Opaque models: Using drugs and dreams to explore the neurobiological basis of mental phenomena

Nicolas Langlitz[1]

The New School for Social Research, New York, NY, United States

[1]*Corresponding author: Tel.: +1-212-2295757; ext. 2443, e-mail address: langlitn@newschool.edu*

Abstract

On the basis of four historical and ethnographic case studies of modeling in neuroscience laboratories, this chapter introduces a distinction between transparent and opaque models. A transparent model is a simplified representation of a real world phenomenon. If it is not patently clear, it is at least much better comprehended than its objects of representation. An opaque model, by contrast, looks at one only partially understood phenomenon to stand in for another partially understood phenomenon. Here, the model is often just as complex as its target. Examples of such opaque models discussed in this chapter are the use of hallucinogen intoxication in humans and animals as well as the dreaming brain as models of psychosis as well as the dreaming brain as a model of consciousness in general. Several functions of opaque models are discussed, ranging from the generation of funding to the formulation of new research questions. While science studies scholars have often emphasized the epistemic fertility of failures of representation, the opacity of hallucinogen intoxications and dreams seems to have diminished the potential to produce positive knowledge from the representational relationship between the supposed models and their targets. Bidirectional comparisons between inebriation, dreaming, and psychosis, however, proved to be generative on the level of basic science. Moreover, the opaque models discussed in this chapter implicated cosmologies that steered research endeavors into certain directions rather than others.

Keywords

Models, Hallucinogens, Psychedelics, Dreaming, Consciousness

Historians of science have explored models created in scientists' minds and workshops—think of neuroscientists' imagination of the brain as a computer and of the porcelain head busts on the desks of phrenologists. This chapter examines a different practice of modeling: the use of one mind–brain state to represent another

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state of mind and brain. More specifically, it analyzes neuroscientists' and psychiatrists' investigations of hallucinogen inebriation and dreaming as models of psychosis and consciousness in general. This kind of modeling confronted researchers with an epistemological problem that had not troubled the users of theoretical and classical physical models. They did not see through their models any more than they saw through the objects they represented. These models were not epistemically transparent, but opaque.

A famous transparent model in the history of science was Watson and Crick's double helix assembled from wire and cardboard. It was transparent in that its users could easily grasp its makeup. To understand the structure of DNA, Watson and Crick did not have to study wire and cardboard. The model in their office primarily helped them to visualize what they already knew about DNA from chemical analyses and X-ray diffraction images (Kamminga and Chadarevian, 1995). Such transparent models are ubiquitous: walk into any doctor's office, medical school, or neuroscience laboratory and you will find some. A neurologist might use a physical model of the brain to explain to his patient or students where a lesion is located. Or a diagram might represent a theoretical model of how different parts of the brain interact with each other to generate consciousness. Such two- and three-dimensional representations of the brain became epistemic objects for anthropologists, sociologists, and historians of science, but for neuroscientists, they have never been more than cognitive tools to understand something else, namely, the brain itself. These theoretical and physical models are simplified or idealized representations of real world phenomena. Their simplicity is an important part of the reason why they help us to order our thoughts about a more complex and often messy object of study. They abstract from properties, which researchers take to be irrelevant and thus contribute to an interpretive process, which is crucial to scientific reasoning. These models are largely transparent to the scientific community using them because this very community made them the way they are.

Of course, opaque models are also human creations in that scientists chose one phenomenon to stand in for another one because of particular properties they share, which the modelers deem characteristic of the target phenomenon. But, even if neuroscientists and psychiatrists intoxicated test persons or put them to bed in the sleep laboratory, they did not create or fully understand what happened in their subjects' drugged or dreaming brains. As one state of the mind–brain came to serve as the model of another, even though neither of these states was fully understood, the *representatum* did not serve as a transparent window onto the *representandum*. It remained itself an object of ongoing investigations.

The conceptual distinction between transparent and opaque models is ideal-typical: most, maybe even all models that the student of science examines are located along a continuum between these two poles. Whether there is anything about the plastic brain in his office that an anatomically well-trained neurologist is unaware of seems questionable, but for her patients, this model might be less transparent. That is to say, transparency and opacity are not essential, but relational qualities dependent on how much the user knows about the model and what it is a model of. To use another example: the possibility to explore the molecular model of the DNA double

helix visually and haptically may have helped Watson and Crick to grasp its structure beyond what they had already fathomed on the basis of their calculations. Even though they had made this model themselves, its value as a cognitive tool might have laid in the fact that it enabled the modelers to better comprehend some of the spatial properties of the molecule's helical structure. To be of any use, every model needs to maintain at least a minimal degree of opacity for someone—if not for the researchers themselves, then for their audience; if not for the doctor, then for her patients. At the same time, even highly opaque models such as the dream model of psychosis or many animal models gain their validity as models from a number of already known similarities between *representatum* and *representandum*. Had they been completely opaque, it would not have occurred to anyone to study these phenomena as models of other phenomena.

But the blurring of boundaries between transparent and opaque models is no reason to discard the conceptual distinction. Like any good conceptual distinction it simplifies and organizes a more complex reality and thereby enables us to perceive important differences between the functions of various kinds of models in the research process. Most consequentially, no neurologist would ever propose a study of the plastic brains on her colleagues' desks to learn something about the human brain, whereas neuroscientists did propose to study the dreaming brain to better understand the psychotic brain. Both polyethylene and dreaming brains are looked at as models, but one is a highly transparent, the other a profoundly opaque model. Only in the case of highly opaque models does it make sense to treat the model not just as a representation of a research object, but also as a research object in its own right.

