Published June 27, 2017

Mental Organs and the Breadth & Depth of Consciousness

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Abstract

Psychedelic drugs produce a wide range of alterations of human consciousness, from subtle to dramatic. Current theory proposes that these changes are mediated by action at the serotonin-2 ($5\text{-}HT_2$) receptors, principally $5\text{-}HT_{2A}$. Based on a synthesis of molecular affinity data with published reports of the subjective experience for twenty-two psychedelic drugs, I propose a set of hypotheses that clarify the role of $5\text{-}HT_2$ and many other receptors in the psychedelic process:

- Modulatory receptors define "mental organs" (populations of neurons expressing a specific receptor).
    - Many mental organs provide content, representing different facets of reality in consciousness. Content mental organs have the capacity to enter and be held in consciousness, and thus may be in or out of consciousness. Content mental organs represent internal, external, and social aspects of reality. Most content mental organs are affective, painting the world in consciousness as feeling; a few are cognitive, painting the world as language, logic, and reason.
    - Some mental organs provide the mechanisms of consciousness:
        - $5\text{-}HT_7$ provides the mental space of adult human consciousness and creativity.
        - $5\text{-}HT_2$ provides the "hands of the mind" which give shape to consciousness, in part by controlling which content mental organs are loaded into or excluded from consciousness.
- Consciousness includes two major dimensions affected by psychedelic drugs:
    - Breadth – corresponds to the number and diversity of mental organs that are held in consciousness; which collectively render the contents of consciousness. A greater number of mental organs in consciousness mean a more multifaceted, more complete rendering of reality. $5\text{-}HT_2$ manages breadth.
    - Depth – Increasing activation of $5\text{-}HT_7$ leads to an increase in the depth of consciousness (resolution, subtlety, nuance, complexity, tangibility, vividness, and capacity; to render thought, feelings, and sensory input). Increase of depth is responsible for the most dramatic effects of psychedelic drugs, including open-eyed creative visuals, ego-loss, and loss of contact with reality.
        - There is a discontinuity in the $5\text{-}HT_7$ spectrum: at a certain degree of activation, the contents of consciousness become more salient than actual reality, and the subject loses contact with reality. This could manifest as a formless void or an alternate reality depending on the participation of other mental organs.
        - While many mental organs render facets of *actual* reality in consciousness, $5\text{-}HT_7$ also renders what *could be*. It adds the spark of creativity.
    - Creativity requires both depth and breadth, emerging from the interaction of a wide variety of mental organs.

Introduction

For over three decades, the 5-HT_2 paradigm of psychedelic drug action (Glennon, Titeler, & McKenney, 1984) (Glennon, Titeler, & Young, 1986) (Titeler, Lyon, & Glennon, 1988) (Nichols, 1997) (Nichols, 2004) (Nichols, 2016) has resulted in a narrow focus on 5-HT_2, with only lip service to the roles of other receptors in the psychedelic experience. Here I would like to provide a broader and more balanced view of the psychedelic process as it emerges from diverse neural systems in the brain. I will describe the roles of multiple receptors and their corresponding mental organs (Ray, 2012, 2016), as well as some of their interactions.

Within this complex process we will see that 5-HT_2 plays an important if not uniquely central role. I will focus on two mental organs, 5-HT_2 and 5-HT_7, which play central roles. They are intimately intertwined. 5-HT_7 mediates consciousness; multiple mental organs provide content to consciousness; and 5-HT_2 gives shape to consciousness, in part by controlling access to consciousness of the multiple mental organs providing content.

We will try to understand these complex relationships by first considering those mental organs that provide content to consciousness. Then we will consider the role of 5-HT_2 in mediating access to consciousness. Finally we will look at 5-HT_7 and two of its facets: consciousness and creativity. Out of these considerations will emerge an understanding of the qualitative diversity of psychedelic drugs, as well as an understanding of the structure of the mind itself.

Mental Organs

I put this study in motion with a conceptual framework: receptor space (Supporting Information S01ReceptorSpace.pdf; It was an earlier version of the receptor space essay that prompted Bryan Roth to invite me to submit a proposal to the National Institute of Mental Health – Psychoactive Drug Screening Program (NIMH-PDSP)). Receptor space has a dimension for each specific kind of receptor expressed in the brain (e.g. 5-HT_{2A}, 5-HT_7, imidazoline-1), where the magnitude along any axis is proportional to the level of expression (e.g. activation/number/density) of receptors. At the outset I viewed the mind as a complex dynamical system, tracing a path through attractors in receptor space. Drugs would perturb the mind from the un-medicated attractors to some other attractors.

However, as I grew to know the data, the receptor space conceptual framework gave no clarity, made no predictions, and had no explanatory power. I began to see the mental effects mediated by each receptor or closely related group of receptors as a very coherent mental phenomenon in itself, apart from the mental effects of each other receptor. The mental effects at each class of receptor had great depth, coherence, and human quality.

That most of the receptors that psychedelics interact with are G protein coupled receptors (GPCR), a large gene family that also includes the odor and taste receptors, helped to facilitate the emergence of a new conceptual framework: full-flavor psychopharmacology. I call the current paradigm, "key-receptor psychopharmacology", which is the idea that a psychoactive drug, or even an entire class of chemically diverse psychoactive drugs interacting with dozens of receptors, can be understood through their action at a single key receptor or group of closely

related receptors. In the current paradigm the effects of psychedelic drugs are understood to be primarily mediated through 5-$HT_{2A/C}$, the two closely related key receptors (Nichols, 2004) (Nichols, 2016). They are believed to be responsible for most of the effects of psychedelics, including consciousness expansion, creative open-eyed visuals, ego-loss, loss of contact with reality, alternate realities, mystical experiences, and experiences of substantial personal meaning and spiritual significance.

In the "full-flavor psychopharmacology" paradigm, there is no key psychedelic receptor. Rather, psychedelic drugs interact with dozens of different receptors (Ray, 2010), and every receptor produces a perceptible effect when activated (Ray, 2012). Just as odorants produce the rich world of odor and flavor by interacting in different patterns with hundreds of odor receptors (Buck & Axel, 1991), psychoactive drugs produce their rich diversity of mental effects by interacting in different patterns with hundreds of neurotransmitter receptors. The distinct and unique flavor of each drug arises from its pattern of interaction with various receptors. The concept of the flavor of a drug is discussed in the S02Methods.pdf document included in the supporting information.

While I still find the full-flavor paradigm useful, its explanatory power seems limited to certain categories of modulatory receptors: those that provide content to consciousness. Eventually I found it more productive to think in terms of mental organs, which I have described elsewhere (Ray, 2012, 2016). This new conceptual framework has brought the mind into sharp focus. It is a big picture with lots of detail. Mental organs have great explanatory and predictive power (Ray, 2016).

In (Ray, 2012) I laid out the basic concepts of mental organs, as well as hypotheses about thirteen specific mental organs (5-HT_1, 5-HT_2, 5-HT_7, alpha-1, alpha-2, beta, dopamine, histamine-1, imidazoline-1, kappa, mu, sigma, cannabinoid-1) and some of their interactions. The concept of mental organs emerged from a synthesis of two bodies of data: molecular affinity of drugs for receptors (Ray, 2010), and previously published reports of the subjective experience of the same drugs.

In (Ray, 2012) I said: "In this nontechnical chapter I will present my findings on the nature of mental organs and the implications of their existence, without doing the heavy lifting of providing the supporting evidence. That technical work will be published elsewhere." The present manuscript is the first publication in which I do "the heavy lifting" by fully presenting the evidence of subjective experience of drugs together with the molecular data; the synthesis which has led to my views on mental organs. This manuscript is lengthy due to being richly illustrated by the subjective reports from which the hypotheses emerged.

Because this manuscript builds directly on my previous work, some text previously published in (Ray, 2012) (a chapter in a book with little circulation) will be woven into this presentation. Because fragments of text from (Ray, 2012) have been scattered through this manuscript and subsequently edited, it would be distracting to attempt to quote and cite each portion of overlapping text. But I have included notes where significant excerpts appear.

"Mental organ" is defined as a population of neurons that express a specific modulatory receptor (e.g., serotonin-7, histamine-1, alpha-2C, imidazoline-1). Due to being defined by the expression of specific genes, mental organs can evolve by duplication and divergence, and provide a mechanism for evolution to sculpt the *mind*. This concept of mental organ was presented by (Ray, 2012), and later, (Ray, 2016) further developed the concept of mental organs by observing that the molecular messenger cascades from these modulatory receptors set the parameters of the properties of these neurons, creating a population of neurons with properties in common that can function as a tissue in the brain supporting a specific mental function.

This additional conceptualization of the individual receptors defining tissues by controlling the parameters of the neurons through the molecular cascades initiated by the modulatory receptors, is complicated by the existence of multiple types of modulatory receptors on some neurons. If the receptors defining two mental organs are found on a single neuron, does that neuron have the properties of both mental organs, or do the two molecular cascades add up to a third set of properties that would define a third mental organ? What are the patterns of co-occurrence of different types of modulatory receptors on the same neurons? When different types of receptors co-occur on the same neuron, are they segregated into different components of the neuron: dendrites, cell body, axons; or do they intermingle in these distinct regions? These issues need to be explored to clarify this aspect of the concept of mental organs. The patterns of overlap of different modulatory receptors on the same neurons and on the same mental organs need to be viewed through the conceptual framework of mental organs, to determine if these patterns make sense in this context. In this process we may deepen our understanding of mental organs.

The human mind is populated by mental organs, which play diverse roles within the mind. Some mental organs provide consciousness (in separate adult and childhood forms); some function as gatekeepers to consciousness (in long and short time scales); some provide content to consciousness, while some give salience, meaning or significance to the contents of consciousness. Some function as the hands of the mind, shaping consciousness, in part by moving content mental organs in and out of consciousness. Some provide the conscious space to hold the content mental organs; and also the spark of creativity, allowing us to go beyond what is, and consider what could be. Some mental organs support the faculties of language, logic and reason, which appear to have arisen in the last one or two hundred thousand years in humans.

I will refer to language, logic and reason simply as "cognition". The faculties of cognition appear to be fully developed only in modern adult humans. The children we develop from and the animals we evolved from lack those faculties, and yet have fully functional minds and are capable of making their way in the world. Some mental organs provide affective ways of knowing the world, which richly paint the world in consciousness through feeling alone, and provide the complete archaic mind in our developmental and evolutionary antecedents. The separate adult and childhood forms of consciousness mentioned above also correspond to the modern and archaic minds. Archaic consciousness can hold only affective content, while the modern adult mind can hold both cognitive and affective content. (previous two paragraph derived from (Ray, 2012))

Most mental organs have not yet been characterized. Some of the thirteen hypotheses of specific mental organs presented by (Ray, 2012) are based on much information, while others are based

on little. There remains much to learn about them all. For the purposes of the presentation in this manuscript, the thirteen characterized mental organs can be grouped as follows:

- Conscious mental space
  - 5-HT_7 – Adult, modern, cognitive and affective consciousness
  - κ – Childhood (and likely pre-human), only affective consciousness
- Management of access to consciousness
  - 5-HT_2 – Dynamic, moment-to-moment
  - CB_1 – Long-term, progressive, cumulative, semi-permanent selective blocks
- Contents of consciousness
  - Cognitive
    - 5-HT_1 – Language, logic, reason, concepts, thought, patterns in nature
  - Affective
    - β – Home, family, community, society, humanity, joy
    - H_1 – Empathy; dynamic, persistent, and cumulative theory of mind
    - α_2 – Sense of the essence or soul of things (rasa), or events shaping one's self
    - α_1 – Sense of continuity, history, flow of events
    - D – Meaning, significance, awe, and certainty; integration
    - I – Ecstasy, empathy, openness, compassion, peace, acceptance, forgiveness, healing, oneness, caring; letting go of anger, grudge, guilt, shame, anxiety; ability to safely experience and contemplate mental pain
    - μ – Comfort, security, peace, gentleness; dissipation of pain, hunger, tension, anxiety, frustration, fear, anger and aggression; Edenic
- σ – Core of our being, our heart & soul; purely affective

These groupings remain fluid, and are likely to change as we characterize more mental organs, and as we gain a better understanding of each one, and of their interactions. Mental organs provide a language of description for the mind, which will be used throughout this essay.

One of the most fundamental results to emerge from this work is a hypothesis of the origin of complex mind through the emergence and evolution of "mental organs." Mental organs provide a direct connection between mental properties (e.g. compassion, comfort, awe, joy, reason, consciousness), neural structures (populations of neurons, tissues within the brain), receptor proteins, the molecular cascades they regulate, and the corresponding genes and their regulatory elements. Mental properties associated with mental organs have heritable genetic variation and are thus evolvable. Mental organs can evolve by duplication and divergence. Each mental organ must contribute to the fitness of the organism in order to persist through evolutionary time. Over three hundred different G protein coupled receptors (GPCR) are expressed in the human brain (mental organs are not limited to GPCR), providing a genetic and regulatory system that allows evolution to richly sculpt the *mind* (Ray, 2012).

Because mental organs are defined by the expression of receptors, the word "receptor" and the phrase "mental organ" can be used interchangeably in many instances. I have attempted to use the word "receptor" when discussing the molecular or cellular level, and the phrase "mental

organ" when discussing the mind. The distinction is discussed further in the section "Limbs of the mind".

Methods – Natural History of the Mind & Psychedelics

Natural History

I am trained theoretically as an evolutionary biologist, and practically as a naturalist studying beetles, ants, butterflies, and behavior of climbing plants in the lowland rainforests of Costa Rica. As a naturalist I have gone into one of the most complex ecosystems on Earth to make patient and careful observations to detect patterns in living nature. While focused on one pattern (Strong, 1977, 1981, 1982) I may stumble across other unrelated patterns and opportunistically explore them (Ray & Andrews, 1980; Strong & Ray, 1975). A haphazardly encountered pattern can develop into a major research program (Ray, 1976) (Ray, 1981) (Ray, 1989) (Ray, 1990) (Ray, 1992).

I bring this same style and sensibility to the study of the human mind. I believe that even today, in 2017, the *mind* remains a relatively unexplored wilderness as does much tropical rainforest. Given what I consider the primitive level of our understanding of mind, I believe that science is at the stage where the natural history approach (Drummond & Steele, 2017) can productively precede the application of more structured scientific methods.

An important methodological property of natural history is that it can be practiced without a hypothesis or even a question. It can be guided by curiosity and interest. Natural history has been described as "A practice of intentional, focused attentiveness and receptivity to the more-than-human world, guided by honesty and accuracy" (Fleischner, 2002) and "Patient interrogation of a landscape" (Lopez, 1986). The insights that emerge from successful natural history can be framed as hypotheses to advance to more formal scientific methods. Natural history is a productive method to begin the exploration of an unfamiliar domain.

