwise rarely experienced except in dreams, contemplative and religious exaltation, and acute psychoses. The term hallucinogen seems to be somewhat inappropriate, since not all these drugs reliably produce visual and auditory hallucinations.<sup>1,2</sup> Therefore hallucinogens have been also called psychotomimetic (psychosis-mimicking), psycholytic (psyche-loosening), or psychedelic (mind-manifesting), reflecting the widely different attitudes and intentions with which these substances have been approached.

As plant drugs, psychedelic hallucinogens have a long and colorful history. Because of their ability to produce a visionary and ecstatic state, they were often ascribed magical or mystical properties. For centuries, they were used restrictedly as sacraments in religious rites and people in the Western world were hardly aware of their existence. Examples of the use of naturally occurring hallucinogens in various cultures include psilocybin derived from the Aztec sacred magic mushroom teonanacatl, mescaline derived from the peyote cactus taken by Native Americans, or *N,N*-dimethyltryptamine (DMT), the active ingredient of ayahuasca, a hallucinogenic plant extract employed by Amazonian Indians.<sup>3</sup> However, with the discovery of the hallucinogenic properties of the semisynthetic ergoline *d*-lysergic acid diethylamide (LSD) by the Swiss chemist Albert Hofmann in 1943, hallucinogens and related compounds have become the focus of modern scientific research. The LSD-induced psychosis-like syndrome and the struc-

**Keywords:** *hallucinogen; psilocybin; entactogen; MDMA; NMDA antagonist; ketamine brain imaging; behavioral study*

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## Selected abbreviations and acronyms

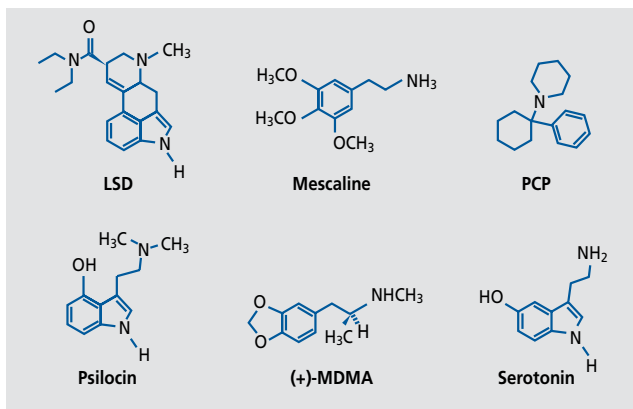
<b>AED</b>	<i>anxious ego-dissolution</i>
<b>ASC</b>	<i>altered states of consciousness</i>
<b>CMRglu</b>	<i>cerebral metabolic rate of glucose</i>
<b>CSPT</b>	<i>cortico-striato-pallido-thalamic</i>
<b>CSTC</b>	<i>cortico-striato-thalamo-cortical</i>
<b>DA</b>	<i>dopamine</i>
<b>DMT</b>	<i>N,N-dimethyltryptamine</i>
<b>DOI</b>	<i>2,5-dimethoxy-4-iodoamphetamine</i>
<b><sup>18</sup>FDG</b>	<i><sup>18</sup>F-fluorodeoxyglucose</i>
<b>5-HT</b>	<i>5-hydroxytryptamine</i>
<b>LSD</b>	<i>d-lysergic acid diethylamide</i>
<b>MDE</b>	<i>3,4-methylenedioxyethylamphetamine</i>
<b>MDMA</b>	<i>3,4-methylenedioxymethamphetamine</i>
<b>NMDA</b>	<i>N-methyl-D-aspartate</i>
<b>OB</b>	<i>oceanic boundlessness</i>
<b>PCP</b>	<i>phencyclidine</i>
<b>PPI</b>	<i>prepulse inhibition</i>
<b>VR</b>	<i>visionary restructuring</i>

tural similarity between LSD and serotonin (5-hydroxytryptamine [5-HT]) prompted the hypothesis that 5-HT is involved in the pathophysiology of schizophrenia. Since then a number of newly discovered hallucinogens or psychotomimetic agents, such as phencyclidine (PCP) and ketamine, have been used as models to study the neuronal basis of drug-induced ASC and its relation to naturally occurring psychoses.<sup>4,6</sup>

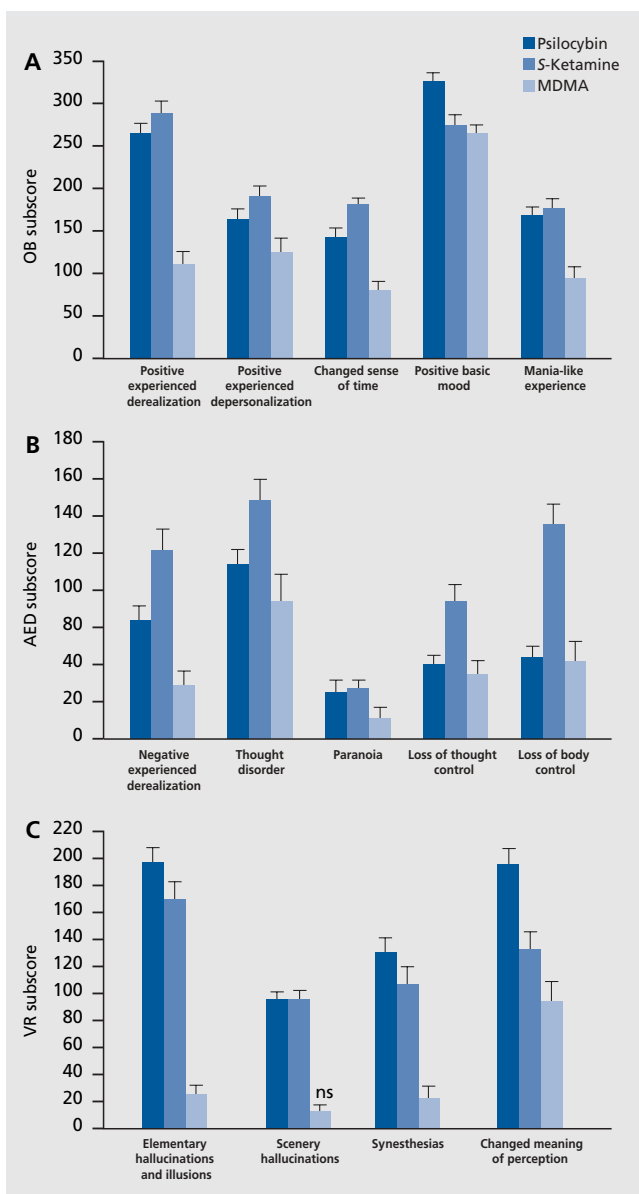
Psychedelic hallucinogens can be classified by either chemical structure or their primary mode of action. The so-called serotonergic hallucinogens include *indolamines*, such as psilocybin and LSD, and *phenylethylamines*, such as mescaline and 2,5-dimethoxy-4-iodoamphetamine (DOI) (Figure 1). Serotonergic hallucinogens act primarily upon 5-HT<sub>1</sub>, 5-HT<sub>2</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors and partly upon the dopamine (DA) receptors D<sub>1</sub> and D<sub>2</sub> and the adrenergic α<sub>2</sub> receptors. A second class of drugs with hallucinogenic properties often referred to as *psychedelic or dissociative anesthetics* includes *arylcylohexylamines*, whose most important representatives are PCP and ketamine. These agents primarily act as antagonists of the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor. Finally, a third class of drugs, the so-called “entactogens,” produce psychedelic-like effects, but virtually no hallucinations. They are closely related structurally to hallucinogenic phenylethylamines and stimulant amphetamines and