What is puzzling about the use of opaque models is that they lack the relative simplicity that makes them easier to understand than the target phenomenon. Based on historical research and ethnographic work at Swiss and American neuropsychopharmacology laboratories studying hallucinogens in humans and animals as well as at a Finnish sleep laboratory looking at the dreaming brain as a model of psychosis and consciousness in general, this chapter examines how and why researchers availed themselves of such opaque models.

1 PHARMACOLOGICAL MODELS OF PSYCHOSIS

The use of hallucinogenic drugs in the wider sense can be traced back to Moreau de Tours' study *Du haschisch et d'aliénation mentale* (1845), in which the French psychiatrist described the effects of hashish on painters, poets, and other members of his circle. "In the way in which it affects the mental faculties," he wrote "hashish gives to whoever submits to its influence the power to study in himself the mental disorders that characterize insanity, or at least the intellectual modifications that are the beginning of all forms of mental illness" (quoted in Jay, 1999, p. 20). In 1921, the German psychiatrist Kurt Beringer established a modified version of Moreau's approach at the University of Heidelberg. He employed mescaline rather than cannabis and looked at the resulting inebriation as a model of psychosis, not delirium. But, just like Moreau, Beringer focused on the drug experience as a model of the experience

of mental illness. These psychiatrists had established an experiential model, in which one experience stood in for another. It allowed medical professionals to familiarize themselves with a state of mind resembling that of their patients, developing an empathetic understanding that would improve their clinical work. In contrast to graphic representations or three-dimensional models of molecules, such experiential models did not contribute to the visual culture of science, it was not primarily the sight of the inebriated test subjects that helped psychiatrists to grasp mental illness, but what they reported about their insides (Langlitz, 2012, pp. 143–149).

Both Moreau and Beringer sought to *describe* the inner experience of a psychiatric disorder recreated in healthy volunteers. They assumed that physicians trained in psychopathology or artists endowed with a particular sensibility would provide better introspective accounts than actual psychotics. In the tradition of Karl Jaspers's phenomenological psychiatry, Beringer privileged such descriptions of the soul "from inside" over the physician's clinical observations of their patients' behavior. A synopsis of his test subjects' written self-reports produced a general phenomenological account of the psychosis-like effects of mescaline. Following Ankeny (2000), Beringer's monograph *Der Meskalinrausch* (1927; see also Pieper, 1999) can be read as offering a preexplanatory or descriptive model of the mescaline intoxication. Considering that Beringer's description of the drug experience stood in for descriptions of his patients' psychotic experiences, this descriptive model functioned as a second-order model of psychosis. It highlighted those properties, which Beringer took to be characteristic of both the inebriation and psychotic episodes. Although their materialization in a body makes pharmacological models of psychosis a particular kind of physical model, it is always a mind–brain state under a description that stands in for another.

After the discovery of the effects of LSD by the Swiss industrial chemist Albert Hofmann in 1943, his employer, the pharmaceutical company Sandoz, marketed the new drug as a so-called psychotomimetic, a substance that would enable psychiatric researchers to mimic psychoses. In the 1950s, more biologically oriented psychiatrists adapted the hallucinogen model of psychosis to their conceptual framework. Soon it constituted an experimental system, which allowed for the search of a shared psychosis-inducing metabolite also found in the bodies of mentally ill patients causing similar symptoms in both drugged and schizophrenic brains. The most important articulation of this idea was Humphry Osmond, John Smythies, and Abram Hoffer's transmethylation hypothesis. They suspected an erroneously methylated hallucinogenic derivate of adrenaline to be the cause of schizophrenia (Baumeister and Hawkins, 2004; Dyck, 2008; Hoffer and Osmond, 1959; Hoffer et al., 1954). This conceptual model motivated the search for an endogenous hallucinogen that brought on the mental disorder. The transmethylation hypothesis no longer just described the phenomenological common ground between mental illness and intoxication but provided an explanation for it. In experimental psychosis research, it marked the transition from descriptive to explanatory models.

However, the hallucinogen model of psychosis temporarily lost its rationale when the transmethylation hypothesis gave way to the dopamine hypothesis of schizophrenia, which Arvid Carlsson, Jacques van Rossum, Solomon Snyder, and others,

elaborated in the 1960s and 1970s. This theory suggested that the mental illness was caused by a hyperactivation of the dopaminergic system. It also materialized in a pharmacological model system: amphetamine-stimulated dopamine D_2 receptors, which—in higher doses—could elicit psychoses in otherwise healthy people. Classical antipsychotics like chlorpromazine and haloperidol counteracted this effect by binding to these dopaminergic receptors (Baumeister and Francis, 2002). While the transmethylation hypothesis had been of largely academic interest, the dopamine hypothesis of schizophrenia helped to market antipsychotic medicines and was therefore widely propagated by the pharmaceutical industry (Healy, 2002, pp. 192, 207–219). There was no place for hallucinogenic drugs in this new model of psychosis: mescaline, psilocybin, and LSD-stimulated serotonin receptors, while another group of substances with hallucinogenic qualities, comprising phencyclidine and ketamine, turned out to deactivate glutamate receptors. If an overactivation of the dopamine system caused schizophrenia, it seemed nonsensical to model the condition with two sets of drugs that targeted entirely different neurotransmitter systems.