Natural history was likely the original science, before the emergence of civilization, when the mind's full faculties were put to the task of facilitating our survival while living in nature. This was achieved in part by observing nature and finding the patterns in it, such as the spatial and temporal patterns of edible plants or movements of game animals. The original recognition of a pattern in nature emerges as insight. This would have had tremendous survival value when we lived close to nature. Insights emerging from natural history can be considered hypotheses, which our ancestors tested by acting on them, and which today can be tested by the scientific method. Our innate talent for natural history remains relevant to science today. Wandering with eyes open for interesting patterns is central to the practice of natural history.

The editor of a methods journal told me that the methods published in his journal should be like an algorithm, that any post-doc or PI should be able to crank through, and spit out the answer. But I am describing a method that involves wandering and insight. Wandering is not like an algorithm; insight does not predictably spit out the answer, although it is common for scientists who are exposed to similar experiences or data to have very similar insights. Charles Darwin and Alfred Russel Wallace both traveled the world, playing the role of naturalist on a ship

expedition through tropical areas, and both read the essay on population by Thomas Malthus. Both then had the insight to envision evolution by natural selection.

I embarked on this study not knowing what I would find, but sure that there was much potential. The human mind is the most complex entity in the known universe, and is one of the last great frontiers of science. I believe that we can productively advance this frontier as naturalists of the mind. I will describe the insights and hypotheses that have come to me while exploring the mind as a naturalist, and I will describe the phenomena that provoked the insights and hypotheses.

Psychedelic Drugs

In approaching the human mind, I have chosen to begin by using psychedelic drugs as probes in humans, because their mental effects are dramatic and diverse and can be described by the subject. Psychedelic drugs alter core human mental properties. In a 1996 interview in Mexico (Sala, 2007), Alexander Shulgin said "I'm looking for tools that can be used for studying the mind, and other people then will use the tools in finding out the aspects of the mental process and how it ties to the brain. But my main drive is a tool maker, making of tools, and letting other people exploit them." The project described in this manuscript consists of using Sasha's tools to probe the human mental process and how it ties to the brain.

I consider Sasha's work to be the natural history of the chemistry of the mind. As a graduate student working in the rainforests of Costa Rica, I heard it said among the researchers, that natural history is alpha community ecology; acknowledging that community ecology is built on the foundation of natural history. I see my work built on Sasha's in a similar fashion. I see my work as being within the legacy of Shulgin, yet I start where he left off, and he built an amazing launch pad. Sasha was onto something big. I believe that the greatest scientific value of Sasha's work is that he has left behind a diverse toolkit of probes into the human mind, that allow the unlocking of many of its secrets. Sasha has provided us with a methodology for mental discovery. I don't believe that there is any other method that can make as deep a penetration into the structure, function, process, genetics, development, and evolution of the human mind, and mechanisms of consciousness. We can put this knowledge to work not just in providing new approaches to understanding the etiology, diagnosing, treating, and healing mental disorders; but also in understanding ourselves. We owe these discoveries to the foundations that Sasha has laid.

I have synthesized two bodies of data: broad receptor affinity assays conducted by the NIMH-PDSP (Ray, 2010), and previously published reports of the subjective effects of the same drugs. In reviewing the data on subjective effects, I do not use algorithms that examine patterns of word usage (Coyle, Presti, & Baggott, 2012; Dye, 2012), rather I simply read the reports carefully, in order to most fully understand them with my own mind.

I have elaborated overarching hypotheses of what mental organs are, narrower hypotheses for each of thirteen individual mental organs, and hypotheses of the interactions between mental organs (Ray, 2012). Yet at times some specific empirical data is not consistent with some details of this emerging conceptual framework. These are learning moments from which new insights may flow. This manuscript will in part be organized around "problems", where theory and data

were not consistent, and where contemplation has led to insights, and modification and elaboration of emerging theory to resolve these conflicts.

In choosing the drugs for this study, I have included drugs to represent both structural and qualitative diversity. I drew up a list of twenty-five drugs in consultation with Alexander Shulgin, Ann Shulgin, and Dave Nichols (see the relevant correspondence with the Shulgins in S03SelectingDrugs.pdf). Discussion in this manuscript will mostly be based on a set of psychedelic drugs that have all been broadly assayed for affinity including at 5-HT_{2A}, 5-HT_{2C}, and 5-HT_7, and for which subjective human data is available. Twenty-two drugs met these criteria, all assayed by the NIMH-PDSP: DMT, TMA, 5-MeO-MIPT, LSD, 5-MeO-DMT, DPT, 5-MeO-DIPT, Psilocin, 2C-B, 2C-E, DIPT, MDA, DOET, MEM, DOI, DOB, DOM, 2C-T-2, 2C-B-fly, Aleph-2, MDMA, and TMA-2 (Figure 1). Psilocybin is converted to psilocin in the body. The technical aspects of the methods are described in the supporting information file S02Methods.pdf.

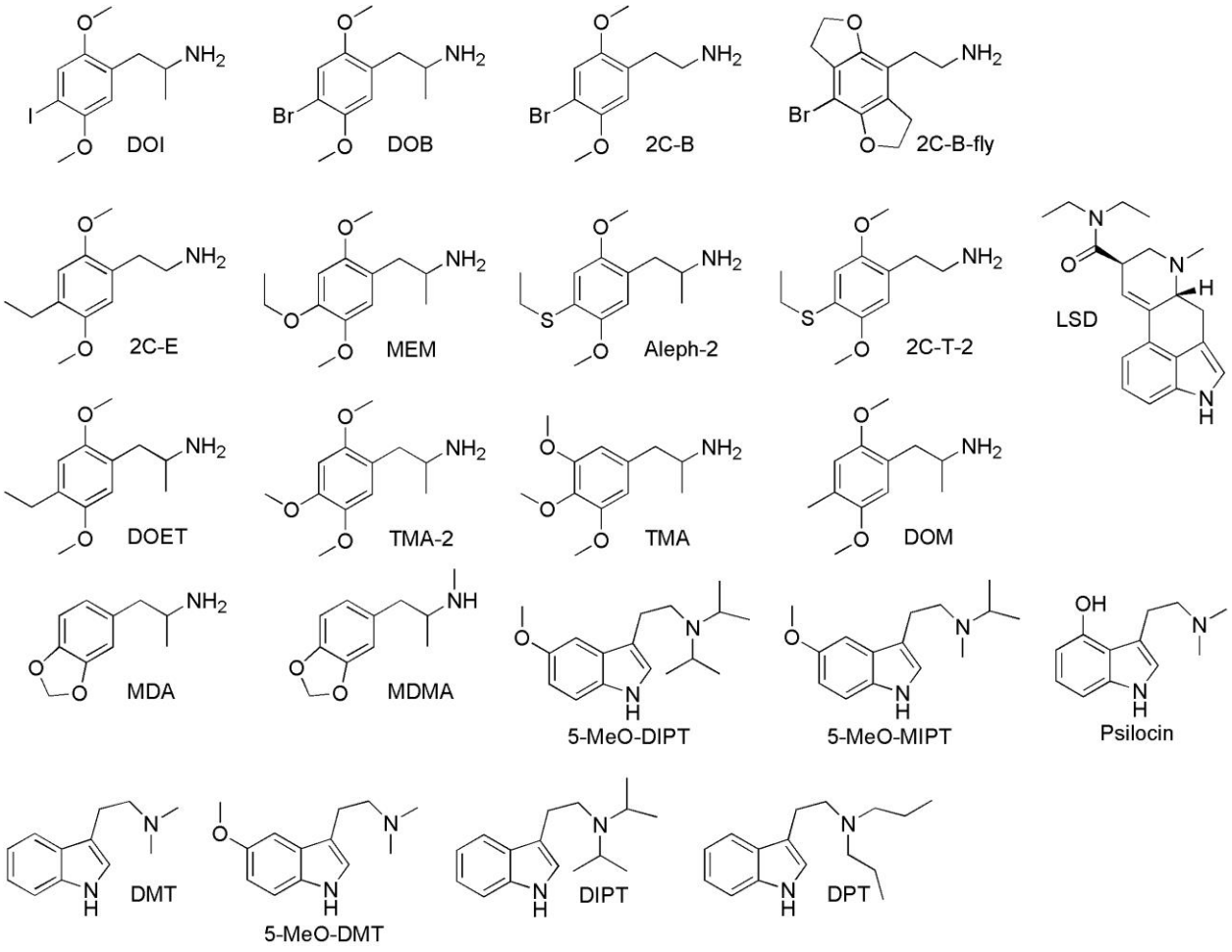


Figure 1: The twenty-two drugs of this study

The Singular Mechanism vs. Qualitative Diversity Problem

The abundant evidence for the qualitative diversity of psychedelic drugs is a problem for the current 5-HT_2 paradigm of psychedelic drug action, in that it is difficult to explain how a single mechanism of action can explain such dramatic qualitative diversity among drugs.

My interest in using psychedelic drugs as probes of the human mind began around 1970 when I learned of the work of Alexander Shulgin and associates in creating a rich toolkit of psychedelic drugs and describing the diversity of their qualitative effects (Shulgin, Bunnell, & Sargent, 1961) (Shulgin, 1963) (Naranjo, Shulgin, & Sargent, 1967) (Shulgin, Sargent, & Naranjo, 1969) (Shulgin, 1970) (Naranjo, 1973) (Nichols & Shulgin, 1976) (Shulgin, 1978) (Shulgin, 1983) (Shulgin & Shulgin, 1991) (Shulgin & Shulgin, 1997). I supposed at the time, that the qualitative diversity was a result of different drugs interacting with different receptors in the brain.

When I subsequently learned of the 5-HT_2 hypothesis, I was not convinced. It did not seem adequate to explain the obvious qualitative diversity. The paradigm which emerged in the 70s and 80s proposed that there is a common simple mechanism responsible for the psychedelic phenomena: activation of 5-HT_2 receptors, most likely 5-HT_{2A}.

On the other hand, when it is acknowledged that the qualitative differences between different drugs need to be explained, strict adherence to the paradigm has led in recent years to an effort to explain how different drugs can produce different effects through a single receptor, 5-HT_{2A}, by supposing that different drugs invoke different intracellular signaling pathways that couple to the 5-HT_{2A} receptor in different proportions (Nichols, 2010, 2016):

> One can easily imagine that each and every structural change made in a series of agonist molecules might lead to distinct ligand-receptor complexes (i.e., a ligand-dependent state) and that these different complexes may lead to activation of different subsets of intracellular signaling molecules. Thus, although functional selectivity has already been demonstrated for the 5-HT_{2A} receptor, it presently remains unknown which particular signaling pathway(s) may be most relevant for the actions of psychedelics. Therefore, when a molecule is classified as a 5-HT_{2A} agonist, what exactly does that mean in terms of cellular responses? Furthermore, how will different proportions of intracellular signaling events affect the qualitative aspects of a "psychedelic" intoxication? (Nichols, 2016)

Functional selectivity aside, the strong version of the 5-HT_2 paradigm has embraced the independently developed view that all psychedelic drugs (that act by this common mechanism) have essentially the same subjective effects, with variations due to set and setting:

> Psychedelic chemicals are not drugs in the usual sense of the word. There is no specific reaction, no expected sequence of events, somatic or psychological.
> The specific reaction has little to do with the chemical and is chiefly a function of *set* and *setting*; preparation and environment. The better the preparation, the more ecstatic and revelatory the session. (Leary, Metzner, & Alpert, 1964), p. 103

> … careful analysis of the LSD data strongly indicates that this substance is an unspecific amplifier of mental processes that brings to the surface various elements from the depth of the unconscious. What we see in the LSD experiences and in various situations surrounding them appears to be basically an exteriorization and magnification of the conflicts intrinsic to human nature and civilization. (Grof, 1975), p. 6.

> One can clearly see that a relationship exists between gasoline and automobile travel. What one cannot predict is whether a particular tank of gasoline is destined to propel a car towards Canada, Mexico, the Northeast, etc. The outcome is dependent on the whims of the owner of the vehicle. Similarly, one can predict that psychoactive substances such as LSD will move the psyche from what has been called consensus reality, to some altered state of consciousness. What cannot be predicted is the nature of the change or the 'direction' the altered state will take. It is an erroneous assumption to believe that medicinal chemistry can design in elements of molecular structure that will lead the psyche in a particular direction. The state of the art in medicinal chemistry is not so advanced! This would be akin to assuming that a particular blend of gasoline could somehow determine the direction that the car will be driven. (Nichols, 1998).

> Just as turning on the power switch of a television enables the TV to display images, but is not responsible for what is seen, psychedelic molecules, by activating this brain receptor [5-HT_{2A}], "turn on" some other set of amplifiers and processors that allow nonordinary feelings and states of consciousness to occur. (Nichols, 1998)

> … envisage an analogy between this receptor [5-HT_{2A}] and an automobile's ignition system, that must be switched on with a key before the car may go in any direction. It is up to the motivations of the driver, the power of the engine, the condition of the roads, etc. (i.e. the "set" and the "setting") to determine where and when the journey will actually begin and end. (Nichols, 1998)

The strong claim that "classical" psychedelics act through a common mechanism and qualitative differences are due to set and setting, contrasts dramatically with the subjective reports accumulated by Shulgin and colleagues (Naranjo, 1973) (Shulgin & Shulgin, 1991, 1997; Shulgin, 1983) which clearly imply that different psychedelic drugs produce qualitatively different subjective effects. (Shulgin, 1983) provided brief characterizations of the distinctive flavor of several drugs:

> [MMDA] exceeded [TMA] in both potency and virtue (pleasantness of experience with fewer physical side-effects)...

> … DOET… has been found by several research groups to facilitate the unblocking of imagination and creativity.

> … DOB and DOI, both extremely potent … and allowing an exceptionally long-lasting, rich, visual and sensory experience.