include *phenylisopropylamines*, such as 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyethylamphetamine (MDE), and related compounds. This review summarizes recent experiments to elucidate the neurobiological basis of the psychological effects of psilocybin, ketamine, and MDMA, each representing one of the three classes of psychedelics. Functional brain imaging with positron emission tomography (PET) was used to identify the brain regions or functional interactions among the neurotransmitter systems involved in the action of these drugs. Furthermore, receptor mechanisms of hallucinogenic and related drugs have been investigated by exploring the effects of specific receptor antagonists on drug-induced psychological alterations and information-processing functions, such as sensorimotor gating as indexed by prepulse inhibition (PPI) of the startle reflex.

The premise of the present review is that many of the shared psychedelic effects of serotonergic hallucinogens and NMDA antagonists can be understood as an effect downstream of a common neurotransmitter system or final pathway. First, both serotonergic hallucinogens and NMDA antagonists produce sufficient overlapping psychological alterations despite different primary modes of



**Figure 1.** Chemical structures of some important representatives of hallucinogens. Classic serotonergic hallucinogens include indolamines, such as the semisynthetic lysergic acid diethylamide (LSD) and psilocybin/psilocin (the active principle of the sacred Aztec magic mushrooms), and phenylethylamines, such as mescaline (the active principle of peyote cactus). Indolamines and phenylethylamines share close structural features with the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]). Dissociative or psychedelic anesthetics include phencyclidine (PCP) and related drugs, such as ketamine. Entactogens, such as 3,4-methylenedioxymethamphetamine (MDMA), which produce psychedelic-like symptoms but virtually no hallucinations, are structurally closely related to both serotonergic hallucinogens (mescaline) and classic stimulants (amphetamines).



**Figure 2.** Subscale scores of the altered states of consciousness (APZ) questionnaire for S-ketamine (n=68; 0.012 mg/kg/min IV), psilocybin (n=99; 0.26 mg/kg PO), and 3,4-methylenedioxymethamphetamine (MDMA) (n=74; 1.5-1.7 mg/kg PO) in healthy volunteers. With the exception of complex hallucinations after MDMA, S-ketamine-, psilocybin-, and MDMA-induced scores are all significant compared with placebo. Values are means $\pm$ SE, all  $P < 0.05$  or less. **A.** The oceanic boundlessness (OB) scale measures derealization and depersonalization associated with a positive basic mood ranging from heightened feelings to exaltation and alterations in the sense of time. **B.** The anxious ego-dissolution (AED) scale measures ego-disintegration and loss of autonomy and self-control associated with arousal and anxiety. **C.** The visionary restructuralization (VR) scale measures alterations in perception and meaning.

action. Second, there is converging evidence from brain imaging, behavioral, and electrophysiological studies that both serotonergic hallucinogens and NMDA antagonists disrupt information processing within cortico-striato-thalamic pathways implicated in the pathogenesis of psychotic disorders. Since entactogens such as MDMA are expected to produce only mild psychedelic symptoms, it will be of interest to know to what extent MDMA-induced neurobiological alterations differ from those seen in the states induced by hallucinogens and NMDA antagonists.

## Serotonergic hallucinogens and NMDA antagonists

### Psychological effects

Among the key psychological functions that are altered by hallucinogens or NMDA antagonists are: (i) psychotic-like symptoms; (ii) changes in mood; and (iii) changes in perception of time, self, and environment, including both threatening or pleasant experiences of derealization and depersonalization phenomena. These psychological functions share many aspects of prominent psychiatric symptoms of disorders such as schizophrenia or delusional disorder, and can be assessed via standard psychiatric or psychological rating scales.<sup>1</sup>

According to the work of Dittrich,<sup>7</sup> the common nucleus of drug-induced ASC can be described by three dimensions (factors) of the APZ questionnaire, which is an ASC rating scale.<sup>2,8</sup> These dimensions are: (i) *oceanic boundlessness* (OB), referring to dissolution of ego boundaries associated with positive emotions ranging from heightened mood to sublime happiness and serenity or grandiosity; (ii) *anxious ego-dissolution* (AED), including thought disorder and loss of autonomy and self-control variously associated with arousal, anxiety, and paranoid ideations; and (iii) *visionary restructuralization* (VR) referring to auditory and visual illusions, hallucinations, and altered meaning of perception.<sup>2,8</sup> As seen in Figure 2, both psilocybin and ketamine produce either loss of ego boundaries associated with positive emotions or negative ego-disintegration associated with thought disorder and loss of autonomy and self-control.<sup>9-12</sup>

The ego-disintegration and the loss of self-control over thought process and intentionality, and the uncertainty or lack in differentiating between ego and nonego spheres observed in psilocybin- and ketamine-induced psychoses

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are highly reminiscent of acute schizophrenic decompensation.<sup>13-17</sup> Also, the finding of heightened awareness associated with euphoria in psilocybin- and ketamine-treated subjects is consistent with the view that the earliest affective changes in schizophrenic patients are often pleasurable or exhilarating.<sup>18-21</sup> Furthermore, prospective<sup>22</sup> and comparative studies indicate that perceptual disturbances including the heightened sensitivity, auditory and visual illusions, and hallucinations reported by ketamine- and psilocybin-treated subjects are prominent features of prodromal, early, and acute schizophrenic patients.<sup>21,23-25</sup> Similar findings were reported in comparable studies in healthy volunteers receiving psilocybin or the phenylethylamine hallucinogen mescaline.<sup>26,27</sup> Thus, the present evidence suggests that hallucinogen-induced ASC share many common phenomenological features with the early acute stages of the schizophrenic disorders and may provide useful models to elucidate the neuronal basis of productive symptoms of schizophrenic pathophysiology. However, despite the number of similarities between the psilocybin and ketamine models of psychoses, substantial differences have also become apparent in the limited human studies. Specifically, 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 produced transient apathy, emotional withdrawal, and feelings of indifference, which resembled the negative symptoms of schizophrenia in many ways. This finding is consistent with the view that ketamine and PCP induce thought disturbances and cognitive impairments in healthy subjects, which mimic those seen in schizophrenia, including deficits in working memory, attention, abstract reasoning, decision making, and planning.<sup>28-31</sup> Thus, it has frequently been argued that the state produced by NMDA antagonists may more closely mimic naturally occurring schizophrenias (*Table I*).<sup>10-12,28-41</sup>