As the dopamine hypothesis challenged the theoretical foundation of the explanatory hallucinogen model of psychosis, the US psychopharmacologist Snyder (1989, p. 175) also called into question the underlying descriptive model, challenging its phenomenological plausibility: "Psychotomimetic drugs such as LSD by definition elicit psychosis. However, the psychosis that follows LSD ingestion is clearly unlike schizophrenia. Few psychiatrists will mistakenly label an individual under the influence of LSD as a schizophrenic. By contrast, many amphetamine users admitted to hospitals have been diagnosed as paranoid schizophrenic until the history of drug use was uncovered days or weeks later. In this sense, amphetamine psychosis is one of the best drug models of schizophrenia."

The resurgence of psychedelic research in the late 1980s also comprised a more modest rearticulation of the hallucinogen model of psychosis. The dopamine hypothesis had been qualified as alterations in the serotonergic and glutamatergic pathways had come to the fore in brains of schizophrenic patients. Moreover, the success of a novel therapeutic strategy provided further evidence that neurotransmitters other than dopamine played a key role in the mental disorder's pathogenesis. While antidopaminergic pharmaceuticals such as chlorpromazine and haloperidol reduced certain symptoms of schizophrenia, newly developed so-called atypical antipsychotics such as clozapine docked to serotonin rather than dopamine receptors and also proved effective (Baumeister and Francis, 2002; Healy, 2002, pp. 214–215). In light of this more complex understanding of schizophrenia, no single drug could generate a pharmacological model of the disease. Instead, a whole range of substances, including LSD, mescaline, psilocybin, ketamine, and phencyclidine, were used to mimic different neurochemical aspects of schizophrenia in humans and animals.

The temporary loss of interest in the hallucinogen model of psychosis had overlapped with the two-decade long interruption of psychedelic research in the wake of the countercultural upheavals of the late 1960s. When this line of research was revived in the second half of the 1980s, newly available methods and instruments such as neuroimaging technologies enabled significant advances in knowledge about the drugs' psychotropic effects. For example, Franz X. Vollenweider and his group at the

University Hospital in Zurich gave a strong impetus to the renaissance of model psychosis research using positron emission tomography (PET). They demonstrated an increased activation of the frontal lobes under the influence of both psilocybin and ketamine, which resembled the hyperfrontality found in the brains of schizophrenic patients suffering from acute psychotic episodes (Vollenweider et al., 1997a,b).

But the new insights also produced new puzzles. For instance, Vollenweider associated the activation of the frontal cortex with an increased internal production of stimuli and a psychological turn inward. The activity of neural pathways processing visual stimuli appeared to have decreased. Vollenweider was unsure about how to reconcile this with test subjects' reports that psychedelics had enabled them to perceive more, not less, of the outside world, seeing their surroundings in an almost microscopic manner (Langlitz, 2012, p. 130). More recently, the laboratory of Robin Carhart-Harris at Imperial College London conducted a functional magnetic resonance imaging (fMRI) study suggesting that the subjective effects of psilocybin in particular and psychedelic drugs in general were caused by *decreased* activity and connectivity between different brain areas. Thereby, he contradicted Vollenweider's interpretation of the hyperfrontality found in his PET scans (Carhart-Harris et al., 2012).

These inconsistencies indicate that the pharmacological effects of psychedelics are no better understood than the brain chemistry underlying schizophrenia. What is more transparent about the pharmacological model of psychosis is the primary cause of the hallucinations and other psychosis-like symptoms. The experimental intervention allows ascribing them unambiguously to the ingestion of drugs stimulating particular neurotransmitter receptors. But how exactly this initial neurochemical stimulation subsequently translates into a broad spectrum of psychopathological symptoms, not to speak of the alteration of the test subjects' conscious experience, remains equally if not more opaque as the emergence of schizophrenic experiences from their neurobiological substrates. The model's opacity is not at all surprising considering the much smaller scale of research on these exotic drugs in comparison with the much more significant efforts made to explain and cure a common psychiatric disorder like schizophrenia. What does seem surprising though is that a phenomenon as ill-comprehended as the effects of psychedelics is used to model another ill-comprehended derangement of the mind–brain. After all, the hallucinogen intoxication was at least just as complex and opaque to researchers as the psychotic states it was meant to represent.

2 AN ANIMAL MODEL OF PSYCHOSIS

At first glance, the animal version of the hallucinogen model of psychosis seems to come a little closer to a simplified representation of the modeled phenomenon, presupposing that the minds and brains of rodents are less complex than those of humans. The idea to look at an intoxicated mouse or rat as the proxy of a

schizophrenic patient emerged from the countercultural discourse around psychedelic drugs (Langlitz, 2012, pp. 169–176). As an undergraduate, in 1963, the psychopharmacologist-to-be Mark Geyer heard Aldous Huxley speak about the mystical revelations he had experienced under the influence of mescaline. Following James (1999/1898) and Bergson (1932), Huxley (2009/1954) regarded the brain as a filter. From the abundance of sensory information with which living organisms are constantly confronted, it was supposed to filter out those stimuli that do not help to survive—thereby barring human beings from experiencing their unity with the cosmic mind. However, hallucinogen ingestion—as well as various mystical practices—disturbed the cerebral "reducing valve" and thereby provided a glimpse of dimensions of reality not of immediate value in the fight for biological survival, but beneficial to our spiritual well-being (Huxley, 2009, p. 26).