> Replacing the one carbon atom with a sulfur atom produced the first of a still largely unexplored 'aleph' series, which bids fair to evoke the richness and introspection of LSD, with the added possibility of teasing out specific aspects of action for emphasis.
>
> … 2C-B, which allows a luxury of sensory enhancement (visual, sexual, gustatory) with a minimum of introspective demands.
>
> … 2C-E, which permits extraordinary fantasy, both factual (childhood reliving) and insightful.
>
> … thiomescaline, which disorganizes the logical patterning of thought processes, with surprisingly little visual or sensory modification.
>
> … MDMA … is deceptively simple in action, leading to a sensory and verbal disinhibition, a state of mutual trust and confidence between subject and therapist, but without the distractions of visual distortion or compelling introspection. This 'window' effect is almost always graciously accepted…. it allows a flow of communication (intra- as well as interpersonal). (Shulgin, 1983)

In the 1950s before the emergence of the 5-HT_2 paradigm, a view of psychedelics as diverse probes to the human mind was entertained:

> The methylenedioxy-amphetamine hallucinatory experience was notable in comparison with previously reported mescaline phenomena, however, in that no color phenomena were noted. Whether this is a real difference in the type of action of this compound as compared to mescaline, I do not know. I, personally have not taken enough mescaline to have a full-fledged hallucinatory experience. But it is suggestive, and I want to bring it out because I think that the important point to be made about the compound I am talking about here [MDA], in comparison with amphetamine and in comparison with the trimethoxy compound (which I will discuss next), is that there may be distinctions in the central effects of these various compounds. Our interest lies in the possibility that with very small changes in chemical structures we may get some specificity of the central action of compounds such as we are dealing with here. (Alles, 1959)
>
> … it seems to me that this conference has far greater potentialities, as implied in its title: "A Pharmacological Approach to the Study of the Mind". In emphasizing chemical and biochemical aspects the conference may well point the way to a methodology of the greatest promise for the analysis of the discrete and integrated functions of the central nervous system. The great variety of known chemical substances acting upon the nervous system and the highly selective action which they possess on its parts may provide a tool of unparalleled importance for the fractionation or chemical dissection of nervous function in the first or analytical phase prerequisite to an attack on the greatest of all problems – the problem of the mind-brain relationship… as William James said some 60 years or more ago, the attainment of a genuine glimpse into the mind-brain

> relationship would constitute the scientific achievement before which all past achievements would pale. (Saunders, 1959)

Solomon Snyder began his career on a path to developing a kind of full-flavor paradigm, with a series of nine publications on clinical studies with the psychedelics DOM and DOET (Snyder, Faillace, & Hollister, 1967, 1968; Snyder, Faillace, & Weingartner, 1968, 1969; Snyder, Unger, Blatchley, & Barfknecht, 1974; Snyder, Weingartner, & Faillace, 1970; Snyder, Weingartner, & Faillace, 1971; Weingartner, Snyder, & Faillace, 1971; Weingartner, Snyder, Faillace, & Markley, 1970) and six other publications on psychedelics (Hendley & Snyder, 1971; Snyder & Richelson, 1970; Snyder & Merril, 1965; Snyder & Reivich, 1966; Snyder & Richelson, 1968; Snyder, Richelson, Weingartner, & Faillace, 1970) in which he addressed the same fundamental questions addressed in this manuscript:

> Perceptual effects include perceptual distortions, pseudo-hallucinations, and hallucinations. There are also feelings of enhanced awareness of the self and of the universe (mind-manifesting, hence psychedelic), alterations in mood, and impairment of intellectual processes. Do these numerous perceptual and cognitive effects derive from a single primary action of the drug? The cross tolerance between psychedelic compounds of different structures (2, 5) favors this possibility, as does a molecular conformational (13) and electronic (10, 11) analogy among numerous psychedelic compounds. A knowledge of which psychological effects precede and determine the others might clarify the "mental organization" of the psychedelic experience. The hypothesis of multiple primary actions of psychedelic drugs would be favored if compounds existed after whose administration a single component of the psychedelic effect predominated. (Snyder, Faillace, & Weingartner, 1968)

> Despite the similar effects of the psychedelic drugs as well as the cross tolerance that exists among them, differences in the nuances of subjective effects occur among the different drugs. Such differences include many reports that mescaline produces a more sensual experience than does LSD. (Snyder, Weingartner, et al., 1970)

> By relating chemical structures to a pattern of behavioral effects, it may be possible to develop a systematic picture of brain chemistry and behavior. (Weingartner et al., 1971)

However, Snyder soon accepted the emerging paradigm that all psychedelic drugs have a common site of action (Snyder et al., 1974):

> All of the drugs that produce psychedelic effects, including LSD, several tryptamine derivatives, mescaline, and several methoxyamphetamines, appear to act at the same or very similar receptor sites in the brain. (Snyder et al., 1974)

The prohibition on human studies put an end to Snyder's clinical studies, and the emergence of the 5-HT_2 paradigm altered his thinking, ending his study of the role of receptor diversity in the qualitative diversity of psychedelics, causing him to abandon his path to full-flavor psychopharmacology. Snyder remains a firm believer in the 5-HT_2 paradigm (Snyder, 2006). The emergence of the 5-HT_2 paradigm resulted in a very narrow focus on the two paradigmatic

receptors, 5-$HT_{2A/C}$. In this context, one might observe that the 5-HT_2 paradigm is a mind altering paradigm.

After the emergence of the 5-HT_2 paradigm the full-flavor concept appeared mainly outside of the mainstream of neuroscience (Shulgin & Shulgin, 1991) (Goldsmith, 2007) (Doyle, 2011) (Coyle et al., 2012) (Ray, 2012). A concept of complex action was advanced by (Shulgin & Shulgin, 1991):

> There is something of the Fourier Transform in any and all drug experiments. A psychedelic drug experience is a complex combination of many signals going all at the same time. Something like the sound of an oboe playing the notes of the A-major scale. There are events that occur in sequence, such as the initial A, followed by B, followed by C-sharp and on and on….
> But within each of these single events, during the sounding of the note "A," for example, there is a complex combination of harmonics being produced at the same time, including all components from the fundamental oscillation on up through all harmonics into the inaudible. This mixture defines the played instrument as being an oboe. Each component may be shared by many instruments, but the particular combination is the unique signature of the oboe.
> This analogy applies precisely to the study of psychedelic drugs and their actions. Each drug has a chronology of effect, like the notes of the A-major scale. But there are many components of a drug's action, like the harmonics from the fundamental to the inaudible which, taken in concert, defines the drug. With musical instruments, these components can be shown as sine waves on an oscilloscope. One component, 22%, was a sine wave at a frequency of 1205 cycles, and a phase angle of +55!. But in psychopharmacology? There is no psychic oscilloscope. There are no easily defined and measured harmonics or phase angles. Certainly, any eventual definition of a drug will require some such dissection into components each of which makes some contribution to the complex whole. The mental process may some day be defined by a particular combination of these components. And one of them is this Beth state. It is a state of uncaring, of anhedonia, and of emotionlessness.
> Many drugs have a touch of this Beth state, ALEPH-7 more than most. If a sufficient alphabet of effects (I am using the Alephs, Beths, Gimels, and Daleths of the Hebrew as token starters only) were to be accumulated and defined, the actions of new materials might someday be more exactly documented. Could depression, euphoria, and disinhibition for example, all be eventually seen as being made up of their component parts, each contributing in some measured way to the sum, to the human experience? The psychologists of the world would be ecstatic. And drugs such as ALEPH-7 might be useful in helping to define one of these parts. (Shulgin & Shulgin, 1991) p. 474-475

The "psychic oscilloscope" has become available in part, in the form of full receptorome screening of drugs as provided by the NIMH-PDSP, as well as various kinds of brain scans. Another musical metaphor was articulated by Goldsmith:

> Plant-based or laboratory-conceived psychoactive chemicals mimic or block the operation of neurotransmitters (chemical messengers in the nervous system that influence

> perception and mood). The numerous neurotransmitters (e.g., serotonin, norepinephrine, dopamine, and acetylcholine) act by triggering or blockading the firing of corresponding receptor sites in our brain (the neurotransmitters fit into the receptor sites like keys into locks). The receptor sites associated with each neurotransmitter come in an array of subtypes. For example, serotonin (5-hydroxytryptamine or 5-HT) has approximately fourteen receptor site subtypes. To make this even more complex, most psychedelics operate on more than one neurotransmitter system (e.g., peyote interacts with the dopamine and serotonin systems, among others). One way to get one's mind around this complexity is to think of SARs [structure activity relationships] – the way neurotransmitters trigger (agonize) or blockade (antagonize) receptor sites – using the metaphor of a large church pipe organ, with multiple keyboards. Imagine each keyboard represents a different neurotransmitter system, serotonin on one keyboard, dopamine on the next, and so on. Next, imagine that the white keys represent the release (agonism) of a neurotransmitter and the black keys represent the suppression (antagonism) of a neurotransmitter. Finally, let us think of chords as the complex interweaving of agonism and antagonism of receptor site subtypes involved with a particular drug's mode of action. Using this model, when a subject experiences LSD, for example, serotonin is the neurotransmitter most heard, but "chords" on the dopamine, norepinephine [sic], and other keyboards are also played. Furthermore, LSD is likely to play a different chord on the 5-HT keyboard than 5-HT itself (because even at the level of individual receptors, the binding action of LSD is not identical to the binding action of 5-HT), adding yet another level of complexity to the mechanism of action. This rich mix of interactions helps explain how each drug, while based on the same building blocks, will have often dramatically different effects. (Goldsmith, 2007) p 117-118.

Doyle also articulated the full-flavor concept:

> Correlating molecular mechanisms of psychedelic compounds with ecodelic testimony and the fine-grained description of the "non Euclidean space" of the hallucination-perception continuum could provide us with a veritable imaging system of the imagination, one which suggested to early 1960s scientists such as Lynn Sagan that indeed consciousness, like life, was on the brink of being a technoscientific object and thus subject to radical transformation as mind achieves a putatively new threshold and connectivity – its own physical manipulation and evolution through feedback. (Doyle, 2011)

Coyle and colleagues said:

> analysis of drug narratives in combination with *in vitro* pharmacology could lead to novel hypotheses concerning the effects of specific receptors and signaling pathways on consciousness (Coyle et al., 2012)

I have stated it like this:

> The diverse set of psychoactive drugs collectively represents a rich set of tools for probing the chemical architecture of the human mind. These tools can be used to explore

> components of the psyche whose discreteness is normally obscured by their being embedded in the complete tapestry of the mind. By activating specific components of the mind, they are made to stand out against the background of the remainder of the psyche. Thus both their discreteness and their specific contribution to the psychic whole can be better appreciated. That the revealed mental elements can be pharmaceutically manipulated suggests that they may be naturally modulated through chemical systems. These receptor mediated mental components are the distinct elements from which the mind has been fashioned through evolution. (Ray, 2012)

While there is a near universal acceptance of the notion that psychedelics are nonspecific psychic amplifiers, and that the specific contents of the psychedelic experience are a result of "set" and "setting", some observers on both sides of the issue have been able to find middle ground. They illustrate how we can look past the variation caused by set and setting to see the characteristic properties of a particular drug:

> This set-and-setting hypothesis is a useful model for understanding the experiences with MDMA also: the specific insights, feelings, and resolutions of problems that occur are unique to the individual. Nevertheless, a certain commonality exists in the kinds of feeling states usually named: ecstasy, empathy, openness, compassion, peace, acceptance, forgiveness, healing, oneness, and caring. (Adamson & METZNER, 1988)

> Sometimes it may be hard to discern anything in common between different possible reactions to the same drug, but in other instances we may discover that what appears to be very different is only a different presentation of the same process. Just as the ego loss brought about by LSD may be experienced as an ecstasy of unity with all things or a desperate clinging to a tenuous identity, fear of chaos and of madness, so, too, the realistic enhanced awareness of the present brought about by MMDA may be experienced as a serene fullness or, for one who is not ready to confront the moment, tormenting anxiety, shame, guilt. (Naranjo, 1973)

Variation due to set and setting (Hartogsohn, 2017), and variation due to activation of different mental organs or their combinations by drugs, are different components of variation in psychedelic experience. Neither precludes the other.

Two Dimensions of Consciousness: Breadth and Depth

Back in the day, psychedelic drugs were often described as "consciousness expanding" drugs (Solomon, 1964). It appears that this is literally true. I hypothesize two forms of consciousness expansion: one form that can be facilitated by the participation of 5-HT_2 (breadth), and one form that can be facilitated by the participation of 5-HT_7 (depth).

Breadth – Grinspoon and Bakalar define "consciousness expanding" this way: "it is as though more of the neurophysiological activity of the brain is passing the usual defensive barriers and coming into awareness" (Grinspoon & Bakalar, 1997) p. 90. Psychedelic drugs act at a wide variety of mental organs that mediate mental phenomena that do not normally enter into consciousness. Breadth of consciousness is expanded when unconscious mental organs are

brought into consciousness, thereby expanding consciousness in the manner described by Grinspoon and Bakalar. In (Ray, 2016) I defined some relevant terms:

> I will define "psychedelic" as expansion of consciousness…. here I will speak only of expansion of breadth of consciousness, which I will define as bringing more mental organs into consciousness... When a drug causes the effects of a mental organ that is not normally in consciousness, to enter consciousness, it expands the breadth of consciousness, and is psychedelic by my definition. The breadth of consciousness expands when the number of mental organs held in consciousness increases. (Ray, 2016)

For example DOI at alpha-2 and beta, mescaline and MDMA at alpha-2 and imidazoline-1, MDA at alpha-2, DOM and Aleph-2 at beta-2, and TMA-2 at histamine-1 all expand breadth of consciousness in this sense, by bringing the corresponding mental organs into consciousness. This form of consciousness expansion (breadth) is produced by many drugs regardless of whether they interact with 5-HT_7 or not, but interaction with 5-HT_2 provides one principal mechanism of expanding breadth (Ray, 2016) (there are other mechanisms).

Depth – In an attempt to define consciousness, (Jaynes, 1976) said "Mind-space I regard as the primary feature of consciousness", and (Baars, 2001) has called this mental space the "theater of consciousness". 5-HT_7 appears to either mediate conscious space itself, or to act directly on consciousness such that it affects anything that enters consciousness. 5-HT_7 appears to create a mental space where we conjure whatever we are aware of: the current scene, fantasy, imagination, theory, feelings, visions of the future, and memory. The depth of this mental space is expanded through increasing activation of 5-HT_7, in the sense that there is greater resolution, subtlety, nuance, complexity, tangibility, vividness, and capacity; to render thought, feelings, and sensory input in consciousness.

Consciousness expansion through breadth can provide a more profound and multifaceted experience of actual reality, that which actually exists, internally, externally, or socially. Consciousness expansion through depth adds the spark of creativity, and allows us to go beyond actual reality, using our imagination, our creative capacity, to add to actual reality, to add novelty generated by our mind to that which actually exists. Depth provides the capacity to entertain counterfactuals.

Consciousness expansion through either breadth or depth is fully psychedelic (mind manifesting), and both are very dramatic subjective experiences. Figure 2 and Table 1 quantify the propensity of each drug to expand consciousness through depth and breadth. Depth for each drug is measured as relative affinity (npK_i) for 5-HT_7. Breadth for each drug is measured as the square root of the sum of squares of the relative affinity values of all forty-two assayed sites at which the drugs of the study have measurable affinity.