## Cortico-striato-thalamic loops: a common pathway?

Theories regarding the neuronal basis of the symptomatology of schizophrenic psychoses have often suggested that deficits in early information processing may underlie the diversity of psychotic symptoms and cognitive disturbances observed in the group of schizophrenias.<sup>42-44</sup> Such theories posit that a fundamental feature of information processing dysfunction in psychosis is the

inability of these patients 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 stimuli, which, in turn, could lead to a breakdown of cognitive integrity and difficulty in distinguishing self from nonself.<sup>44,45</sup>

In recent years, this theoretical construct has been successfully operationalized by measuring the behavioral plasticity of acoustic startle responses, such as PPI and habituation.<sup>46</sup> Symptomatic schizophrenia patients exhibit deficits in both PPI and habituation. Extensive lesion and drug studies in rodents have demonstrated that sensorimotor gating functions, such as PPI, are subject to considerable forebrain modulation from cortical, limbic, striatal, pallidal, and thalamic structures, including cortico-striato-pallido-thalamic (CSPT) circuitry.<sup>46,47</sup> Moreover, animal studies indicate that hallucinogens, amphetamines including MDMA, and NMDA antagonists disrupt sensorimotor gating in rats by interacting with different components of the CSPT loop. These findings are consistent with the “thalamic filter hypothesis of psychosis,” advanced by Carlsson and Carlsson.<sup>48</sup> This theory proposes that corticostriatal pathways exert a modulatory influence on the thalamic gating of sensory information to the cerebral cortex (*Figure 3*).<sup>49</sup> Theoretically, an impairment of thalamic filtering should result in sensory overload of the cortex, leading to a breakdown of integrative cortical functions, and subsequently to positive symptoms such as delusions, hallucinations, thought disturbances, persecution, and 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.

On the basis of these findings and the thalamic filter model, ACSs induced by hallucinogens and NMDA antagonists in humans can be conceptualized as complex disturbances that arise from more elementary deficits of sensory information processing in cortico-striato-thalamo-cortical (CSTC) feedback loops.<sup>6,50</sup> The model proposes that NMDA antagonists may disrupt thalamic filter functions and produce sensory overload of cortical areas, particularly of the prefrontal cortex, by blocking NMDA receptors located on corticostriatal pathways, while serotonergic hallucinogens may alter thalamocortical transmission by stimulation of 5-HT<sub>2</sub>

	Psilocybin	Ketamine	MDMA	Schizophrenias
<b>Receptor level</b>				
Primary locus of action	5-HT <sub>2A</sub> , 5-HT <sub>1A</sub>	NMDA	5-HT transporter,* 5-HT <sub>2A</sub> , 5-HT <sub>1A</sub> , $\alpha_2$ , H <sub>1</sub>	Unknown
Downstream effects on	GABA, D <sub>1</sub> , D <sub>2</sub> , mGluR	5-HT <sub>2A</sub> , GABA, D <sub>1</sub> , D <sub>2</sub> , mGluR	D <sub>1</sub> , D <sub>2</sub>	
<b>Psychopathology</b>				
<i>Positive symptoms</i>				
• Hallucinations/illusions	++	+	-	++
• Delusions	+	+	-	++
• Thought disorder	+	++	+	++
<i>Negative symptoms</i>				
• Blunted affect	0 - +	+ - ++	-	++
• Withdrawal	+	+ - ++	-	++
<i>Depersonalization</i>	+ - ++	++	+	++
<i>Derealization</i>	+	++	+	++
<b>Neuropsychology</b>				
• Attention disturbance	+ - ++	+	+	++
• Distractibility	+	++	-	++
• Working memory	+	++	?	++
• Associative deficits	+	+ - ++	?	++
• Planning/mental flexibility	++	?	?	++
<b>Cortical activity</b>				
• Frontal (PET)	++ (acute)	++ (acute) -- (chronic)**	(+)	++ (acute) -- (chronic)

**Table I.** Comparison of effects of psilocybin (0.2-0.24 mg/kg PO), S-ketamine (0.01-0.02 mg/kg/min), and 3,4-methylenedioxymethamphetamine (MDMA) (1.5-1.7 mg/kg PO), and symptoms in schizophrenias (summarized from references 10-12, 28-31, and 33-41). 5-HT, 5 hydroxytryptamine; GABA,  $\gamma$ -aminobutyric acid; NMDA, N-methyl-D-aspartate; mGluR, metabotropic glutamate receptor; D<sub>1</sub>, D<sub>2</sub>, dopamine receptors; H<sub>1</sub>, histamine receptor;  $\alpha_2$ ,  $\alpha_2$  adrenergic receptor. \*MDMA has highest affinity for the 5-HT transporter ( $K_i=0.61 \mu\text{M}$ ) and lesser for  $\alpha_2$  ( $K_i=3.6 \mu\text{M}$ ) and 5-HT<sub>2</sub> receptors ( $K_i=5.1 \mu\text{M}$ ) in rat brain. \*\*Chronic administration of NMDA antagonists in rats decreases frontal cortical activity.

receptors located in several components of the CSTC loop, including the prefrontal cortex, striatum, nucleus accumbens, and thalamus (for details, see reference 49).