Huxley (2009, p. 56) was well aware of the psychiatric use of hallucinogen intoxication as a model of psychosis but assumed that the schizophrenic was simply "not holy enough" to cope with permanent exposure to the divine. In principle, he regarded model psychosis research and the instant mysticism granted by psychedelic drugs as compatible. But, in contrast to the prevalent medical interpretation, he did not conceive of the hallucinogen experience as a mere hallucination or delusion, but as a revelation of metaphysical truth.

Inspired by the idea that psychedelics opened our "doors of perception," Mark Geyer got interested in gating or neural filter functions. He operationalized Huxley's metaphor of a cerebral reducing valve by measuring prepulse inhibition or PPI. The concept of PPI describes the following phenomenon: sudden and intense sensory stimuli trigger a startle reflex, which comprises blinking as well as a jerk of the whole body. If a weak, nonstartling stimulus (e.g., a low noise referred to as prepulse) precedes the stimulus (e.g., a loud noise referred to as pulse), it inhibits the startle response. PPI is an aspect of neural information processing elementary enough to be common to all mammals.

The idea of a general biology as it had emerged at the outset of the 20th century suggested that such widely shared attributes could be studied in a particular model organism representative of all others (Rheinberger, 2010, p. 6). Since mid-20th century psychiatry had identified the brain instead of the human mind as its primary scientific object, it had thus become reasonable to use animal brains as models of human brains, presupposing that human neurobiology did not differ fundamentally from that of other mammals.

Since the 1970s, Geyer's laboratory at the University of California, San Diego, has contributed significantly to turning this prepulse inhibition of the startle reflex into an operational measure for "sensorimotor gating," i.e., the ability of the nervous system to filter out irrelevant sensory stimuli. In 1978, Geyer and his coworkers managed to establish PPI as an operational measure of sensorimotor gating by demonstrating PPI deficits in schizophrenic patients (Braff et al., 1978). They presented a breakdown of the perceptual filter and the subsequent overload of sensory stimuli as an explanation for a number of symptoms of schizophrenia such as distractibility, hallucinations, and formal thought disorders and thus introduced PPI into psychiatry.

Geyer's team replicated this result in rats that had been given a range of pharmaceuticals, including hallucinogens (Krebs-Thomson et al., 2006; Mansbach and Geyer, 1991, 1989; Sipes and Geyer, 1995; Swerdlow et al., 1986). They also managed to demonstrate in animals that several substances already administered as antipsychotics restored a normal PPI after its inhibition by psychedelics (Bakshi et al., 1994; Mansbach et al., 1988; Sipes and Geyer, 1995; Swerdlow et al., 1991). This nurtured the hope that hallucinogen-induced PPI deficits in rodents would provide a high-throughput drug-screening mechanism that allowed to discover novel antipsychotic compounds. Thus, an animal model of psychosis was established.

Its simplicity and transparency turned out to be treacherous though. The assumption that a biological mechanism as basic and highly conserved as the startle reflex would be similarly affected by psychedelic drugs in all mammals turned out to be false. When measuring the PPI of healthy human subjects on psilocybin, the Greek-German psychiatrist Gouzoulis-Mayfrank et al. (1998) found that, unlike schizophrenics and rats on psilocybin, their test subjects showed an *increased* PPI. In this puzzling case, the animal model of psychosis adequately represented its object, i.e., schizophrenia, whereas its human counterpart failed to do so (Vollenweider et al., 1999). Later investigations revealed that, in humans, the increased PPI only occurred at longer intervals between prepulse and pulse, while shorter intervals led to a reduction of PPI (Vollenweider et al., 2007). The picture was muddled even further by subsequent research conducted at Geyer's laboratory. They found that the discrepancies were not confined to the difference between humans and animals (as a pre-Darwinian *differentia specifica* would have suggested), but turned out to be distributed across a range of species, so much so that even rats and mice did not always show the same responses (Langlitz, 2012, pp. 167, 197–200). Hence, the story of PPI added another chapter to the history of how behavioral pharmacologists' underestimation of species differences thwarted the contributions of their animal models to clinical drug development (Rose and Abi-Rached, 2013, pp. 93–98).

In the case of PPI, attempts to account for its puzzles proved to be complex and inconclusive. One scientist I spoke to during my fieldwork in Geyer's laboratory suggested that interspecies differences in metabolism and different dosages administered to the differently sized organisms might be the reason for the divergent responses to hallucinogens. Closer examination of Gouzoulis's findings showed that psilocybin altered PPI differently, depending on the length of the intervals between prepulse and pulse, but this contingency was not found in the case of schizophrenia. Geyer's group also discovered that when they repeatedly administered psilocybin to animals they failed to get consistent results. Only other hallucinogens such as mescaline, DOI, or DOM provoked replicable PPI deficits. Modeling a multifaceted human mental illness by modulating the startle reflex of rats and mice was undoubtedly reductionist, but it also showed, as the sociologist of science Latour (2004, p. 226) once remarked, "how impossible it is for a reductionist scientist to be reductionist." Or, as Mark Geyer put it in an interview with me: "We chose such a simple behavior that a lot of people think it's not relevant to anything complex, but it's certainly

complex enough for me to get frustrated about it." Again the model—like most animal models that involve organisms more complex than yeast or nematode worms—was everything but transparent. One complex and ill-understood phenomenon stood in for another.