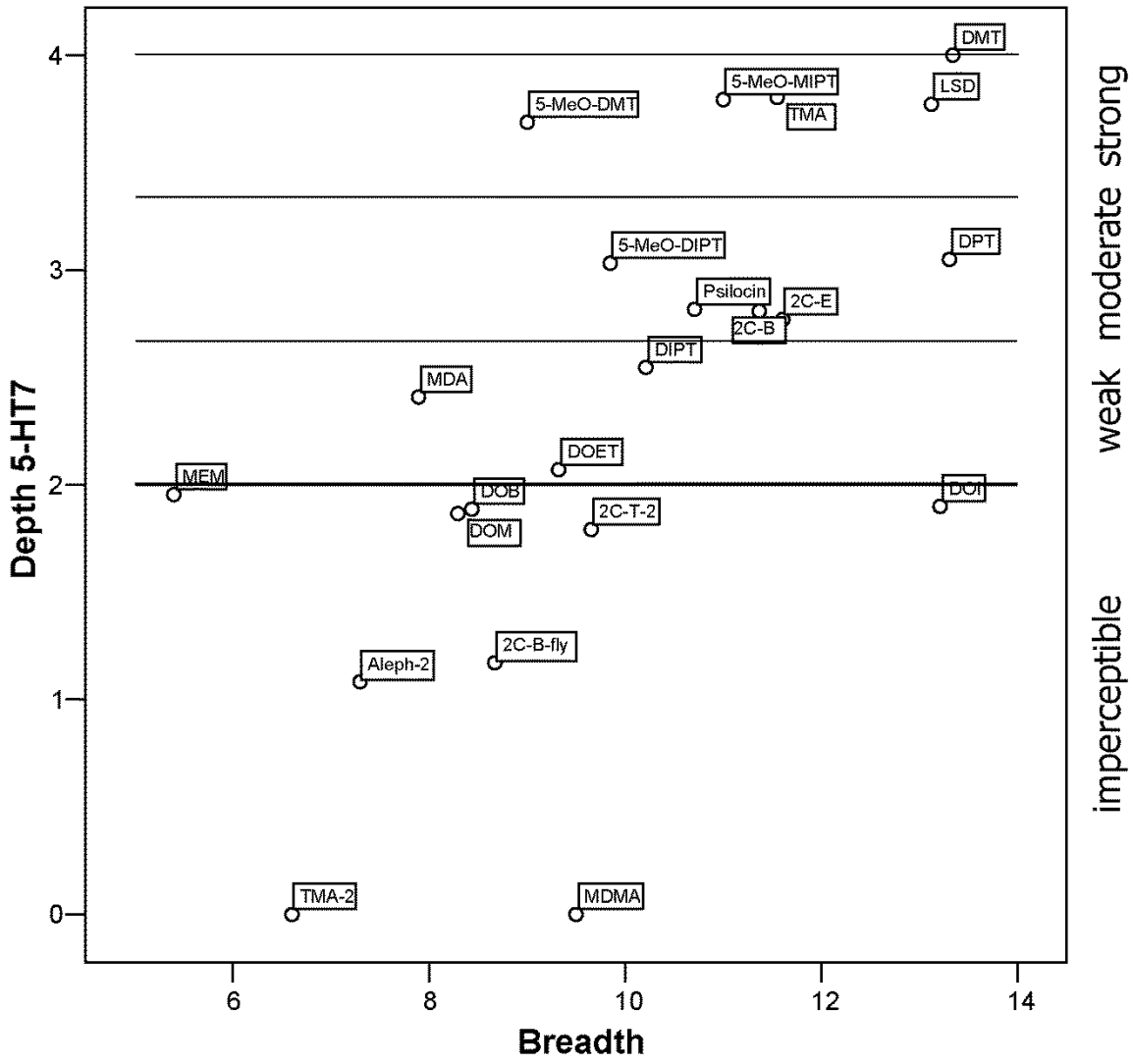


Figure 2: Depth measured as the relative affinity (npK_i) value at 5-HT_7 vs. breadth measured as the square root of the sum of squares of the npK_i values of all forty-two assayed sites at which the drugs of the study have measurable affinity (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{5A}, 5-HT_6, 5-HT_7, D1, D2, D3, D4, D5, Alpha1A, Alpha1B, Alpha2A, Alpha2B, Alpha2C, Beta1, Beta2, SERT, DAT, NET, Imidazoline-1, Sigma1, Sigma2, DOR, KOR, MOR, M1, M2, M3, M4, M5, H1, H2, CB1, CB2, Ca+Channel, NMDA).

Depth		Breadth	
npKi 5-HT7		Sqrt Sum Sq All Rec	
DMT	4.00	**DMT**	13.34
TMA	3.80	**DPT**	13.30
5-MeO-MIPT	3.79	DOI	13.21
LSD	3.77	**LSD**	13.12
5-MeO-DMT	3.69	**2C-E**	11.61
DPT	3.05	**TMA**	11.55
5-MeO-DIPT	3.03	**2C-B**	11.37
Psilocin	2.82	**5-MeO-MIPT**	11.00
2C-B	2.81	**Psilocin**	10.71
2C-E	2.77	DIPT	10.21
DIPT	2.55	**5-MeO-DIPT**	9.85
MDA	2.41	2C-T-2	9.65
DOET	2.07	MDMA	9.50
MEM	1.95	DOET	9.32
DOI	1.90	**5-MeO-DMT**	9.00
DOB	1.89	2C-B-fly	8.67
DOM	1.87	DOB	8.44
2C-T-2	1.79	DOM	8.29
2C-B-fly	1.17	MDA	7.89
Aleph-2	1.08	Aleph-2	7.30
MDMA	0.00	TMA-2	6.60
TMA-2	0.00	MEM	5.40

Table 1: Depth measured as the relative affinity (npK_i) value at 5-HT_7 vs. breadth measured as the square root of the sum of squares of the npK_i values of all forty-two assayed sites at which the drugs of the study have measurable affinity (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{5A}, 5-HT_6, 5-HT_7, D1, D2, D3, D4, D5, Alpha1A, Alpha1B, Alpha2A, Alpha2B, Alpha2C, Beta1, Beta2, SERT, DAT, NET, Imidazoline-1, Sigma1, Sigma2, DOR, KOR, MOR, M1, M2, M3, M4, M5, H1, H2, CB1, CB2, Ca+Channel, NMDA). Drugs with moderate or strong relative affinity ($npK_i > 2.66$) for 5-HT_7 are highlighted in bold.

Breadth – Contents of Consciousness

The synthesis of NIMH-PDSP affinity assays together with descriptions of the subjective effects of psychedelic drugs involves a layering process (described in S02Methods.pdf), in which we first examine the effects of drugs that act at a single receptor (or group of closely related receptors), then we look at drugs that add one additional receptor at a time. The layering process begins with DOB and MEM which have perceptible interactions (the concept of perceptibility is described in S02Methods.pdf) only with the three 5-HT_2 receptors (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}), and then considers DOET and 2C-B-fly which additionally act at 5-HT_1 receptors. These four

drugs are found to have very subtle and transparent effects (see section "The Hands of the Mind – 5-HT_2" below).

After characterizing the effects of DOB, MEM, DOET, and 2C-B-fly, it becomes possible to layer on additional receptor interactions. There are a few drugs that add only a single kind of receptor in addition to 5-$HT_{1/2}$: MDA which adds alpha-2 (at high doses it also acts at 5-HT_7), DOM and Aleph-2 which add beta-2, and TMA-2 which adds histamine-1. At the next stage of layering we consider drugs that add two additional receptors, one of which has already been characterized. So for example mescaline and MDMA each add both alpha-2 and imidazoline-1. Because alpha-2 was previously characterized, we can now characterize imidazoline-1.

The subtlety and transparency of the effects of the four selective 5-$HT_{1/2}$ drugs (DOB, MEM, DOET, 2C-B-fly), set them apart from the remaining eighteen drugs of this study: DMT, TMA, 5-MeO-MIPT, LSD, 5-MeO-DMT, DPT, 5-MeO-DIPT, Psilocin, 2C-B, 2C-E, DIPT, MDA, DOI, DOM, 2C-T-2, Aleph-2, MDMA, and TMA-2. The eighteen drugs with actions beyond 5-$HT_{1/2}$ all bring new contents into consciousness in a dramatic way that the four selective 5-$HT_{1/2}$ drugs do not.

The DOB vs DOM problem

The comparison of DOM to DOB is a problem for the 5-HT_2 paradigm, in that it illustrates that the primary psychedelic effects of the drug come from non-5-HT_2 receptors. Here, DOM is used as a token for all psychedelic drugs that act at other receptors in addition to 5-$HT_{1/2}$ (i.e., the eighteen listed above).

While drugs selective for 5-$HT_{1/2}$ were found to have subtle effects, drugs that also act at alpha-1, alpha-2, beta, histamine-1, dopamine, imidazoline-1, sigma, or 5-HT_7, all produce clear and dramatic psychedelic effects, and the different kinds of receptors produced consistently different and characteristic effects. The coherence of the mental phenomena brought into consciousness by the activation of each different class of receptor is what led to the concept of mental organs.

These observations suggest that specific psychedelic effects are coming not from 5-HT_2, but rather from the many other mental organs that these drugs act upon, and that the qualitative diversity of effects is due to the interaction of different drugs with different mental organs. This is what I call "full-flavor psychopharmacology". These observations are reported by (Ray, 2012) who proposed hypotheses for the mental phenomena mediated by thirteen kinds of receptors, and who introduced the concept of mental organs.

The non-5-HT mental organs paint meaning in consciousness through the medium of feelings. Each mental organ paints a different facet of reality, such that collectively they present a rich multifaceted representation of the world in consciousness. The different facets of reality could be viewed as natural ontological categories, found through evolution, for representing the world in consciousness (modified from (Ray, 2012)):

- Laws and patterns of nature (logic, reason) – serotonin-1
- Essential nature of things, or events shaping yourself – alpha-2
- Continuity of scene and events from past through present into future – alpha-1
- Home, family, community, joy – beta
- Beings – histamine

Cognitive & Affective

The inclusion of 5-HT_1 among the ontological categories brings us to the most fundamental division among the content mental organs: that between cognitive and affective. Here I use the word "cognitive" to apply to language, logic, and reason; and I use "affective" to refer to feelings and emotions. The division between cognitive and affective is explored in some depth by (Ray, 2012), thus I will present only an overview here.

I presume that the mental organs that provide cognition are evolutionarily new, perhaps less than 200,000 years, or about 10,000 human generations. These are the mental organs that provide much of what comes qualitatively new with the modern human mind. I will talk about the modern human mind and the archaic human mind. I use archaic to refer to the human mind as it was before the emergence of the key novel elements of the modern mind. The key novel elements of the modern mind are:

- the capacity to know the world through language, logic, and reason
- a new form of consciousness capable of accommodating this new cognitive form of knowing
- mental organs which provide mechanisms to regulate and shape this new form of consciousness
- the capacity to go beyond the actual reality rendered by the content mental organs, to also be able to render what could be, the spark of creativity

This modern form of creative consciousness presumably found only in humans appears to be mediated by 5-HT_7, whereas the capacity to know the world through language, logic, and reason appears to be mediated by 5-HT_1. Affective content in consciousness appears to originate entirely through non-5-HT mental organs, while cognitive content appears to originate exclusively through 5-HT mental organs.

Cognitive

The hypothesis that 5-HT_1 mediates cognition is based on the properties of drugs that are relatively selective for 5-HT_1. However, there is a strong correlation between relative affinity for 5-HT_1 and 5-HT_7 (supporting information S04ProspectiveReceptors.pdf, right side of Figure 3). Yet some drugs violate these correlations (2C-B-fly, 2C-T-2, DOM, and DOI at 5-HT_{1D}; DOET, DIPT, and DMT at 5-HT_{1A}; DMT at 5-HT_{1B}; supporting information S04ProspectiveReceptors.pdf, right side of Figures 4-8). Insight into the mental effects of 5-HT_1 come through examination of some of the drugs that break the correlation between 5-HT_1 and 5-HT_7. The best information comes from the work of Shulgin and of Snyder and colleagues in their studies of DOET (Snyder, Faillace, & Weingartner, 1968) (Snyder et al., 1969) (Snyder,

Weingartner, et al., 1970) (Snyder et al., 1971) (Weingartner et al., 1970) (Snyder et al., 1974) whose best hit affinity is 5-HT_{1A}.

> **DOET**: "I can skip readily from one thing to another … but if something gets my attention I can get very involved and really focus…"
> "I am more likely to have interesting or new associations of ideas… A number of things are closer to the surface than they would normally be (on DOET)…"
> DOET produced a marked decrease in the proportion of high frequency associations… This effect was greatest at four hours, corresponding to the peak subjective effects and the highest urinary excretion of unchanged DOET… The decline in high frequency associations under DOET was related to an increase in low and medium strength association, with no increase in idiosyncratic associations… The DOET subjects produced less common, but not bizarre, associations. Strikingly, these less common associations under DOET were as reproducible (97.5 percent) as the high frequency baseline associations (94 percent). Usually, uncommon associations are not reproduced as readily as high frequency associations (3). This suggests that the highly reproducible "uncommon" associations produced by DOET are meaningful to the subjects but not normally accessible to consciousness. This finding accords with the enhanced "insight" reported by subjects under DOET…
> The associative changes and the subjective effects suggest that DOET may make accessible to consciousness associative material which is not normally available, hence it might be useful as an adjunct to insight psychotherapy. (Snyder, Faillace, & Weingartner, 1968) p. 114-119.

> "… DOET… has been found by several research groups to facilitate the unblocking of imagination and creativity." (Shulgin, 1983). p. 208

> **DOET 2 mg**: I worked on some problems in my software. A certain problem had been plaguing me for the last two days. I had been putting in patches all over the place to fix the problem. Now I stumbled onto an elegant solution which made the problem evaporate. I replaced two pages of code with five elegant lines, and I was able to go back and pull out all the patches. (Shulgin, 2016) Pharm 1, p. 13

> **DOET 4 mg**: I wrote an article for a magazine who wanted a popularization of my work with a personal touch. Wow, am I glad I tried! The words poured out, rather nicely. I really like the way I wrote with it. I felt that it was a voice I hadn't used before, and I liked it. I was so free and playful with the words. I think I was able to write it just the way the editor asked me to. Eventually, the article was published, and subsequently translated into several languages and re-published in many places. I think this could be a very valuable material for a writer, and perhaps in other circumstances requiring creative work as well.
> The next time I sat down to write, without using any drug, much to my surprise, what came out was of the same style and quality that I first developed with DOET, and flowed with the same ease as did writing under the influence. It appears that with my first DOET experience, I found a new writing voice, one that I feel very comfortable with, and which

> I have retained. I would describe this new style as more simple and straight-forward, less jargonesque, and more honest and enthusiastic.
> DOET is really strange. A tiny dose has a distinct effect, which is largely unmistakable due to some sensations in the body. However the mental effects are so subtle as to be virtually non-existent, until I put myself to work. My written verbal ability is clearly enhanced with DOET, but there is little other mental effect that I can clearly put my finger on. I really don't "feel" any different mentally, on DOET. (Shulgin, 2016) Pharm 1, p. 13

Another line of evidence that 5-HT_1 may mediate cognitive function is the practice of micro-dosing of LSD. Three of the top five relative affinities of LSD are 5-HT_1 receptors:

> **LSD:** 4.00 5-HT_{1B}, 3.77 5-HT_7, 3.75 5-HT_6, 3.73 5-HT_{1A}, 3.70 5-HT_{1D}

When taken at very low doses, 5-HT_{1B} will be the primary influence, yet it should be possible to find an individualized dose at which the top five rank-order relative affinities listed above are the only perceptible receptor interactions of LSD. This would activate three of the four assayed 5-HT_1 receptors, together with the creative contribution of 5-HT_7 (see below). This might be a good combination for cognitive enhancement.