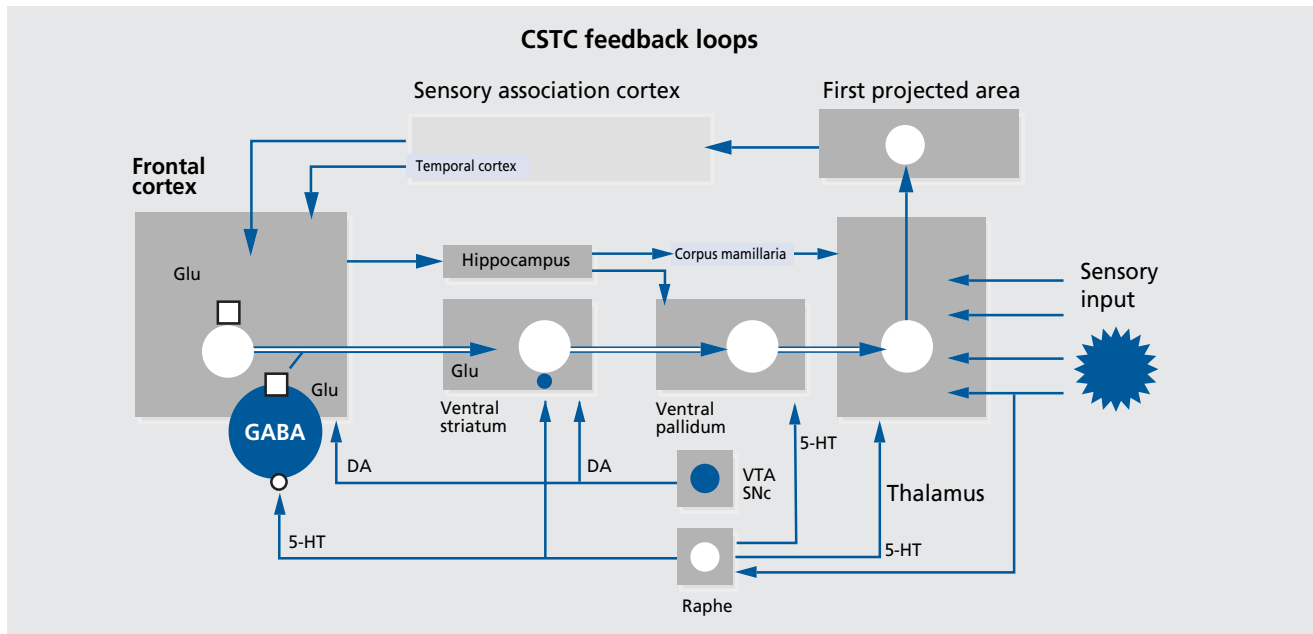
### Brain imaging studies

Until recently, many neural circuit models were based on animal studies, and implications for the effects of hallucinogenic drugs or disease models in humans were based on inferences from these studies. However, functional neuroimaging studies enable one to examine these neural circuit models directly and test specific hypotheses about the role of specific neural systems in the expression of ASC.

PET with the radiotracer <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>FDG) was used to assess drug-induced changes in the regional cerebral metabolic rate of glucose (CMR<sub>glu</sub>), as an index of cerebral activity. We found that a hallucinogenic dose of racemic ketamine increased neuronal activity in the prefrontal cortex (hyperfrontality) and associated limbic regions, as well as in striatal and thalamic structures in healthy volunteers, giving the first evidence that functional alterations in CSTC loops may underlie the symptomatology of drug-induced ASC.<sup>50</sup> This hyperfrontality finding was corroborated and extended in subsequent studies in healthy volunteers in which the effects of hallucinogens and NMDA antagonists including psilocybin, racemic ketamine, and S-ketamine were compared.



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**Figure 3.** The limbic cortico-striato-thalamic-cortical (CSTC) feedback loops are involved in memory, learning, and self–nonself 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/reentry loops, is postulated to protect the cortex from exteroceptive sensory information overload, as well as from internal overarousal. The model predicts that sensory overload of the cortex and psychosis may result from thalamic gating deficits, which may be caused by ketamine by blockade of *N*-methyl-*D*-aspartate (NMDA)–mediated glutamatergic (Glu) corticostriatal and/or by increasing mesolimbic dopaminergic (DA) neurotransmission. Excessive stimulation of serotonin 5-HT<sub>2</sub> receptors (for example, by psilocybin) may lead to a similar neurotransmitter imbalance in the CSTC loops, which again results in an opening of the thalamic filter, sensory overload of the cortex, and psychosis. VTA, ventral tegmental area; SNc, substantia nigra pars compacta; GABA,  $\gamma$ -aminobutyric acid;  $\square$ , NMDA receptor.

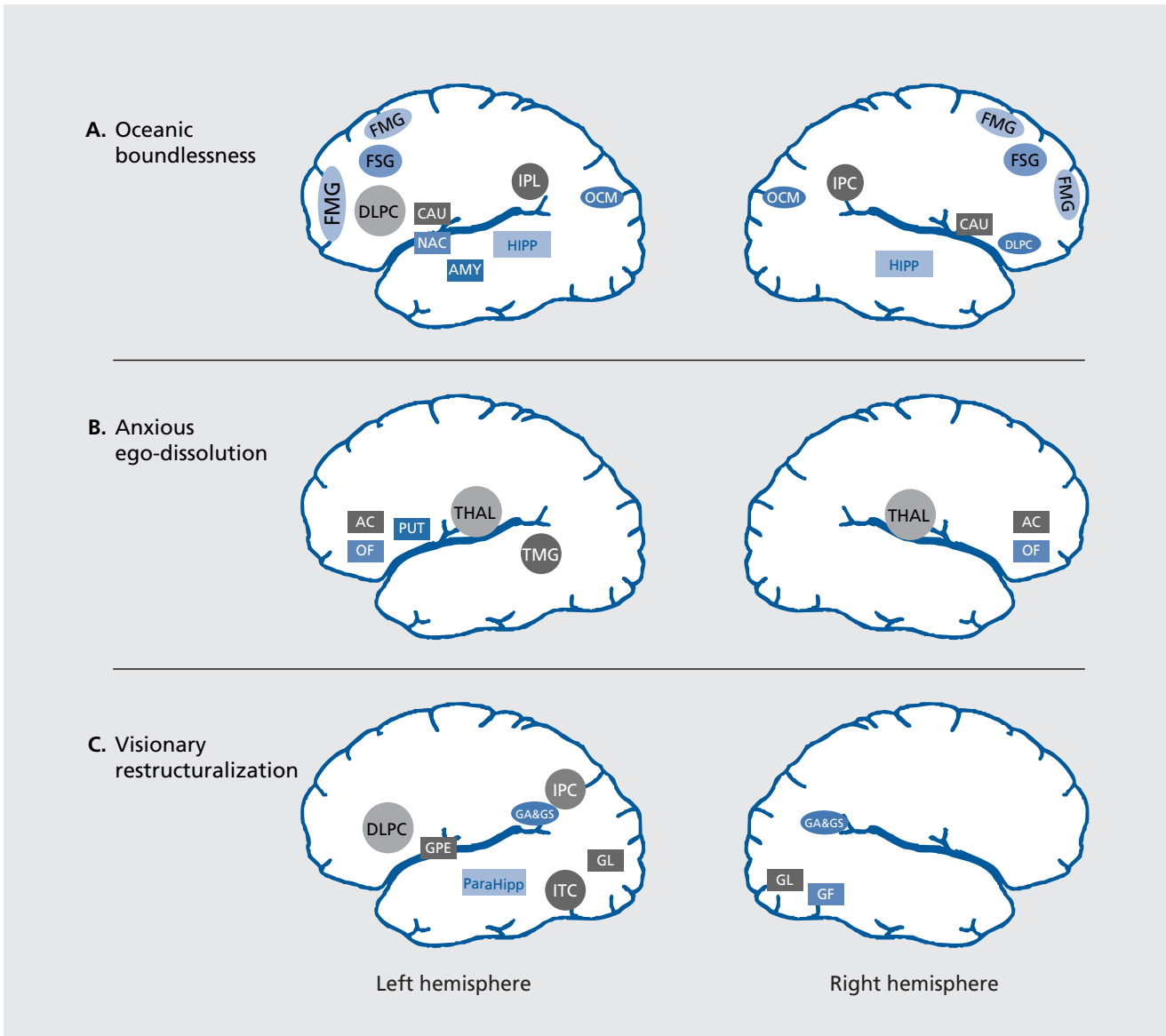
Modified from reference 49: Vollenweider FX, Greyer MA. A systems model of altered consciousness: integrating natural and drug-induced psychoses. *Brain Res Bull.* 2001;56:495-507. Copyright © 2001, Elsevier Science.