In this case, however, the value of the model did not lie primarily in its representational qualities. "The success or failure of such an approach is in its predictive power," Geyer explained to me. "There is really only one proof of the pudding in science and that is: Can you predict what's gonna happen next? The rest is all fluff and theory and opinion." The hope was that the animal model would provide a fast and cheap mechanism to tell in advance which new compounds would show antipsychotic effects when tested in humans. If a drug could reverse hallucinogen-induced filtering deficits in animals, it might also have the potential to alleviate the suffering of schizophrenics. In this model, classical antipsychotics indeed behaved as predicted. However, to this day, more than four decades after its introduction, the model still had not identified a single new medicine, which passed clinical trials and was admitted to the market.

3 DREAMING AS A MODEL OF PSYCHOSIS

Hobson (2011, pp. 256–257), an eminent figure in neuroscientific dream research, wrote: "The fact that there is really no good animal model for schizophrenia or for major affective disorder suggests that a well-developed mind is a prerequisite for insanity. One may have to have a highly developed mind in order to go out of it! Put another way, if you possess a virtual-reality projector in your head, that device can get out of its box when you sleep. It does so regularly when you dream." The analogy between dreaming and psychosis can be traced back to early 20th century psychiatrists like Jung (1909/1907) and Bleuler (1911). Jung (1909, p. 86) famously said: "Let the dreamer walk about and act like one awakened and we have the clinical picture of *dementia praecox*." Whereas Jung and Bleuler associated dreaming with the condition that the latter would soon call *schizophrenia*, Hobson (1999, p. 32) reopened the question of what kind of psychosis dreams were like: "Could our nightly madness be likened to the bizarre thinking and emotional dulling of schizophrenia? Or do we see the wild fights of mania or encounter the dolorous delusions of depression? Is dreaming most like the delirium of organic brain rot—the spoilage that occurs when people persistently pickle their brain cells in beer, wine, and pot? Or does dreaming resemble the dementia that occurs in older people as their neurons die away?"

Building on Bleuler's (1911, pp. 356–357) identification of the symptomatologies of schizophrenia and dreaming and his claim that the patients appeared equally removed from reality as dreamers, living in their own private worlds, Hobson (1988, p. 9) proposed to study dreams as a "model of mental illness." He followed Bleuler rather than psychoanalysts such as Jung or Freud (2010/1900) in focusing not on dream content but form. Although Hobson (1999, pp. 32–33) acknowledged that

a loosening of associations was not just the most essential characteristic of dreams, but also a defining symptom of schizophrenia, he diverged from both Jung and Bleuler as he concluded from the analysis of formal features that dreaming differed in an important way from schizophrenia: there was no separation of thoughts and feelings.

Instead, Hobson (1996, pp. 88–89) argued dreaming shared all significant characteristics of another kind of psychosis, organic mental syndrome or delirium. The common features of dreaming and delirium were disorientation, inattention, impoverished memory, confabulation, visual hallucinations, and intensified emotions. In another publication, Hobson maintained "an absence of phenomenologic difference—in terms of cognitive bizarreness—between dreaming and waking state of psychotic subjects," but also emphasized that this did not necessarily imply pathophysiological similarity (Scarone et al., 2008, p. 5). Hobson hypothesized that the neurochemical imbalance characteristic of REM sleep—a deactivated monoaminergic system and a hyperactivated cholinergic system, linked to a demodulation of cortical activity—could explain both dreaming and delirium. Moreover, REM sleep, the sleep phase most closely associated with dreaming, also turned out to go along with reduced PPI measurements, Hobson and his colleagues pointed out (Scarone et al., 2008, p. 2). In his eyes, the similarity between these states of the "brain–mind" was so pronounced that he concluded: "Dreaming, then, is not like delirium. It is delirium. Dreaming is not a model of psychosis. It is a psychosis. It's just a healthy one." (Hobson, 1996, p. 88).

During my fieldwork on psychedelic science, Franz Vollenweider said something very similar when I emphasized the difference between a model and what it is a model of, i.e., between hallucinogen intoxication and schizophrenic psychosis: "There is absolutely no doubt that hallucinogens cause psychosis," Vollenweider assured me. "That's already the case by definition. There is nothing to compare [between inebriation and psychosis]. In psychiatry, all ego dissolutions, including religious experiences, are pathological."

Hobson's and Vollenweider's remarks point to an important feature shared by their practices of modeling: whereas a tin-and-cardboard model of the DNA double helix was no DNA and Hobson's chemical imbalance model of dreaming was no dream, their experimental models of psychosis did not serve as simplified representations but were studied as special cases of psychosis. This, by the way, was not true for Geyer's model psychosis since he never claimed that his drugged mice were actually "psychotic"—such anthropomorphism would have been an anathema to behavioral pharmacologists. If we followed Rheinberger's (2015) typology of scientific objects, which requires models to articulate data from the target phenomenon in a different medium, the hallucinogen and the dream model of psychosis might not count as models at all because the medium remained the same: experiences served as models of experiences, brains as models of brains. By contrast, Hoffmann (2012, p. 67) recognizes "models in their own material" as a deviation from classical models, namely, "models in another material," but thinks of durable preparations rather than the short-lived neurophenomenological phenomena discussed in this chapter.