James Fadiman (Fadiman, 2011) reports that low doses of LSD (e.g. 10 micrograms) act as a cognitive enhancer. He is in an ongoing process of collecting data about this phenomenon by way of the "Tener Study" (tener, as in ten micrograms). There are reports that some scientists, engineers, tech workers, business persons, and programmers use very low doses of LSD as a cognitive enhancer (Fon, 2015) (Leonard, 2015) (Koebler, 2015) (Weller, 2015) (Burns, 2015) (Gregoire, 2016) (Woods, 2016) (The-Third-Wave, 2016) (Battan, 2016) (Malone, 2016) (Solon, 2016).

Pahnke and Richards claimed that low doses of LSD enhance cognition:

> **LSD**: There is a form of psychedelic experience that occasionally occurs when small dosage is administered or just before returning to usual consciousness when one feels capable of thinking unusually sharply, quickly, and clearly. Such experience is *cognitive* as opposed to *intuitive*; that is, it is the process we usually call *thinking*. Visionary imagery is seldom seen during this time and few changes in feeling-tone are manifested. One often feels acutely sensitive to the meaning of words and to very fine differentiations between similar words. Further, one seems to be conscious of the presuppositions underlying one's thoughts and of the interrelations between different ideas. Chain reactions of associations and inferences may occur, and one may feel as though one is able to think on several different levels of discourse all at once. (Pahnke & Richards, 1966) p. 188-189.

Crick is rumored to have benefited from the use of low doses LSD:

> Crick told him [Dick Kemp] that some Cambridge academics used LSD in tiny amounts as a thinking tool to liberate them from preconceptions and let their genius wander freely

> to new ideas. Crick told him that he had perceived the double-helix shape while on LSD. (Rees, 2004)

Affective

Most mental organs characterized by (Ray, 2012) are affective. While it appears that archaic/childhood kappa consciousness can hold only affective content, modern/adult 5-HT_7 consciousness appears to be backward compatible, in the sense that it can hold both affective and cognitive content. Kappa consciousness has been described as "thought free awareness" (Arthur, 2010). While kappa may have provided the only form of consciousness available to the archaic mind throughout the lifespan, it appears that modern humans are born into kappa consciousness, but by adulthood kappa consciousness has been replaced by 5-HT_7 consciousness. As adult humans, we experience a largely cognitive mentality, and it can be difficult to understand affective mental states. Thus I will illustrate affective states with examples of three affective content mental organs (alpha-2, beta, histamine):

Alpha-2:

Ramachandran discusses a word from Sanskrit, "rasa": "Capturing the very essence, the very spirit of something, in order to evoke a specific mood or emotion in the viewer's brain" (Ramachandran, 2004; Ramachandran, 2007a, 2007b; Ramachandran & Hirstein, 1999), which precisely describes the affective way of knowing mediated by alpha-2:

> … going back to Indian art manuals in the third century B.C., in Sanskrit, there is a word that repeatedly appears in art manuals, called rasa, which is very hard to translate, but roughly it means, capturing the very spirit of something, the very soul of something, the very essence of something, in order to evoke a specific mood, sentiment, or emotion in the viewer's brain. That whole paragraph is encapsulated in that word rasa. (Ramachandran, 2007b)

Mescaline is the only drug of the thirty-five reviewed by (Ray, 2012) to have alpha-2 (alpha-2C) as its best hit, and DOI has the second highest relative affinity for alpha-2 (alpha-2A) after mescaline:

> **Mescaline**: … it lets you put aside the intellectual overlay for a while and just have an immediate, direct experience of something. (Shulgin & Shulgin, 1991) p. 271.

> **Mescaline**: … there is an intensification of what I may call intrinsic significance. That which is seen, either with the eyes closed or open, is felt to have a profound meaning. A symbol stands for something else, and this standing for something else is its meaning. But the meaningful things seen in the mescaline experience are not symbols. They do not stand for something else, do not mean anything except themselves. The significance of each thing is identical with its being. Its point is that it *is*. (Huxley, 1956).

> **Mescaline, 400 mg**: … a sense of special significance began to invest everything in the room, objects which I would normally accept as just being there began to assume some

strange importance. A plain wooden chair was invested with a 'chairiness' which no chair ever had for me before. In the many thousand stitches of a well-worn carpet I saw the footprints of mankind plodding wearily down the ages. Barbed wire on a fence outside was sharp and bitter, a crown of thorns, man's eternal cruelty to man. It hurt me. (Osmond, 1952) p. 65; (Osmond, 1970) p. 24.

Mescaline sulfate 400 mg: More than anything else, the world amazed me, in that I saw it as I had when I was a child. I had forgotten the beauty and the magic and the knowingness of it and me. I was in familiar territory, a space wherein I had once roamed as an immortal explorer, and I was recalling everything that had been authentically known to me then, and which I had abandoned, then forgotten, with my coming of age. Like the touchstone that recalls a dream to sudden presence, this experience reaffirmed a miracle of excitement that I had known in my childhood but had been pressured to forget. (Shulgin & Shulgin, 1991) p. 16.

Peyote: Everything looks the way it's supposed to. I mean, the chairs haven't become mythical beasts or anything, but something's very different about all of it. The way it feels is very personal, sort of nice and intimate, as if my two little rooms *like* me … well, there's a kind of – a friendly feeling to all of it…
The funny thing is that, despite all the newness, there's something about all of it that feels – well, the only way that I can put it is that it's like coming home. As if there's some part of me that already knows – knows this territory, – and it's saying Oh yes, of course! Almost a kind of remembering – ! …
[describing a garden] There was a deliberate juxtaposition of shapes and textures which captured not only eyes, but emotions. I could follow the unfolding of an inner experience created by the gardener, as he sculptured with moss-covered stone, fleshy plant leaves, delicate ferns, moving water and subtle gradations of color in the pebbles that drifted across the floors of the various water bodies. All this, I had in earlier visits glanced at; now, I was truly seeing it, giving grateful acknowledgement to the insight of the person who has so lovingly formed all this for other to see and feel. (Shulgin & Shulgin, 1991) p. 115-127.

Mescaline, 400 mg: I was back where I had been when I was looking at the flowers – back in a world where everything shone with the Inner Light, and was infinite in its significance. The legs, for example, of that chair – how miraculous their tubularity, how supernatural their polished smoothness! … I looked down by chance, and went on passionately staring by choice, at my own crossed legs. Those folds in the trousers – what a labyrinth of endlessly significant complexity! And the texture of the gray flannel – how rich, how deeply, mysteriously sumptuous! … More even than the chair, though less perhaps than those wholly supernatural flowers, the folds of my gray flannel trousers were charged with "is-ness." To what they owe this privileged status, I cannot say. It is, perhaps, because the forms of folded drapery are so strange and dramatic that they catch the eye and in this way force the miraculous fact of sheer existence upon the attention? Who knows? What is important is less the reason for the experience than the experience itself. (Huxley, 1954) p. 22-34.

> **R-DOI 2.2 (±0.2) mg**: The flowers looked beautiful, much more beautiful than usual. They have a presence that is so distinctive, with great detail…The flowers are so in front of me, just bare flowers with their unbelievable presence and beauty which is so intense so detailed so calm that it's almost menacing; and just bare me, facing each other, shining through each other… We went out for a walk to a park. The world I saw was just beautiful. The plants' presence, every leaf, every tiny twig, the pine tree, I felt that I have ignored so much beauty in my daily life. (Shulgin, 2016) Pharm 1, p. 40

The alpha-2 mental organ has two facets, of which rasa directed at things (above) is one. The other facet might be the rasa of one's self. This manifests in the psychedelic experience as vivid recall or reliving of events that significantly shape one's life. These could be long forgotten events from early childhood, or recent events of adulthood.

> **2C-E, 20 mg**: The hours that followed proved to be a time of concepts, revelations, compelling fantasy and authentic memory that was very frightening and yet, in retrospect, of extraordinary value. What I faced, over those three or four hours, were some impressive angels and demons, and I asked questions and experienced insights that went to the roots of my psyche…
> My father, clear, immediate, right there, speaking to me in Russian, reading to me, with his patient voice. I am very little, sitting on his knee. I was not hostile, just arrogant. I was a two-year-old child on my father's lap, being instructed with love in the Russian words that illustrated the alphabet, from a child's book of Russian letters. I heard my father say the letter, then the word, and I was repeating both while squirming in his lap. This was not a memory of being two years old in my father's lap; this was actually *being* two years old in his lap. I was looking out of two-year-old eyes at the pages of the book and I could see the colored letters on the paper, in a room which was extremely high and wide and long. (Shulgin & Shulgin, 1991) p. 93-95.

> **MDA**: Of the four single subjects, one spent much time writing on certain aspects of his life history, which he now wanted to understand better… most of their concern was with their own life and personality. (Naranjo et al., 1967)

> **MDA**: the most characteristic feature of the experience of these subjects was one which we will call here age regression. This is a term employed to designate the vivid re-experiencing of past events… wherein a person … may temporarily believe himself to be a child involved in a situation of the past… in the MDA-elicited state the patient simultaneously regresses and retains awareness of the present self... the person more than conceptually remembers the past, as he may vividly recapture visual or other sensory impressions inaccessible to him in the normal state, and he usually reacts with feelings that are in proportion to the event. (Naranjo, 1973) p. 27.

> **MDA**: … his nanny, his wet nurse. Now he clearly evokes his feeling for this nurse… He then remembers more of his nanny—how she took him out for walks when he was only two to three years old, how he slept with her and caressed her; how unconditional her love was, how at ease he felt with her. He remembers her appearance, her fresh face,

her black hair, her open laughter. And as he remembers her, he feels sadder and sadder, sad at having lost her, of not having his nana any more. (Naranjo, 1973) p. 34

MDA 100 mg: One thing that impressed itself upon me was the feeling I got of seeing the play of events, of what I thought to be the significance of certain people coming into my life, and why my 'dance', like everyone else's, is unique. (Shulgin & Shulgin, 1991), p. 715

Among alpha-2 drugs, mescaline and DOI tend to evoke rasa with respect to things, while 2C-E and MDA tend to evoke rasa with respect to events shaping one's self. It is not clear why alpha-2 shows these two distinct facets. I speculate that it may have to do with the pharmacological environment, that is, what other mental organs are activated. In MDA and 2C-E, alpha-2 is more likely to be the only content mental organ loaded into consciousness, whereas in mescaline and DOI other content mental organs are likely to be loaded together with alpha-2.

Beta:

Just as the Sanskrit term "rasa" captures some aspects of the nature of alpha-2, the French phrase "joie de vivre" captures some aspects of the nature of beta:

French term or phrase: joie de vivre
English translation: exuberance, joy of living, love of life
What is joie de vivre? It can be a joy of conversation, joy of eating, joy of anything one might do. One may speak of a joie de finesse (refinement, grace, elegance), joie de réussite (success), the joy of summer, the joy of an embrace, etc. Alain: Il y a de merveilleuses joies dans l'amitié – joy of friendship.
And joie de vivre may be seen as a joy of everything, a comprehensive joy, a philosophy of life, a Weltanschauung. Robert's Dictionnaire says joie is "sentiment exaltant ressenti par toute la conscience," that is, involves one's whole being.
But it is a joy first of all. "Joy" has been defined by Webster's International Dictionary (1986:1222) as "the emotion excited by the acquisition or expectation of good." Thus, "joy" is an emotion and involves the ethical term "good." To learn about joie de vivre we must, then, have a sound theory of emotion and ethics. (www.proz.com, 2016)

DOM 9.1 mg: These are the feelings that life should give to everyone, the genuine joy of life, the sweetness of it, the richness of it. It's the happiness exuding from your inner heart. When you fall in love or have a high achievement, a spark suddenly lights your life; but this joy is more like a sea from within, not a spark from without. It's very meaningful, loving, and genuine. It's like the happiness of a home, a perfect world where there is no harm (even if you lie in a mountain, the tiger might come but not to harm you, rather as your company), it's so secure, content, so free, and peaceful.
There are a lot of details when I have this feeling. It's like coming home to your mother's arms, the smoke from the chimney when the dinner is getting ready, the bustle in the street, and raindrops on the roof. It's everything come to your life and you feel it and it registers in your mind and is cherished within your heart. It's just lively. It's

abundant. There is the feeling of abundance and richness, a bit elegant, a perfect world, I saw things more artistic. (Shulgin, 2016) Pharm 1, p. 135

DOM 8 mg: It felt like in the season when all the fruits ripen; the world was golden, and it was so full of life. We sat looking out in our yard. It was such a heavenly place, the peaceful world connected with my tranquil consciousness. It was so perfect. (Shulgin, 2016) Pharm 1, p. 135

An excellent rendition of the beta state in cinema can be found in the movie "Perfume: The Story of a Murderer" (Tykwer, 2006), when the perfumer Giuseppe Baldini (played by Dustin Hoffman) experiences "a really good perfume" made by the orphan Jean-Baptiste Grenouille (played by Ben Whishaw). When Baldini, alone in his laboratory, inhales the perfume, he is transported to the season when all the fruits ripen.

Histamine:

Histamine is hypothesized to mediate an affective theory of mind (ToM) that constructs a persistent representation of the affective domain (heart and soul) of close relations, such as close family members (but also works for non-family). ToM is not exclusively constructed on-the-fly. For each person, we build a model of their affective domain, which is stored and refined with each interaction. For close relations it accumulates a complete detailed model, or representation, of their affective domain. We hold their heart and soul within ours, even after they have died. The more we interact with them, the more completely we hold them. (modified from (Ray, 2012))

27 mg of TMA-2: Then I began a journey about how I feel about people. I felt my parents with their very good hearts, my brother with a soft heart but not weak, my sister with a still very innocent heart, and my baby nieces still new and whole. And every grown up has been hurt in some way or another, that their self was shadowed or diminished, or their self was buried in a steel seal of defense (mother-in-law). It's extraordinary to feel people in this way. There is no judgment, just a feeling associated with the people that comes up to my mind (my family and my husband's parents and brother), not about wrong or right, just feeling them, and sometimes these feelings so touched me that I was in tears (when I thought of my grandparents). Seeing my family in photos is great. I could feel them. It's much richer than without the drug… (Shulgin, 2016) Pharm 1, p. 199

31 mg of TMA-2: The transition was quite long, and a lot vivid images of humans appeared in my mind. There was a lot of this kind of activity during the transition. But when everything settled down and I thought I reached the plateau, it slowed down. I was in a good, calm, relaxed mood. The intrusion of human images generally stopped but I could recall it if I wanted to check if I could still conjure the people in that way, and I could still do it.
The TMA-2 had this particular way of conjuring people. The people appeared to have flawless smooth contours like babies, like slight moonshine through their bodies, soft, and gentle. Their existence was quite distinctive, apart from any context. They were

close to me, and I could even feel their breath. It felt like their essence was very much enlarged, and this essence was very simple.
I was listening to a song, it had this marching part, and I could sense the existence of a crowd of people, and they were conjured in my mental image. I remember I looked around the room to see if there were people around because I had the feeling that I wasn't alone.
I had been watching a soap opera. A character from the soap opera appeared in my mind. She didn't appear as her role, she even didn't appear as a woman. She appeared as a human, fleshy, innocent, illuminating, very much present, but without context.
I had also been watching a cartoon series. The main character appeared in my mental image. He was more fleshy and more full than a cartoon figure…
The people conjured in my mind didn't engage in much activity. It's like when I brought up this human in my mind, I gazed into their essence, they accepted my gaze, and there was no obstacle between our essences. (Shulgin, 2016) Pharm 1, p. 199

32 mg of TMA-2: … what seems absolutely unique with this experience is its connection to other people. When I think of my mother, it is as if her presence is with me, in three dimensions. It is not that I see her, actually I see below the surface, her essence is with me. There was a kind of three dimensional representation of her, but it didn't have the facial surface, it had her inner being. This was very strong when thinking of my mother. I went and reviewed a collection of old family photos, and it was very powerful. I really connected with the souls of my family members. (Shulgin, 2016) Pharm 1, p. 199

While receptors, or mental organs, appear to play a wide variety of functional roles in the mind, some of them appear to provide content to consciousness by painting different facets of reality as meaning rendered in consciousness. Before the emergence of the modern mind, affective mental organs had evolved the capacity to paint the world in great detail, subtlety, and nuance in kappa consciousness in the language of feelings, a language older than words. The feelings painted in consciousness by affective mental organs provide a rich language of description for the world, exterior, social, and interior, around which spoken language crystalized when it emerged. I suspect that the modern mind emerged as an adaptation to facilitate the communication of the rich affective language of representation in consciousness, between individuals in a highly social species. The novel elements of the modern mind allow meaning painted in consciousness as either feeling by the affective systems or as logic and reason by the cognitive systems, to be communicated by arbitrary spoken symbols. Some of these mental organs may be the mental organs hypothesized by Pinker in "The Language Instinct" (Pinker, 2007) p. 5, 117.