In particular, we found that, despite different primary mechanisms of action, the two classes of drugs produced strikingly similar brain activation patterns as indexed by normalized CMRglu. Both psilocybin and ketamine markedly increased brain activity bilaterally in the frontomedial and frontolateral cortex, including the anterior cingulate. Lesser increases were found in the temporomedial, superior, and inferior parietal cortices, striatum, and thalamus. Decreases were found in the left caudate nucleus, bilaterally in the ventral striatum, occipital lobe, and visual pathway.<sup>9-11</sup> A correlational analysis revealed that the metabolic hyperfrontality in ketamine and psilocybin subjects was associated with a depersonalization/derealization syndrome, thought disturbances, and mania-like symptoms.<sup>9-11</sup> The hyperfrontality finding in ASC was further supported by evidence from brain imaging studies with ketamine and psilocybin in healthy volunteers<sup>27,51</sup> and was also found in subjects treated with the classic phenylethylamine hallucinogen mescaline.<sup>52</sup>

## Correlations between cerebral activity and psychological alterations

The correlation of changes in cerebral activation with changes in self-assessment enables one to further corroborate the role of specific neural substrates in these psychological functions. Correlational analysis between normalized metabolic activity and psychological scores of the APZ questionnaire revealed that the severity of OB correlated positively with CMRglu bilaterally in frontomedial superior, frontolateral, and left inferolateral prefrontal cortex, anterior cingulate, as well as bilaterally in inferior parietal and occipitomedial cortex.<sup>6</sup> There were negative correlations between OB and CMRglu bilaterally in the hippocampus and caudate nucleus, and left amygdala and ventral striatum (*Figure 4A*).

The OB dimension, which relates to the altered perception of time and space as well as the pleasurable experience of dissolution of ego-boundaries and which can culminate in transcendental or “mystical” states, sub-



**Figure 4.** Correlations between the three dimensions of the APZ questionnaire for altered states of consciousness (oceanic boundlessness [OB], anxious ego-dissolution [AED], and visionary restructuralization [VR]) and regional brain activity (cerebral metabolic rate of glucose [CMRglu]) in healthy volunteers under psilocybin (0.26 mg/kg PO) or S-ketamine (0.012 mg/kg/min IV) challenge ( $n=52$ ,  $P<0.0001$ ). **A.** The OB dimension. The activation of a prefrontal-parietal network in parallel with the deactivation of a striato-limbic-amygdala-centered network correlated with the OB dimension measuring derealization and depersonalization associated with positive emotions ranging from enhanced mood to feelings of happiness and serenity, or grandiosity. **B.** The AED dimension. Thalamic hyperactivity in conjunction with decreased activity in orbitofrontal and ventral anterior cingulate cortex and left putamen correlated with the AED dimension measuring thought disorder and ego-disintegration, and loss of self-control variously associated with anxiety, panic, and paranoid ideations. **C.** The VR dimension. Activation of the dorso-lateral prefrontal cortex (DLPC) and of components of the dorsal (inferioparietal cortex [IPC], angular gyrus [GA], supramarginal gyrus [GS]) and ventral stream (inferiotemporal cortex [ITC]) of higher order visual processing (ITC) in parallel with deactivation of striatal and limbic regions correlated with VR comprising visual hallucinations, synesthesias and changed meaning of percepts. Positive correlations are indicated by circles and negative correlations by rectangles. FMG, frontomedial gyrus; FSG, frontosuperior gyrus; IPL, inferiorparietal lobe; OCM, occipitomedial cortex; CAU, caudate nucleus; NAC, nucleus accumbens; AMY, amygdala; HIPP, hippocampus; OF, orbitofrontal cortex; AC, anterior cingulate; PUT, putamen; TMG, temporomedial gyrus; THAL, thalamus; GL, lingual gyrus; GF, fusiform gyrus; GPE, globus pallidus; ParaHipp, parahippocampus.

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stantially relates to functional alterations in an extended frontolimbic-parieto-striatal network including the amygdala. 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 exteroceptive or interoceptive stimuli, and initiating and expressing appropriate behaviors.<sup>53-55</sup> The parietal cortex is important for determining the relationship of the self to extrapersonal space, based on visuospatial input from the dorsal stream of visual information processing.<sup>56</sup> Together with motor and somatosensory cortical areas, the frontolimbic-parietal network is sometimes called “central neural authority”<sup>57</sup> to express the idea that it constitutes a functional system crucially involved in ego-structuring processes and the formation and representation of a coherent self that is defined in time and space. On the basis of 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. Finally, the concomitant decrease in amygdala activity may account for the more pleasurable experiences associated with the OB dimension.

The severity of anxious ego-dissolution (AED) was positively correlated with CMRglu in the thalamus and left temporomedial gyrus, and negatively correlated with CMRglu bilaterally in orbitofrontal cortex and adjacent anterior cingulate. Thus, it appears that AED and the associated thought disorder depend mainly on thalamic overactivity and orbitofrontal underactivity (*Figure 4B*). This finding may indicate enhanced thalamic transmission and support the view that deficient thalamic gating leads to sensory overload of the cortex and psychosis. In fact, thalamic (and anterior cingulate-parietal) overactivity was associated with disorganization in schizophrenic patients.<sup>58</sup> Malfunction of the orbitofrontal cortex may account for the continuing intrusion of irrelevant stimuli into the stream of mental activity and lead to the perseverations, thought blocking, and difficulty concentrating that are typically associated with AED.<sup>59</sup> The severity of VR (including hallucinations) was positively correlated with CMRglu in the left dorsolateral prefrontal and inferior temporal cortex, bilaterally in temporo-parietal association cortex. Negative correla-

tions were found in left globus pallidus and parahippocampus, and bilaterally in visual pathways (gyrus fusiformis and lingualis). Thus, it appears that visual hallucinations are associated with abnormal prefrontal activation in conjunction with activation of sensory modality-specific cerebral structures involved in normal perception, which is similar to the situation reported in patients with auditory hallucinations (*Figure 4C*).<sup>60</sup>