The epistemic value of using a special case as a model of the whole lay in the fact that the case should incorporate all features that were taken to characterize the phenomenon in general while having certain practical advantages over the other special cases that were lumped together under this rubric. For instance, one strong point many of my interlocutors pointed to was that most schizophrenic patients who could serve as test subjects had already been treated with antipsychotics, which made it difficult to decide whether changes in their brain chemistry had to be attributed to the disease or its treatment. By contrast, hallucinogen- or REM sleep-induced psychoses in healthy subjects were not affected by preexperimental medication and could be compared in a more controlled fashion with nonpsychotic states in the same subjects. Here, the experimental model promised to be less affected by confounding factors than its object. However, since neither the model nor what it was a model of were fully understood, such opaque models entailed continuous comparative work, which transparent physical or theoretical models did not require.

4 DREAMING AS A MODEL OF CONSCIOUSNESS

The fourth and last case of an especially opaque model in the neurosciences that I would like to present used the dreaming brain as a neurobiological model of consciousness in general. Building on Hobson's work, neurophilosopher Patricia Churchland presented dreaming as a special case of consciousness that could be studied in normal subjects everyday while differing significantly from waking. Moreover, objective markers such as electroencephalographic patterns and rapid movements of the eyes during REM sleep enabled researchers to distinguish different sleep phases in animal models allowing for invasive methods to establish correlations between mind and brain states. "If there is a domain relevant to consciousness which has sufficient supporting infrastructure and surrounding theory to enable experimental discovery," Churchland (1988, p. 290) argued, "it is the sleep-dream-awake cycle." Churchland's interest in dreaming, however, was driven by the philosophical intuition that what we commonly call *consciousness* is a potpourri of so many very special cases that comparing and contrasting these very different mind–brain states might eventually lead us to eliminate the overarching category of consciousness altogether.

Although Churchland did not pursue her idea any further that sleep and dreaming could help to unlock the riddles of consciousness, the philosopher and brain researcher Revonsuo (1995) adopted Churchland's proposal and founded a sleep laboratory at the University of Turku to study the dreaming brain as a model of consciousness *tout court*. In contrast to Churchland and Hobson who were both interested in dreaming because it was so different from normal waking consciousness, Revonsuo emphasized how very much these mind–brain states were alike. He advocated this model as an alternative to visual awareness, which Crick and Koch (1990) had promoted as the best model of consciousness. Many experimental approaches operationalize consciousness as an awareness of visual stimuli. For example, in

the binocular rivalry paradigm, horizontal stripes are displayed in front of the test subject's one eye and vertical stripes in front of the other eye. Although subjects are "seeing" both horizontal and vertical stripes at the same time, they fail to superimpose these images. Subjects' conscious perception is not of a grid but oscillates at a particular frequency between horizontal and vertical stripes (Lumer, 2000). This experimental paradigm lent support to externalist accounts of consciousness, presenting a case of visual awareness that emerges in relation to external objects, apparently neglecting internal information processing as an important source of consciousness.

By contrast, the dreaming brain was favored by neuroscientists and philosophers of mind committed to a so-called internalist notion of phenomenal consciousness. They assumed that consciousness supervened on the brain and the brain alone and could emerge even if the brain was in a vat (Langlitz, 2015a). Revonsuo (1995, p. 42) considered dreaming a particularly apt model for exploring this internalist vision of the mind–brain both philosophically and empirically because, according to Hobson and McCarley (1977), the neurophysiological thresholds for sensory input and motor output were so significantly elevated during REM sleep that during most dreams the mind–brain was effectively insulated against the confounding noise of action and perception and cut off from its environment—and yet it produced an experience of immersion in complex surroundings. This supposed isolation of a state of consciousness led Revonsuo to consider the dreaming brain as an experimental model of "pure consciousness." Uncontaminated by interactions with the outside world it promised a higher analytic payoff than visual awareness.

Revonsuo first sketched this model system in a philosophical thought experiment. He assumed that to demonstrate that consciousness supervened on neural activity neuroscientists would have to be able to emulate subjective experiences on the basis of objective recordings. Unlike purely theoretical approaches that seek to bridge the explanatory gap between mind and brain by laying out propositions translating between psychological and neurobiological processes, Revonsuo imagined what he called a dream catcher, a device that would enable researchers to not just understand their subjects' dreams through the medium of theory but to reexperience them in a virtual reality simulation. Measurements of brain activity of the kind already conducted with neuroimaging technologies, only much more fine-grained, would be translated into a scenario scientists could experience with all their senses, effectively reliving a test subject's dream. This representation would eventually bring about what happened in one mind–brain in the medium of a second mind–brain (Revonsuo, 2006, pp. 300–303, 344–347). Just like Moreau's and Beringer's pharmacological models of psychosis, the dream catcher operates as an experiential rather than an explanatory model.

In the mid-2000s, Revonsuo started to develop a much more modest laboratory experiment from this thought experiment. His research team contented itself with the philosophically rather ambitious goal of demonstrating mind–brain identity by detecting *if* and *when* a subject was dreaming without trying to read out *what* this person was dreaming. They hoped to identify moments when dreams as states of consciousness arose in electroencephalograms of sleeping subjects. If they found

neurobiological markers distinguishing dreaming from dreamless sleep during a particular sleep phase, Revonsuo reasoned, these markers would be candidates for the much sought-after neural correlates of consciousness. An unpublished study aimed at contrasting EEG activity from dreaming and dreamless sleep. But no electroencephalographic signature distinguished those recordings that led to dream reports. A PhD student who presented these results at a conference offered four possible explanations for the failure of the study: “Subjective experience is a) not in the brain, b) is in the brain, but not in the EEG, c) is in the EEG, but not in our data, or d) is in the data, but needs more complex and novel methods of analysis.” (Langlitz, 2015a, p. 14).