Heart Opening and Expansion of Breadth

"Heart opening" is a term that is often used to describe the psychedelic state, and is especially associated with MDMA (Adamson, 1985) (Adamson & METZNER, 1988). I would like to define heart opening in relation to breadth of consciousness. Ray (Ray, 2016) proposed these definitions:

- **Psychedelic**: expansion of consciousness
- **Expansion of breadth of consciousness**: bringing more mental organs into consciousness... When a drug causes the effects of a mental organ that is not normally in consciousness, to enter consciousness, it expands the breadth of consciousness, and is psychedelic by my definition. The breadth of consciousness expands when the number of mental organs held in consciousness increases.

I will define heart opening as bringing an affective mental organ fully into consciousness. This differs from the definition of expansion of breadth of consciousness only in that the latter does not restrict the definition to affective mental organs. Yet at this time, the only hypothesized cognitive content mental organ is 5-HT_1, which is presumed to always be present in consciousness. Thus while activation of 5-HT_1 may cause cognitive enhancement, it would not be psychedelic by the above definition because the mental organ is already in consciousness. In short, "expansion of breadth of consciousness" and "heart opening" may be synonymous.

Every affective mental organ produces a qualitatively distinct heart opening; thus there is no one heart opening, rather there are many different heart openings. Yet they also have some features in common that justify grouping them under the term. Some key aspects of the common features are nicely articulated by Tolle:

> Once there is a certain degree of Presence, of still and alert attention in human beings' perceptions, they can sense the divine life essence, the one indwelling consciousness or spirit in every creature, every life-form, recognize it as one with their own essence and so love it as themselves. Until this happens, however, most humans see only the outer forms, unaware of the inner essence, just as they are unaware of their own essence and identify only with their own physical and psychological form. (Tolle, 2005) p. 4.

> … at the heart of the new consciousness lies the transcendence of thought, the newfound ability of rising above thought, of realizing a dimension within yourself that is infinitely more vast than thought. You then no longer derive your identity, your sense of who you are, from the incessant stream of thinking that in the old consciousness you take to be yourself. (Tolle, 2005) pp. 21-22.

> When you don't cover up the world with words and labels, a sense of the miraculous returns to your life that was lost a long time ago when humanity, instead of using thought, became possessed by thought. A depth returns to your life. Things regain their newness, their freshness. And the greatest miracle is the experiencing of your essential self as prior to any words, thoughts, mental labels, and images. For this to happen, you need to disentangle your sense of I, of Beingness, from all the things it has become mixed up with, that is to say, identified with... The quicker you are in attaching verbal or mental labels to things, people, or situations, the more shallow and lifeless your reality becomes, and the more deadened you become to reality, the miracle of life that continuously unfolds within and around you. In this way, cleverness may be gained, but wisdom is lost, and so are joy, love, creativity, and aliveness. (Tolle, 2005) pp. 26-27.

These effects manifest when any one or more affective mental organs are loaded fully into consciousness: when the heart opens.

The Hands of the Mind – 5-HT_2

The DOB & MEM problem – Gatekeeper to Consciousness

DOB and MEM are a problem for the 5-HT_2 paradigm because they are both very selective full agonists for the three 5-HT_2 receptors, yet they lack most of the subjective qualities associated with psychedelic drugs.

DOB and MEM have perceptible interactions only with the three 5-HT_2 receptors: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. DOB and MEM ought to be paradigmatic psychedelics, but they are not. Their effects are relatively subtle, and higher doses do not produce more psychedelic effects. On the contrary, as the dose is increased, they tend to shut thoughts and feelings out of consciousness, producing a mentally closed state, which many users find unpleasant and unproductive.

Careful analysis of the subjective reports along the dose-response curve of DOB and MEM led to the hypotheses illustrated in Figure 3, and to the conception of 5-HT_2 as acting as the "gatekeeper to the consciousness" (Ray, 2012). The hypothesis is that 5-HT_2 provides dynamic moment-to-moment selective inhibition, protection, filtering of access to consciousness, and may focus attention. Activation of 5-HT_2 closes the gates to consciousness, while relaxation or inhibition of 5-HT_2 opens the gates to consciousness. In this sense 5-HT_2 activation is anti-psychedelic.

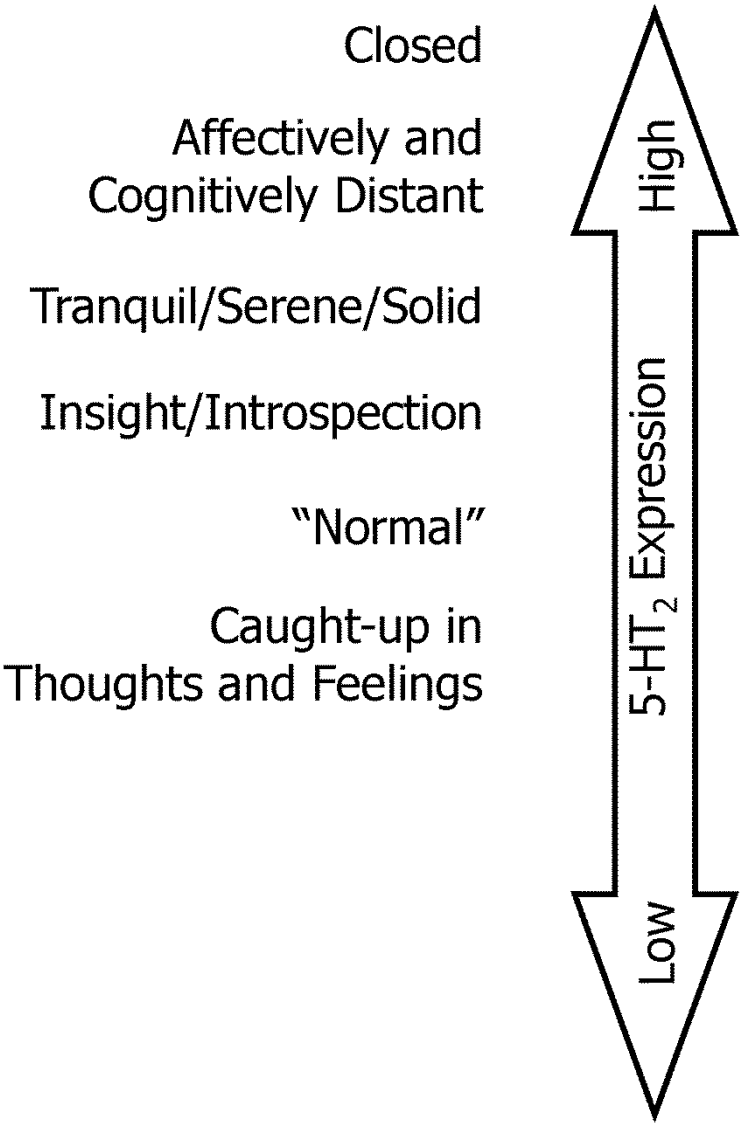


Figure 3: Drugs whose pharmacology is dominated entirely by the 5-HT_2 signal (DOB and MEM) have a peculiar dose-response curve. Activation of 5-HT_2 moves the system up from "Normal" listed in the center of the figure and results in closing of the gates to consciousness, leading to a comfortable sweet spot with moderate activation, although upon higher activation it leads to an uncomfortable contraction of consciousness. See also (Ray, 2012) figure 11.

Drugs whose pharmacology is dominated entirely by the 5-HT_2 signal (DOB and MEM) have a peculiar dose-response curve, illustrated by the spectrum of Figure 3. Activation of 5-HT_2 moves the system up from "Normal" listed in the center of the figure and results in closing of the gates to consciousness.

In the "normal" un-medicated state, many of us tend to be caught up in our thoughts and feelings, and can lose perspective. When the 5-HT_2 system is strengthened by a low to moderate

dose of DOB or MEM, we can gain a little distance from our thoughts and feelings. This facilitates reflection and introspection which can lead to insight.

When the 5-HT_2 system is activated a little further, as by a slightly higher dose of DOB or MEM, these concerns can drop away leading to a state where we may experience feelings of security, tranquility, serenity, contentment, relaxation, and a feeling of being solid. These effects of low to moderate doses are enjoyable and can be rewarding. They reflect the sweet spot of 5-HT_2 activation. Here are examples of the sweet spot:

> **R-DOB 0.8 mg** at 10:15 AM: The music didn't appeal to me, most of the time I could just ignore it. Around 1:15 PM, I noticed that music was a bit complicated. It seemed that there were a lot of elements, even though sometimes I could feel the voice had a lot of feelings. I didn't care about music. And I felt I was shut out, kind of like nothing was going on. I complained to him that music was too complicated and I wanted him to change it. So he changed the music.
> I am not sure if the transition period was passed at that moment. After he changed the music, I felt really good. I was high. For one moment, I felt it's like I was in my parents' hands, in their loving presence. I was relaxed, no worries. It felt warm, stable. I felt good all the rest of the experience. But it also seemed that that's the most I felt.
> I went to take a shower. Even though I could focus on thinking something, there were not a lot of contents. I also laughed when I tried to think of the movie we watched the night before. All the thoughts were brief.
> I didn't feel as empty as I felt in the MEM experience. But there was not a lot going on in my mind. It's quite simple. It's not rich at all, kind of boring. Food didn't taste interesting, but edible.
> At about 6 PM, we went to watch a movie. We tried to watch one, but it seemed that we could not follow it readily, so we watched some part of a comedy again, and I laughed a lot. After that I was down to the baseline enough to watch a more complicated movie. At that time, I noticed the world was more expansive and more connected and richer than what I felt when I was high on the drug. (Shulgin, 2016) Pharm 1, p. 146

> **MEM 26.7 mg** (subject A): When I listened to music, I right away forgot what the last song was, and even couldn't manage to remember it when I tried to. Also after thinking of one thing, and moving on to the next, the thing I had thought a moment ago felt distant. During this time, my husband told me that I was unfair to his brother and mother. I didn't feel offended by his comments about me. It was discussed in a matter-of-fact way, which didn't bother me at all.
> I felt quite normal. It seemed that the thoughts that normally would trouble me didn't matter to me or trouble me or distract me. I also didn't actually have a lot of thoughts. But the thoughts I had were quite nice and straightforward. It's simple and comfortable. I felt quite like the normal state without drug, only more comfortable. There was no dark feeling…
> My thought about this drug is that it seems to make me more with the essence of myself. The things I really care about were closer to me, and the things that don't agree with me were more distant, and they didn't bother me (even the things that bother me often in the normal state). I was with the matter of myself, more together. This was nice, and simple,

> it seemed to filter some thoughts out (the thoughts that don't agree with my heart). I didn't feel empty. (Shulgin, 2016) Pharm 1, p. 176

Higher doses take the subject beyond the sweet-spot into realms in which the filtering/inhibitory functions of 5-HT_2 activation are so strong that too much is filtered out and the experience becomes relatively detached and distant from thoughts and feelings. If one goes further still, the experience becomes mentally closed. High doses of these drugs produce a kind of stoned emptiness. Ann Shulgin described this state:

> **DOB 3.0 mg**: There was a grey, iron weight on my soul.
> *I'm stoned out of my gourd. No fun, no fun. Wonder if there's going to be a glimmer of hope anywhere in this.*
> *The image I'm getting is of an awful cosmic indifference…* (Shulgin & Shulgin, 1991) p. 291

The following are additional reports of DOB and MEM beyond the sweet spot:

> **DOB 2.8 mg**: About three hours into this I had a severe cramp, and had a near fainting response to the pain, and yet there was no pain! I felt that I was very near a loss of consciousness, and this was most disturbing. (Shulgin & Shulgin, 1991) p. 620

> **MEM 40 mg** (subject A): I felt strengthless. And the more pronounced change was that I could not muster one single thought in my brain or feel anything. The music I usually like could not touch me at all. I always enjoy thinking, and being unable to think was so obvious that it upset me. I felt my brain was empty, blank. I was worried that I might be overdosed. Then I checked reality, and I didn't feel I was blown away, so it was good. Then I thought that I might actually be able to think, I just wasn't able to feel I could think. So I decided to try to fall asleep, since there wasn't any thought in my brain that could distract me, I should be able to sleep. I was in a dozing state, but I noticed it was more empty with my eyes closed, so occasionally I opened my eyes to have a reality check because after some time with my eyes closed I felt the emptiness was just a bit too much. It was less empty with my eyes open, even though there were not a lot of things going on in my brain either. Music felt a little far. I could have a little chat with my husband, and the chat seemed normal, even though it didn't have a lot of contents. There was no or little visual effect. The drug is simple, and it didn't have a dark tone on it. So I was comfortable most of the time. (Shulgin, 2016) Pharm 1, p. 176

> **MEM 33.3 mg** (subject B): The feeling was clear, and normal. After the transition, I was mostly bored and restless, and needed something to do. Sex was good, though difficult. At about five hours we went to watch movies because I was bored and restless. I think my dose was a little too high, whereas my wife really liked it, and was relaxed, comfortable, and not bored. (Shulgin, 2016) Pharm 1, p. 176

> **MEM 50 mg** (subject B): It was a pretty empty experience, devoid of thoughts or feelings, meaningless. (Shulgin, 2016) Pharm 1, p. 176

More rewarding results come from low to moderate doses. Users of the psychoactive drugs that are truly selective for the 5-HT_2 receptors (MEM and DOB are pure 5-HT_2 drugs; 2C-B-fly and DOET are pure 5-$HT_{1/2}$ drugs) find the experience of the sweet spot enjoyable, but relatively subtle, simple, and boring compared to what drugs such as LSD, psilocybin and mescaline are capable of. Thus there is a tendency for users to try them at higher and higher doses hoping for more dramatic effects. This dose escalation is futile and counter-productive, and leads to a more distant or closed experience.