## Hyperfrontality as an index of acute psychoses

The hyperfrontality finding and its association with positive psychotic symptoms seen in drug-induced ASC is of particular interest because it appears to parallel similar findings in some studies in acutely ill schizophrenic and nonschizophrenic psychotic patients.<sup>36,38,61,62</sup> Interestingly, one of these studies reported that hyperperfusion in the frontal, anterior cingulate, parietal, and temporal cortices, which correlates with positive symptoms including formal thought disorder and grandiosity in drug-naïve schizophrenic patients, was normalized after neuroleptic treatment, and that persisting negative symptoms correlated with frontal, cingulate, basal, and thalamic hypoperfusion.<sup>38</sup> An activation of prefrontal and cingulate cortex with transient exacerbation of positive psychotic symptoms was also reported in chronic schizophrenics during ketamine challenge.<sup>63</sup> These findings suggest that metabolic hyperfrontality (rather than hypofrontality, as seen in chronic schizophrenia) is a pathophysiological manifestation of certain acute psychotic symptoms in drug-induced and naturally occurring psychoses. This view is further supported by the finding that pretreatment with the atypical antipsychotic clozapine reduced *S*-ketamine-induced hyperfrontality and thalamic activation associated with psychotic symptoms in normal volunteers.<sup>64</sup> In the 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 on neurotransmitter systems

The hyperfrontality 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 of their primary locus of action. In particular, the similarity of the effects of psilocybin and ketamine on ego functions, 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.

Of particular relevance to sensory overload theories of drug-induced ASC are behavioral measures of sensorimotor gating functions, such as PPI of the startle response.<sup>65</sup> The cross-species study of homologous gating functions such as PPI in animal and human models of psychosis offers a unique possibility for the exploration of neurobiological substrates relevant to schizophrenia. Symptomatic schizophrenics and never-medicated first-episode schizophrenia patients exhibit deficits in PPI, which have been suggested to be central to the psychotic symptomatology of the illness.<sup>42,66</sup> Indeed, the most striking correlate of deficient PPI in schizophrenia is a measure of thought disorder derived from the Rorschach test.<sup>67</sup> Similarly, in rats, both serotonergic hallucinogens and NMDA antagonists produce deficits in PPI.<sup>68</sup> Extensive pharmacological studies in animals demonstrate that PPI is modulated by multiple interacting neurotransmitters, including the dopaminergic, serotonergic, cholinergic, GABAergic, and glutamatergic systems within CSPT pathways.<sup>46</sup>

#### *Role of dopamine*

In keeping with the DA hyperactivity hypothesis of schizophrenia, we hypothesized that increased striatal DA activity could also contribute to the *S*-ketamine- and psilocybin-induced symptomatology in humans, although *S*-ketamine and psilocybin have no affinity for D<sub>2</sub> receptors.<sup>69,70</sup> This hypothesis has been tested using PET and [<sup>11</sup>C]raclopride. Reduction in [<sup>11</sup>C]raclopride binding potential (BP) has been well established as an indirect measure of the change in synaptic DA concentration in animal and human studies.<sup>71,72</sup> Indeed, both *S*-ketamine and psilocybin significantly reduced [<sup>11</sup>C]raclopride BP in ventral striatum consistent with an increase in striatal DA concentration.<sup>73,74</sup> Moreover, these changes in [<sup>11</sup>C]raclopride BP significantly correlated with depersonalization, supporting the view that excessive DA transmission at D<sub>2</sub> receptors contributes to the generation of positive psychotic symptoms in ketamine- and psilocybin-treated subjects. However, the DA-mediated change in [<sup>11</sup>C]raclopride BP at D<sub>2</sub> receptors explained

only about 36% of the variance of positive symptoms, indicating that other neurotransmitter systems contribute to the pathogenesis of ketamine- and psilocybin-induced symptomatology. In support of this view, we found that the D<sub>2</sub> antagonist haloperidol has virtually no effect on psilocybin-induced cognitive impairments and reduced psychotic symptoms by only about 30% in psilocybin-treated subjects.<sup>12</sup> Similarly, recent results in healthy subjects demonstrate that ketamine psychosis is not ameliorated by haloperidol pretreatment.<sup>41</sup> Comparably, haloperidol had also virtually no effect on the PPI-disruptive effect of the hallucinogenic 5-HT<sub>2</sub> agonist DOI and the NMDA antagonist PCP in animal models of psychosis.<sup>65,75</sup> Given these findings, it appears that increased DA activity may play a minor role in both psilocybin- and ketamine-induced ASC.

#### *Role of serotonin*

During the last decade, accumulating evidence from binding, electrophysiological, and behavioral studies in animals suggested that indoleamine and phenylethylamine hallucinogens may produce their psychological effects via the 5-HT<sub>2A</sub> receptors in the brain (for details, see references 76 and 77). However, although the preponderance of evidence suggested that hallucinogens are agonists at 5-HT<sub>2A</sub> receptors, this issue was clouded by studies that demonstrated LSD to be a partial agonist<sup>78</sup> or even an antagonist<sup>79</sup> at 5-HT<sub>2A</sub> receptors. Moreover, since LSD, 5-methoxy-DMT, DMT, and psilocin have been shown to display high affinity for, and to act as agonists at, 5-HT<sub>1A</sub> receptors, the role of 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors in the generation of hallucinosis in man remains elusive.