Revonsuo’s lack of success in pinning down dreaming neurobiologically also raised an important question about its use as a model of psychosis. Since nobody could tell the difference between a brain that was dreaming and one that was not, Hobson’s analogies between supposedly dreaming and psychotic brains took REM sleep as the sleep phase that generated most dream reports as a proxy for dreaming, even though subjects awakened from REM sleep often failed to remember any dreams while subjects awakened from NREM sleep occasionally did report a dream. Consequently, the philosopher Windt and the neuroscientist Noreika, a student of Revonsuo’s, wondered "whether one should talk about a ‘dreaming model’ or a ‘REM sleep model’ of psychosis" (Windt and Noreika, 2011, p. 1099).

By now readers will recognize the chorus: neither dreams nor consciousness were neurobiologically well understood, and yet dreaming—as a peculiar form of consciousness arising during sleep—had come to serve as an opaque model of consciousness at large. In the case of the hallucinogen models of psychosis, experimenters could at least determine unequivocally the initial pharmacological triggers of the following neural commotion. But the neurophysiological generation of dreams remained highly controversial (Hobson, 2009; Nielsen, 2000; Solms, 2000). Along the continuum between transparency and opacity, the dream models of psychosis and consciousness come closest to the ideal type of opaque models.

5 THE FUNCTIONS OF OPAQUE MODELS

What are opaque models good for, considering that they are often as obscure as their objects, if not more so? First consider that there has never been much money for people who are simply intellectually curious about strange states of mind such as dreams or psychedelic experiences. No lucrative applications emerged for hallucinogenic drugs, especially since their prohibition in the late 1960s stalled all medical uses for two decades (Langlitz, 2011, 2012, pp. 30–38). In the 1980s, funding priorities for sleep research shifted to sleep apnea, leaving few resources for scientific studies of dreaming (Kroker, 2007). Sociological cynicism might suggest that presenting these phenomena as models of psychiatric disorders was a clever strategy of tapping into the rich sources of funding available for biomedical research.

But I have also pointed to a number of ways in which these experimental systems were meant to actually advance psychiatric and neuroscientific knowledge. Although the hope that the hallucinogen-based animal model of psychosis would help to identify new clinically efficacious antipsychotics has not been fulfilled, PPI research in rodents shed light on the surprisingly complex and varied neurobiology of the startle reflex. In the 2000s, the discovery that drug-induced changes of PPI not only differed across species or between healthy subjects and schizophrenic patients but even within the patient population lent support to dissecting the complex phenotype of schizophrenia into a multiplicity of simpler so-called endophenotypes, i.e., characteristics reflecting the actions of genes which predispose an individual to a disorder, even in the absence of diagnosable pathology (Thaker, 2008; Turetsky et al., 2007). One day such differentiation might lead to more targeted treatment strategies. For the time being, however, it mostly helps to understand the genetic and neurobiological underpinnings of psychopathology and to assess the disease susceptibility of relatives of schizophrenic patients.

Similarly, the Greek-German model psychosis researcher Euphrosyne Gouzoulis saw the value of the revived hallucinogen model of psychosis in contributing to a more differentiated image of schizophrenia. In her eyes, there were two pharmacological models, the serotonergic one based on substances such as psilocybin, LSD, and DMT, and the glutamatergic model employing ketamine and phencyclidine, which allowed to model different psychotic syndromes. "One can say, With this substance we model this syndrome and with that substance another one," she explained to me in an interview (Langlitz, 2006, p. 176). Rather than presupposing a shared neurobiological substrate of schizophrenia and its pharmacological models, Gouzoulis compared and contrasted these different mind–brain states. Considering the epistemic opacity of all these phenomena, nothing could be extrapolated from the effects of hallucinogens about the neurobiological mechanism of schizophrenic psychoses. Yet the drug models could "give interesting clues, which then need to be verified in patient populations," Gouzoulis explained (Langlitz, 2006, p. 176). Thus, the hallucinogen models did not primarily aim at confirming hypotheses or answering questions but at generating new questions for further research. The historian of science Rheinberger (1997, p. 28) aptly called such experimental systems “machines for making the future.” In his eyes, it is precisely their permanent failure of representation that makes models epistemically fertile (Rheinberger, 2015, p. 329)—a perspective which I adopted in previous publications on model psychosis research (Langlitz, 2006, 2012, pp. 132–165).

Doing fieldwork with empirically oriented philosophers of mind and brain researchers on the knowledge culture of neurophilosophy, during which we repeatedly visited Revonsuo’s sleep laboratory in Turku, I encountered a very different way of thinking about models. Two members of the group I worked with, Windt and Noreika, read my work on the hallucinogen model of psychosis as a foil against which they reviewed various proposals for using another altered state of consciousness, namely, dreaming, as a model system. Like Rheinberger and myself, they took the epistemic opacity of the dreaming brain as a productive feature, which stimulated

rather than hindered research not by providing answers, but by raising new questions. However, instead of celebrating the "shattering of representation" (Rheinberger, 2015, p. 329), Windt and Noreika (2011, p. 1098) continued to assess models according to their traditional representational function: "the adequacy of a model depends on whether or not it is epistemically transparent—that is, whether the insights it generates can be transferred from the model to the target itself or certain of its properties." This privileging of transparency made the hallucinogen and dream models of psychosis and consciousness appear inadequate as models.