An interesting property of drugs such as LSD is that they are used over an exceptionally large dose range. LSD has been used at doses as low as 10 micrograms for cognitive enhancement (Fadiman, 2011), and as high as thousands of micrograms to produce an "overwhelming" experience as in "psychedelic therapy" (Abramson, 1967), thus with doses spanning two orders of magnitude. For drugs like LSD, higher doses are subjectively felt as producing higher levels of consciousness expansion. Not so for 5-HT_2 drugs like DOB and MEM where higher doses produce a greater *contraction* of consciousness. The hypothesis suggests that activation of 5-HT_2 closes the gates of consciousness. The data are consistent with this view. We observe in the two pairs of MEM reports above (subject A, 27.5 mg & 40 mg; subject B, 33.3 mg & 50 mg), that within subjects, higher doses produced a more empty experience. Shulgin also observed that MEM defied his expectation that higher doses would produce more interesting results:

> I explored MEM quite thoroughly in the 20 to 30 milligram area, in these early years, and found it to be a most impressive psychedelic. In 1977, I went up to 60 milligrams and found it not to be the profound self-analysis drug I had hoped it would be… I learned to recommend dosages in the 20-30 milligrams area… (Shulgin & Shulgin, 1991) p. 50

When 5-HT_2 is mildly stimulated, such as by low doses (e.g., R-DOB 0.8 mg, MEM 26.7 mg), the sense of self is strengthened. The ability to dynamically and selectively filter is enhanced ("The things I really care about were closer to me, and the things that don't agree with me were more distant, and they didn't bother me"). This can produce a strengthened sense of self, a state in which the subject feels relaxed, worry-free, warm, stable, secure, simple, solid, comfortable, and self-confident (SSRIs may act in part through this mechanism).

However when 5-HT_2 is strongly stimulated, such as by high doses (DOB 3 mg, MEM 40 mg), the system is saturated and the gates are forced shut, such that the dynamic and selective properties of filtering are lost, and a closed state results, which is not pleasant or productive. MEM and DOB appear to produce very similar effects, and MEM is 60-fold selective for 5-HT_{2B}. I consider all three 5-HT_2 receptors, A, B, and C, to participate in filtering and gating of consciousness.

These observations left me with the view of 5-HT_2 as a "gatekeeper of consciousness", in which increasing activation of 5-HT_2 closes the gates, such that 5-HT_2 is actually anti-psychedelic. I held this view for about a decade.

The clonidine problem – the primer/probe mechanism

Clonidine presents a problem for the full-flavor/mental organs paradigm because it acts at alpha-2 and imidazoline receptors (as do mescaline and MDMA) and at alpha-1, yet it does not have any psychedelic effects.

The primer/probe method was originally proposed by (Ray, 2016) as a result of contemplating the clonidine problem. (Ray, 2016) suggested that if a drug such as clonidine that activates mental organs (the probe) were to be taken together with a drug such as DOB or MEM that selectively activates 5-HT_2 mental organs (the primer), the psychedelic effects of the probed mental organs would manifest. Subsequently, reports have appeared in the Shulgin archive (Shulgin, 2016) which confirm the hypothesis:

> **0.2 mg clonidine and 9.0 mg of 2C-B-fly at noon, cannabis at 3:00 pm**: I felt it strongly by 30 minutes. By an hour I was pretty sure that it is more than 2C-B-fly. By 1.5 hours I felt that my heart may open, but it did not. By 2.5 hours I felt that I had reached the plateau and was bored, and disappointed. I took cannabis vapor at 3:00 pm, and this was the beginning of a full heart opening. It took until perhaps 3:30 or so before the heart fully opened, but certainly it had done so by 4:00 pm. At this point I could not feel the cannabis at all. This beautiful state lasted many hours longer than the cannabis would be expected to. I felt that I was of a philosophical mind, and could write beautiful language about the human condition. I found that this state is what makes life worth living. This is what I want out of life. I was not incapacitated in any way, and felt that I could go through life in this state, and would be better for it. I felt the rebirth of my love for my wife, no small thing. I have taken 2C-B-fly several times at various doses, and it was always relatively boring. This was completely different, much more than 2C-B-fly alone. It was spectacular that the primer/probe method worked. Clonidine (unlike 2C-B-fly) is a beautiful psychedelic. I felt that I recognized a sensibility of continuity in my thoughts, e.g. thinking about the changes we go through as we mature from childhood through adolescence into adulthood. I observed: "I believe that I feel a sense of continuity, in that I exist in the moment, and in the time around it. I occupy a greater temporal breadth. This provides a great connection." I was very present, but not just in the moment. (Shulgin, 2016) Pharm 2, p. 25

> **8.0 mg 2C-B-fly and 2.0 mg of rilmenidine at 12:30 pm; cannabis vapor at 4:00**: The result was spectacular. I got a +4 experience from a pure imidazoline blood pressure medication! It is probably the entactogenic core of MDMA. I tend to think of the effects of MDMA as sweeter and gentler than this, but this was much stronger than any MDMA I have previously experienced. It turns out that 2.0 mg of rilmenidine is a very high dose. This is much more intense than the 0.2 mg of clonidine. Probably 1.0 mg would be adequate, and more comparable to a typical dose of MDMA. It also lasted longer than MDMA.… I took cannabis vapor. Within minutes my heart opened and the rilmenidine fully blossomed. At this point I could not feel the cannabis at all, although I had taken it only a few minutes before. I was astonished by the experience. Not because it worked, I had already seen the clonidine work. I was astonished by the depth of the experience, and I remained astonished for two weeks. I was ecstatic. Not ecstatic because it worked,

rather the mental state was ecstatic, somewhat un-sober. I recalled Martin Ball calling 5-MeO-DMT the "crown jewel of the entheogens". I felt that rilmenidine must also be a crown jewel. I described the state with superlatives.… Qualitatively, it is very hard to characterize the rilmenidine state, apart from the depth of it. At 3:52 hours she asked me how I feel, and I responded "It is like a peaceful lake, it feels eternal… in a peaceful sense". Perhaps most telling, just 25 minutes after taking the cannabis, 3:55 hours after taking the rilmenidine, I spoke to my wife about what for me were the core issues in our relationship. These are things that are very hard to discuss because they are painful, and discussion tends to lead to anger. But we discussed it peacefully. I expressed my sadness with tears. I believe this capacity for calm contemplation and discussion of painful personal issues is a core feature of the entactogenic state of MDMA, and here I was experiencing it with blood pressure medication…. For me it's really, astonishingly among the best psychedelic experiences I've ever had. Unbelievable. (Shulgin, 2016) Pharm 2, p. 26-27

1.1 mg R-DOB + 0.3 mg clonidine (no cannabis): … based on our past experiences with highly selective 5-HT2 agonists coupled with Clonidine, from which we had begun to expect long, highly sober transitions lasting 4-5 hours, followed by comfortably mild psychedelic states induced by marijuana consumption. Our expectations were blown away…. All of the perceptual elements of the psychedelic state began to align on this walk: the almost magical fluttering of the fall foliage; the saturated colors of artificial objects; the ape like reminiscences in my partner's facial structure; the glee; the mums appearing as technicolor humps of alpaca pelt from a distance; all the while feeling fleet of foot. I know indubitably, that this was among the most intense and persistent psychedelic experiences I have had, no doubt fueled by the fact that I was completely taken aback, having expected to have the typical Clonidine experience. (Shulgin, 2016) Experience Reports, p. 24

3.9 mg DOET + 0.2 mg clonidine (no cannabis) at 10:45am: 2:00 – full onset, evaporation of drowsiness, every surface replete with arabesque geometric patterning… Compared with 2CB-Fly and MEM, there were virtually no physical side effects. This is similar to the experience with R-DOB, except that because R-DOB was taken with 0.3mg Clonidine, the drowsiness accompanying it was much pronounced. The other reason accounting for the uneventful transition state was that, as with R-DOB, no cannabis was necessary to see the experience blossom…. While looking out at the city from a tall building, I felt as though I could imagine the city anthropomorphized in a sense. I felt like I could feel the gritty industrial character of the city. I felt like the city had a soul, like all cities had a soul and the museum was a window into it. I felt like the city had a personality that affected the character of its inhabitants. I felt like I could see the development of this city as it stands in its current cultural state taking information that I knew of its settlement and its European heritage and that I could see how the modern city, with its cultural and political proclivities, might have come about because of these developments. (Shulgin, 2016) Experience Reports, p. 26

The reports describe success with either clonidine or rilmenidine as probes, combined with DOB, DOET, MEM, or 2C-B-fly as primers. Curiously it was found that when MEM or 2C-B-fly were

used as primers, cannabis was required for the probed mental organs to fully enter consciousness (heart opening); yet when DOB or DOET were used as primers, cannabis was not required. The hypothesis proposed to explain this curious observation is that when 5-HT_{2B} acts as the predominant primer mental organ, cannabis is required; whereas when 5-$HT_{2A/C}$ acts as the primer mental organ, cannabis is not required. Below is a list of the 5-HT_2 relative affinities of the four primers:

DOET: 3.72 5-HT_{2A}, 3.70 5-HT_{2B}, 3.13 5-HT_{2C}
DOB: 4.00 5-HT_{2B}, 3.23 5-HT_{2A}, 2.97 5-HT_{2C}
2C-B-fly: 4.00 5-HT_{2B}, 2.93 5-HT_{2C}, 2.89 5-HT_{2A}
MEM: 4.00 5-HT_{2B}, 2.21 5-HT_{2A}, 0.00 5-HT_{2C}

When cannabis was required to load the mental organs, the heart opening lasted many hours longer than the effects of cannabis could be expected to last. Another surprising result is that while the experiment was successful when the primer and probe were taken together simultaneously, it failed when the probe was taken a few hours later, shortly after the primer had plateaued. Another observation, not unexpected, is that two subjects with about twenty exposures to MDMA in recent years were able to successfully prime and load clonidine but not rilmenidine. It appears that before the primer/probe experiments they had developed chronic tolerance to the entactogenic effects of MDMA that crossed over to primed rilmenidine (although they did not acknowledge prior tolerance to MDMA).

These reports show that when a primer (a simple 5-HT_2 selective drug: DOB, MEM; or 5-$HT_{1/2}$ selective drug: DOET, 2C-B-fly) is taken with clonidine (a probe), clonidine produces psychedelic effects, and the same primer produces qualitatively different effects when it is coupled with a different probe (rilmenidine). 2C-B-fly with rilmenidine produces a state that appears to be equivalent to the entactogenic component of MDMA, while 2C-B-fly with clonidine produces a heart opening reminiscent of mescaline, but with its own distinct qualitative properties.

This reinforces the full-flavor view originally advocated above under "the DOM problem". At the same time, it validates the paradigmatic view that 5-HT_2 plays a key role in the psychedelic phenomena, and I hypothesize the specific mechanism by which 5-HT_2 is psychedelic: it loads the probed mental organs into consciousness. What we are left with is that 5-HT_2 is not psychedelic in the usual sense on its own, but it can be beautifully psychedelic in combination with other mental organs, by loading them into consciousness, thereby expanding the breadth of consciousness. At the same time, the depth of consciousness is independently mediated by the level of activation of 5-HT_7, regardless of whether other mental organs are loaded into consciousness.

"Gatekeeper of Consciousness" becomes "Hands of the Mind"

Close examination of drugs selective for 5-HT_2 led to the conceptualization of the 5-HT_2 mental organ as the "gatekeeper of consciousness." However, no mental organ functions in isolation, and examination in isolation can cause us to miss the more important functions of the mental organ, and this has been the case for 5-HT_2. By coming to understand the role of 5-HT_2 in drugs

that also act at other mental organs, I have replaced the gatekeeper metaphor with "hands of the mind."

"Hands" is deliberately plural. It appears that these hands can perform multiple functions in the mind (including gatekeeper), and perform them simultaneously, suggestive of the Hindu goddess Durga, Figure 4. At this time it is not clear what variety of functions the 5-HT_2 hands may be capable of performing, but some possibilities are exhibited in Figure 5: Upper left, the gatekeeper of consciousness, filtering access to consciousness; Center, focusing attention; Lower right, bringing something into consciousness, such as a mental organ or a memory; Upper right, holding something in consciousness, such as a mental organ or a memory; Lower left, blocking a memory from consciousness.

The gatekeeper function of the hands is illustrated in Figure 6. The un-medicated adult human mind is dominated by serotonin. Consciousness is apparently provided by 5-HT_7, and is represented by the brain icon. The cognitive functions (language, logic, and reason) are always present in 5-HT_7 consciousness, are apparently mediated by 5-HT_1, and are illustrated by 5-HT_1 being held in consciousness in the upturned hand in the upper right of each mind icon. The gatekeeper function is represented by the open hand on the left side of each mind icon, labeled with 5-HT_2. On the left, we see the gatekeeper function of the hand in the un-medicated mind. On the right we see the gatekeeper function strengthened by the action of a selective 5-HT_2 drug such as DOB or MEM, illustrated by a larger hand. Although cognition is always present in the adult human mind, the 5-HT_1 in the upturned hand icon is not shown in Figures 4, 5, 7-9, and 11.

Figure 7 illustrates the case of blood pressure medications such as rilmenidine or moxonidine which selectively activate imidazoline-1 receptors in the brain. The figure illustrates this activation with the large letter "I", which is placed outside of the mind icon, because the mental effects of central imidazoline activation by blood pressure medication do not enter consciousness.

Figure 8 illustrates the case of MDMA whose rank-order highest affinity (best hit) is imidazoline-1, and whose rank-order second highest affinity is 5-HT_{2B}. The figure illustrates the activation of 5-HT_{2B} through an increase in the size of the hand, as was seen in Figure 6 illustrating the effects of DOB and MEM. In the case of MDMA, 5-HT_{2B} acts as the primer mental organ, and imidazoline-1 acts as the probed mental organ. Because they are activated simultaneously, imidazoline-1 is loaded into and held in consciousness. This is represented by the large letter "I" being held inside the mind icon in the upturned palm of a hand. The same mental state can be obtained by taking a primer drug (DOB, MEM, DOET, or 2C-B-fly) together with an imidazoline probe (rilmenidine or moxonidine).

Figure 9 suggests hypothetical roles for the hands of the mind in the therapeutic mechanism of MDMA in healing trauma. Upper left, a hand is blocking something from consciousness. Upper right, we peek inside to see that it is the memory of a traumatic event that is being blocked. Lower left, if the memory were held fully in consciousness, it would be intolerably painful, and may re-traumatize the patient. Lower right, if the imidazoline-1 mental organ is held in consciousness, then the memory of trauma can also be safely held in consciousness in a therapeutic setting, which can allow processing and healing.