The important question as to whether serotonergic hallucinogens are agonists or antagonists at 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors has recently been answered. Consistent with animal studies, we have demonstrated that the psychological effects of psilocybin in humans can be completely blocked by the preferential 5-HT<sub>2A</sub> antagonist ketanserin.<sup>12</sup> In addition, preliminary data demonstrate that the metabolic hyperfrontality and PPI disruptive effects of psilocybin in humans can be reversed by ketanserin.<sup>80,81</sup> Since ketanserin has no affinity for 5-HT<sub>1A</sub> receptors, this finding suggests that serotonergic hallucinogens produce their central effects through a common action upon 5-HT<sub>2</sub> receptors. The fact that ketanserin has about 100-fold greater antagonistic

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potency at 5-HT<sub>2A</sub> than at 5-HT<sub>2C</sub> receptors indicates that the psychological effects of psilocybin are mediated by 5-HT<sub>2A</sub> rather than 5-HT<sub>2C</sub> receptor activation. This interpretation is corroborated by the finding that the highly selective 5-HT<sub>2A</sub> receptor antagonist M100,907, but not 5-HT<sub>2C</sub> antagonists, blocks the disruption of PPI in rats produced by serotonergic hallucinogens.<sup>82,83</sup> Moreover, the effects of serotonergic hallucinogens (LSD and DOI) on sensorimotor gating in rats are mediated, at least in part, through 5-HT<sub>2A</sub> receptors located within the ventral pallidum,<sup>83,84</sup> a component of the CSPT loop.<sup>85</sup> These findings suggest that both indolamine and phenylethylamine hallucinogens may alter thalamic filter functions through 5-HT<sub>2A</sub> receptors associated with pallidothalamic input to the thalamus. They also support the view that antagonist actions at the 5-HT<sub>2A</sub> receptors may have an important contribution to the unique clinical efficacy of atypical antipsychotics such as clozapine in the treatment of the schizophrenias.<sup>86</sup> Although psychotomimetic NMDA antagonists (eg, ketamine) act primarily through a noncompetitive NMDA blockade of the NMDA subtype of the glutamate receptor, there is converging evidence implicating 5-HT mechanisms, particularly those involving 5-HT<sub>2A</sub> receptors, in the action of NMDA antagonists. For example, it has been shown that the psychological effects of ketamine are ameliorated by the mixed 5-HT<sub>2</sub>/D<sub>2</sub> and atypical antipsychotic clozapine, but are virtually insensitive to typical antipsychotics that have preferential actions at D<sub>2</sub> receptors, such as haloperidol.<sup>87</sup> Moreover, preliminary data from our laboratory show that clozapine reduces S-ketamine-induced metabolic hyperfrontality and associated psychotic symptoms in healthy human volunteers.<sup>64,80</sup> These findings parallel observations in animal studies demonstrating that the PPI-disruptive effects of NMDA antagonists in rats are blocked by the atypical antipsychotics (eg, clozapine or olanzapine),<sup>88,89</sup> but are generally insensitive to typical antipsychotics (eg, haloperidol).<sup>90</sup> Moreover, the fact that the highly selective 5-HT<sub>2A</sub> receptor antagonist M100,907 is also effective in blocking the PPI-disruptive effects of NMDA antagonists in rats<sup>91</sup> strongly suggests that the psychotomimetic effects of NMDA antagonists in humans involve 5-HT<sub>2</sub> receptor activation. Finally, 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.<sup>92</sup> Interestingly, NMDA antagonists, like serotonergic hallucinogens,

appear to be ineffective when administered directly into the DA-rich nucleus accumbens.<sup>92</sup>

## *Role of glutamate*

Recent 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.<sup>93,94</sup> Whether this common mechanism contributes to the higher-level cognitive, perceptual, and affective effects of serotonergic hallucinogen and NMDA antagonists warrants further investigation.<sup>40</sup> Taken together, serotonergic hallucinogens and psychotomimetic NMDA antagonists produce schizophrenia-like deficits in behavioral measures of sensory gating such as PPI, and do so by actions localized to different parts of the CSPT circuitry. Despite their different primary mechanisms and sites of action, however, a common denominator of the effects of these drug classes 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.

## **Serotonergic amphetamines: MDMA**

### **Psychological effects**

In contrast to serotonergic hallucinogens and NMDA antagonists, a typical recreational and nontoxic dose of MDMA (1.5-7 mg/kg PO) produces an affective state of enhanced mood, profound well-being, happiness, increased extroversion and sociability, slight derealization and depersonalization, little anxiety, and moderate thought disturbances, but no hallucinations in normal volunteers.<sup>95</sup> Depersonalization phenomena are mild and, in contrast to hallucinogens (eg, psilocybin), not experienced as problematic or psychotic fusion, but experienced as a pleasurable state of loosened ego boundaries as measured by the APZ questionnaire (*Figure 2*). Similar findings were reported with MDMA and its congener MDE in healthy volunteers.<sup>96-100</sup>

### **Brain imaging studies**

To identify the functional neuroanatomy involved in the action of MDMA in humans, the effect of MDMA

(1.7 mg/kg) versus placebo on regional cerebral blood flow (CBF) was investigated in MDMA-naive human subjects using PET and [ $H_2^{15}O$ ]-PET.<sup>101</sup> MDMA moderately increased brain activity as indexed by CBF bilaterally in the ventromedial prefrontal cortex, the ventral anterior cingulate, the inferior temporal lobe, and the medial occipital cortex and in the cerebellum. Decreases in CBF were found bilaterally in the motor and somatosensory cortex, the superior temporal lobe, the dorsal cingulate cortex, the insula, and the thalamus. Unilateral decreases were found in the left amygdala and the right parahippocampus. This activation pattern and associated affective state, which was characterized by heightened mood, increased extroversion, slight derealization, and intensification of vision, substantially differ from those seen in ketamine- and psilocybin-induced psychosis-like syndromes.

The activation of prefrontal and related limbic/paralimbic structures in conjunction with deactivation of the amygdala may underlie the emotional effects of MDMA. This view is consistent with findings implicating the amygdala,<sup>102,103</sup> orbitofrontal cortex,<sup>103</sup> ventral anterior cingulate cortex,<sup>103,104</sup> prefrontal cortex, temporal lobe, and thalamus<sup>104</sup> in the regulation of mood and emotion. In this network, the amygdala appears to play a pivotal role in the mediation of both positive and negative emotions.<sup>102,103,105</sup> Acute administration of MDMA also facilitated social communication, as measured by a significant increase in the “extroversion” subscale of the Adjective Mood Rating Scale. This increase correlated with CBF in the temporal cortex, amygdala, and orbitofrontal cortex. These brain regions are richly interconnected and together form the basolateral circuit, which, according to current theories, is involved in the mediation of social communication.<sup>106,107</sup> Lesions or disturbances of this circuit can lead to decreased social interaction, inadequate social behavior, or even the inability to decode social cues.<sup>108-110</sup> The marked modulation of activity in the basolateral circuit produced by MDMA and its association with increased extroversion provide further support for a critical role of the basolateral circuit in the processing of socially relevant information.

The present findings suggest that an amygdala-centered network including ventral-frontal and temporal cortices underlies the cooccurrence of pleasurable emotion and enhanced social communication, providing a rationale for the interrelatedness of emotional and social processes. Thus, further research into the neurochemical

mechanisms of MDMA could advance our understanding of the neuroanatomical regulation of mood and social interaction.