More could be learned from exploring both similarities and dissimilarities between dreams and other states of consciousness, including psychotic aberrations and hallucinogen intoxications, than from emphasizing similarities that would legitimate one state of the mind–brain to stand in for another, suggested Windt and Noreika. Although this conclusion resembled Gouzoulis's comparative approach, it led them to suspend the practice of modeling altogether until the relationships between the mind–brain states in question had become more transparent. In their eyes, it was premature to look at dreaming as a proxy of psychosis or consciousness as long as there was confusion about the very nature of dreaming. Researchers not only argued over the phenomenology and underlying neurophysiology of dreams but could not even reach a consensus about the definition of dreaming, Windt and Noreika complained. Some considered any mental activity in sleep as a dream, while others expected full-blown hallucinatory experiences. So long as dreaming was so deficiently characterized that researchers could take it as an analogue of such different conditions as schizophrenia, delirium, and wake states, they regarded it as "premature or even principally impossible to identify it as a model for standard waking consciousness or some concrete psychiatric disorder." (Windt and Noreika, 2011, p. 1100).

Instead of using dreaming as a model system, Windt and Noreika (2011, pp. 1001–1004) advocated the development of a framework that would allow comparing dreams to pathological and nonpathological waking states without presupposing a complete theory of consciousness in the dream state. Whereas the epistemic relationship between a model and its object only enabled researchers to apply what they have learned about the model to what it is a model of, Windt and Noreika's so-called contrastive analysis facilitated bidirectional reasoning, allowing new insights into one mind–brain state to shed light on the other—and vice versa.

The difference between Rheinberger's and Windt and Noreika's assessments of models highlights two very different but complementary aspects of science: one cultivates a relationship to the unknown and values the generation of questions, and the other privileges positive knowledge and the giving of answers. Models are involved in both processes. But the more transparent they are, the better they will resolve research problems and advance inquiries toward their conclusion. The more opaque models are the greater their potential to pose new problems and stimulate further inquiries. Models replicate the Janus-like nature of science, which Latour (1987, p. 7) described as having two faces: one that knows and one that does not know yet. While Latour, Rheinberger, and most science studies scholars have honored the ignorant

face more than the knowledgeable one, what I learned from my work with more positivistically minded neuroscientists and neurophilosophers is a symmetrical appreciation of both sides (Langlitz, 2015a,b, 2016).

The anthropological view from afar, juxtaposing and comparing several opaque models with each other, also reveals something else. Studying the dreaming brain as a model of consciousness foregrounds a feature that it shares with the dream model of psychosis: both models emphasize the isolation of the mind–brain from its environment. Revonsuo radicalized Bleuler's and Hobson's assumption that schizophrenics and dreamers live in their own private world detached from reality to the point where conscious life in general takes on an oneiric quality. "Not only are dreams experiences but, in a way, all experiences are dreams," he wrote. "The dreaming brain as a model system leads up to a particular conception of consciousness which I call the world-simulation metaphor of consciousness" (Revonsuo, 2006, p. 75). This image of the brain as a simulator, generating a sense of immersion in a neurally constructed virtual reality, contrasts sharply with Huxley's metaphor of the brain as filter that inspired the hallucinogen model of psychosis, especially PPI experiments. Of course, the natural scientific research following this tradition shed the belief that opening the doors of perception would let in what Huxley had called "Mind at Large" and that schizophrenic patients were not "holy" enough to deal with such profound spiritual experiences. But it did assume that a neurochemical challenge to the brain's gating mechanisms would generate a sensory overload responsible for hallucinations and other symptoms of experimental and naturally occurring psychoses. Whereas the dream model conceived of psychosis as a state of being cut off from the world, the hallucinogen model presupposed that the ego boundaries of psychotics were so porous that the experienced level of exposure to the surrounding world overwhelmed these subjects. This contrast reveals the anthropological function of the opaque models discussed: they carry with them certain assumptions about things human. The choice of model establishes a paradigm: either psychosis—and maybe even consciousness in general—is like a dream or it is like an overpowering revelation. Whole cosmologies are folded into these models (Langlitz, 2012, 2015a).

The anthropologist Geertz (1973, pp. 93–94; see also Fox Keller, 2000; Paxson and Helmreich, 2014) proposed to think of models not just as "models of" but also as "models for" something—as devices that are both descriptive and prescriptive. For instance, the dream model provides an incentive for gathering more evidence for the detachment of the psychotic mind–brain, while the hallucinogen model has generated interest in the failure of other gating mechanisms. Beyond such orientations of research trajectories, explorations of what these models of psychosis are "models for" quickly venture into the speculative or require more extensive ethnographic work than what I can lay out here (for first steps, see Langlitz, 2012, 2015a). But it is important to note that the models' representational opacity does not obstruct their evocative power to guide scientific research into particular directions, which differ from model to model. Whenever we encounter an opaque model, we should ask ourselves where it will take us and what alternative orientations are available.

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