### Neurotransmitter systems involved in the effects of MDMA

On the basis of mechanistic studies in animals, it has been widely assumed that the psychological effects of MDMA in humans might be mediated through its potent ability to release serotonin, and to a lesser extent DA.<sup>111</sup> In addition, MDMA has moderate affinity for the serotonergic 5-HT<sub>2</sub> and adrenergic  $\alpha_2$  receptors.<sup>76</sup> To elucidate the contribution of neurotransmitter and receptor systems in the action of MDMA, the blocking effects of specific receptor antagonists on MDMA-induced psychological and behavioral alterations were investigated. In these studies, we found that pretreatment with the selective serotonin-reuptake inhibitor (SSRI) citalopram markedly reduced all of the psychological effects of MDMA in healthy volunteers, indicating that the effects of MDMA in humans are largely due to 5-HT transporter-mediated enhanced 5-HT release.<sup>112</sup> The 5-HT<sub>2</sub> antagonist ketanserin only moderately attenuated the MDMA experience, but significantly abolished the perceptual effects.<sup>113</sup> This suggests that stimulation of 5-HT<sub>2</sub> receptors mediates the mild hallucinogen-like action of MDMA in humans, such as intensification of colors. Finally, the D<sub>2</sub> antagonist haloperidol only partly reduced the euphoric effects of MDMA suggesting that DA contributes little to the psychological effects of MDMA at the dose tested.<sup>114,115</sup>

Surprisingly, MDMA dose-dependently reduced sensorimotor gating, as indexed by the PPI of startle in rats, but increased PPI in healthy human subjects under comparable conditions.<sup>116</sup> This disparity between the effects of MDMA in rats and humans may reflect a species-specific difference in the mechanism of action of MDMA or in the behavioral expression of a similar pharmacological effect, or both. In accordance with animal studies, we recently demonstrated that this PPI-enhancing effect of MDMA in normals is markedly reduced by the SSRI citalopram, but is not affected by the D<sub>2</sub> antagonist haloperidol or the 5-HT<sub>2A/C</sub> antagonist ketanserin.<sup>117</sup> Thus, it appears that the effect of MDMA on PPI in humans is—like in animals—due to MDMA-induced release of serotonin. However, it is also obvious that some of the functional consequences of the

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released serotonin differ between rats and humans, since MDMA has opposite effects on PPI. In fact, there is more recent evidence that species-specific differences may contribute to the opposite effects of MDMA on PPI in rats and humans. Specifically, it was found that 5-HT<sub>1A</sub> agonists disrupt PPI in rats, but increase PPI in mice.<sup>118,119</sup> Thus, the role of 5-HT<sub>1A</sub> receptors in mediating effects of MDMA on PPI in humans remains to be elucidated. Furthermore, whether the indirect agonistic effects of MDMA on 5-HT<sub>1A</sub> receptors ameliorate psychotic symptom formation needs to be clarified. The present data also demonstrate the compelling need for comparison studies in animals and humans to increase our understanding of the role of the serotonergic systems involved in the regulation of information processing in health and disease.

## Conclusions

The present review discussed evidence that similar neural systems are altered by serotonergic hallucinogens and psychotomimetic NMDA antagonists, despite the differences in the primary sites of action of these drug classes. Furthermore, these same systems appear to

exhibit abnormalities in incipient stages of naturally occurring psychoses. Thus, the elucidation of common mechanisms downstream from 5-HT<sub>2A</sub> or NMDA receptors can provide new targets for investigating the pathophysiology of naturally occurring psychoses such as schizophrenia. Present evidence suggests that the effects of a typical recreational dose of MDMA on regional brain activity and sensory gating functions can be delineated from those seen with psychedelic hallucinogens. The data also indicate that excessive serotonergic activation is not sufficient to produce psychosis. □

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The author would like to dedicate this article to Dr Albert Hofmann on the occasion of his 95th birthday.

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### Mecanismos cerebrales de los alucinógenos y los entactógenos

Esta revisión se centra en recientes estudios conductuales y de imágenes cerebrales de las funciones de regulación sensorial, los cuales evalúan semejanzas entre los efectos de los alucinógenos clásicos (por ej. psilocibina), los anestésicos disociadores (por ej. ketamina) y los entactógenos (por ej. 3,4-metilendioxi metanfetamina [MDMA]) en humanos. Los alucinógenos serotoninérgicos y los anestésicos psicotomiméticos producen un síndrome psicótico sobrepuesto, el cual se asocia con una marcada activación de la corteza prefrontal (hiperfrontalidad) y otros cambios sobrepuestos en las regiones temporo-parietales, estriatales y talámicas, lo que sugiere que ambos grupos de drogas actúan en una vía final común. Junto con la observación que ambos alucinógenos y que los antagonistas del N-metil-D-aspartato (NMDA) desorganizan la regulación sensorial en ratas, al actuar a nivel de los receptores 5-HT<sub>2</sub> de 5-hidroxitriptamina (serotonina) localizados en los circuitos córtico-estriado-talámicos, estos hallazgos sugieren que una desorganización del procesamiento córtico-subcortical que lleve a una sobrecarga de la corteza es común en estas psicosis. En contraste con los alucinógenos, el entactógeno MDMA provoca un estado emocional de ánimo positivo, concomitante con una activación de estructuras prefrontolimbicas / paralimbicas y una desactivación de la amígdala y del tálamo.

### Mécanismes cérébraux des hallucinogènes et des entactogènes

Cet article passe en revue les études récentes portant sur l'imagerie cérébrale et les aspects comportementaux relatifs aux fonctions de filtrage des voies sensorielles, ayant pour but d'évaluer les similitudes entre les effets des hallucinogènes classiques (par ex. la psilocybine), des anesthésiques dissociatifs (par ex. la kétamine) et les entactogènes (par ex. la 3,4-méthylènedioxy méthamphétamine [MDMA]) chez l'homme. Les hallucinogènes sérotoninergiques et les anesthésiques psychosomimétiques induisent des syndromes psychotiques largement comparables en rapport avec une activation marquée du cortex préfrontal (hyperfrontalité) et d'autres modifications affectant les régions temporo-pariétales, striatales et thalamiques, suggérant que les deux classes médicamenteuses agissent sur la même voie finale. Ces résultats, si on les rapproche de la perturbation de la fonction de filtrage des voies sensorielles provoquée chez le rat par les antagonistes du N-méthyl-D-aspartate (NMDA) et les hallucinogènes via leur action sur les récepteurs 5-HT<sub>2</sub> [5-hydroxytryptamine (sérotonine)] du circuit cortico-striato-thalamique, suggèrent que la perturbation opérationnelle cortico-sous-corticale responsable de la surcharge sensorielle du cortex est un point commun à ces psychoses. Contrairement aux hallucinogènes, l'entactogène MDMA provoque un état émotionnel d'humeur positive parallèlement à une activation des structures préfronto-linguistiques et paralinguistiques et à une désactivation des amygdales et du thalamus.

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