The “hands of the mind” does not invalidate the “gatekeeper of consciousness.” In the new view, the gatekeeper is a function performed by one of the hands.

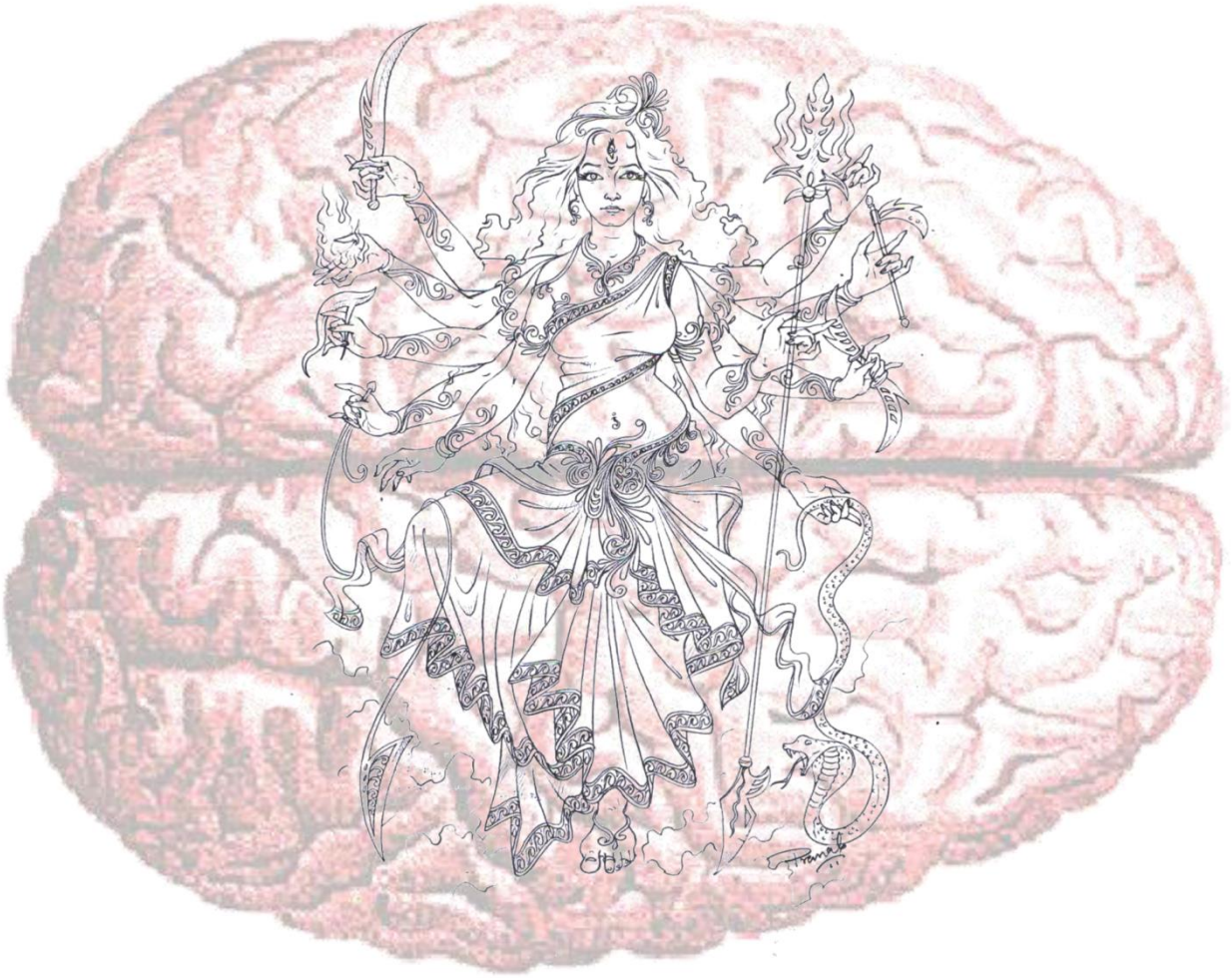


Figure 4. The hands of the mind, envisioned as the Hindu goddess Durga, whose multiple hands are able to perform a variety of tasks simultaneously. In this image, the brain icon represents the mind, not the brain. Durga drawing by Pranab Das, used with permission.

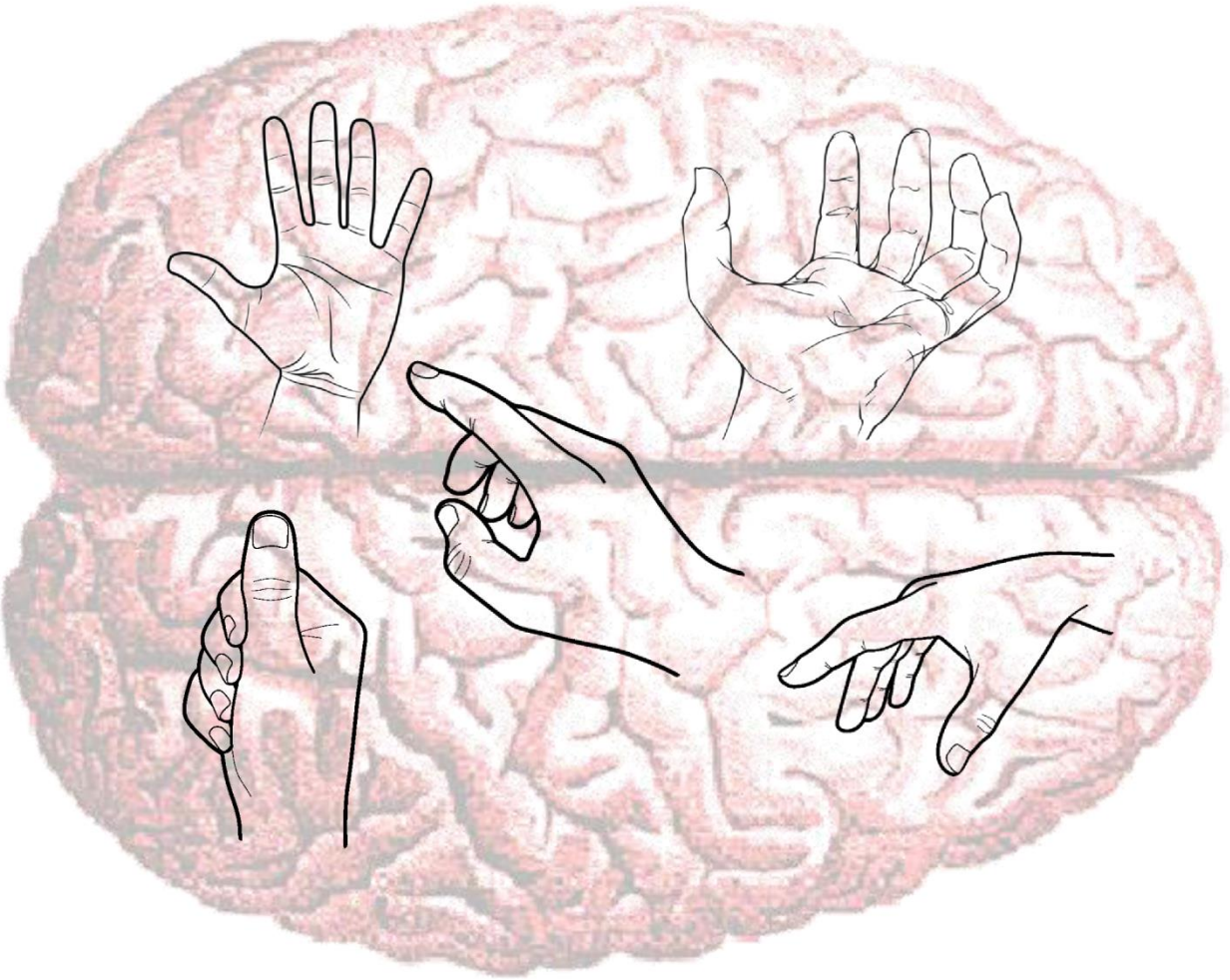


Figure 5. Some possible functions of the hands of the mind. Upper left, the gatekeeper of consciousness, filtering access to consciousness. Center, focusing attention. Lower right, bringing something into consciousness, such as a mental organ or a memory. Upper right, holding something in consciousness, such as a mental organ or a memory. Lower left, blocking a memory from consciousness. Upper left hand PETROO / Shutterstock.com, upper right hand Luis M. Seco / Shutterstock.com, lower three hands Hein Nouwens / Shutterstock.com.

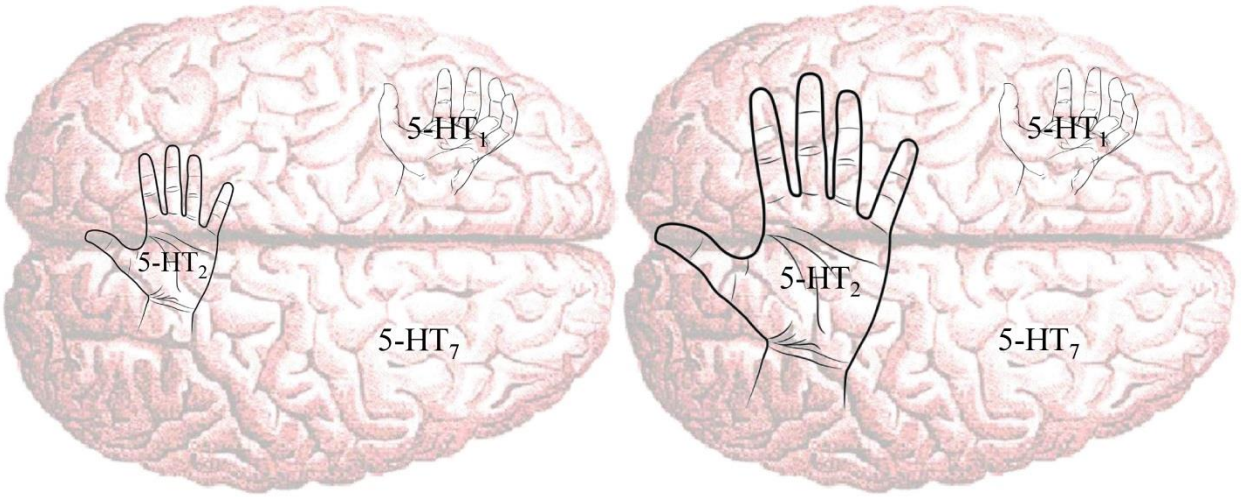
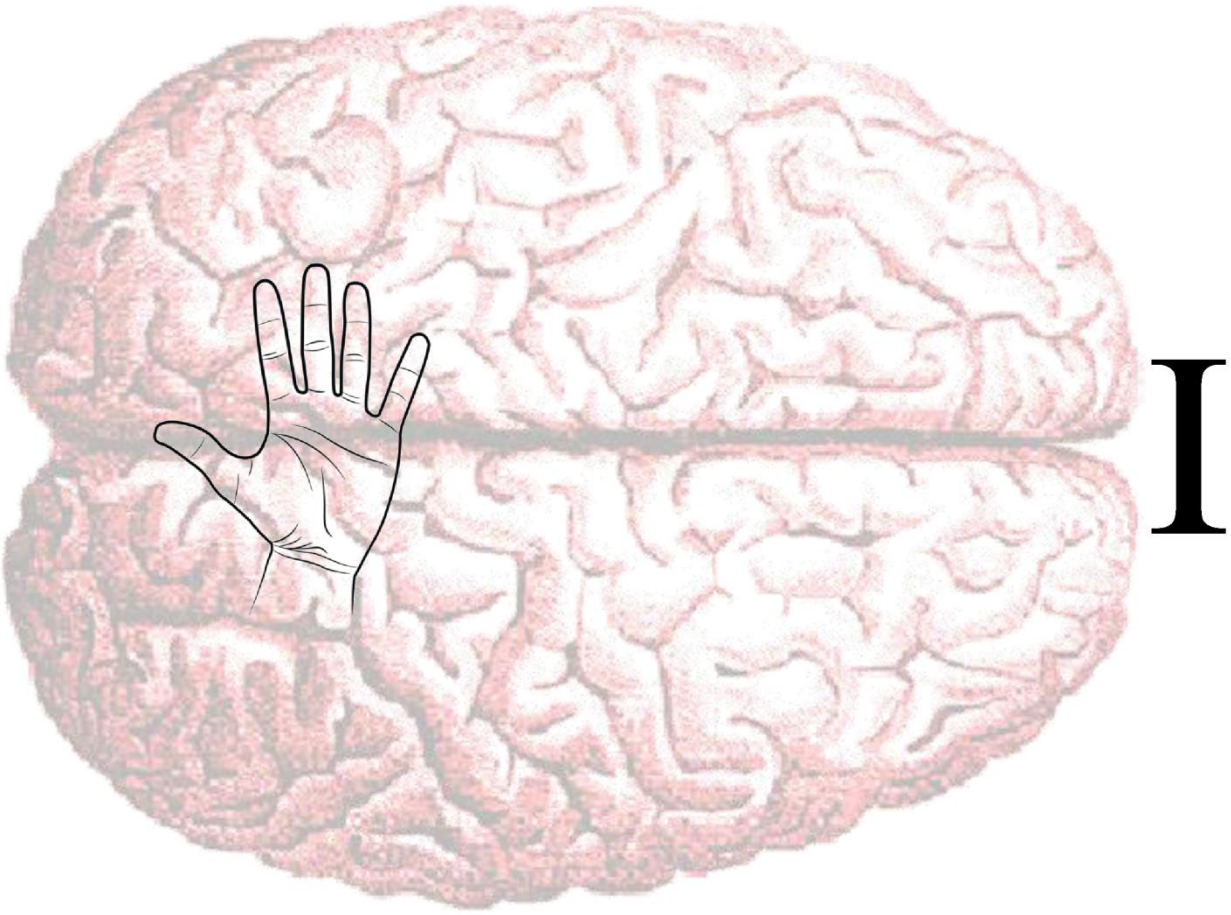


Figure 6. The gatekeeper function of the hands. The un-medicated adult human mind is dominated by serotonin. Consciousness is apparently provided by 5-HT_7, and is represented by the brain icon. The cognitive functions (language, logic, and reason) are always present in 5-HT_7 consciousness, are apparently mediated by 5-HT_1, and are illustrated by 5-HT_1 being held in consciousness in the upturned hand in the upper right of each mind icon. The gatekeeper function is represented by the open hand on the left side of each mind icon, labeled with 5-HT_2. On the left, we see the gatekeeper function of the hand in the un-medicated mind. On the right we see the gatekeeper function strengthened by the action of a selective 5-HT_2 drug such as DOB or MEM, illustrated by a larger hand. Hands on left side of brain icon PETROO / Shutterstock.com, hand in upper right of brain icons Luis M. Seco / Shutterstock.com.



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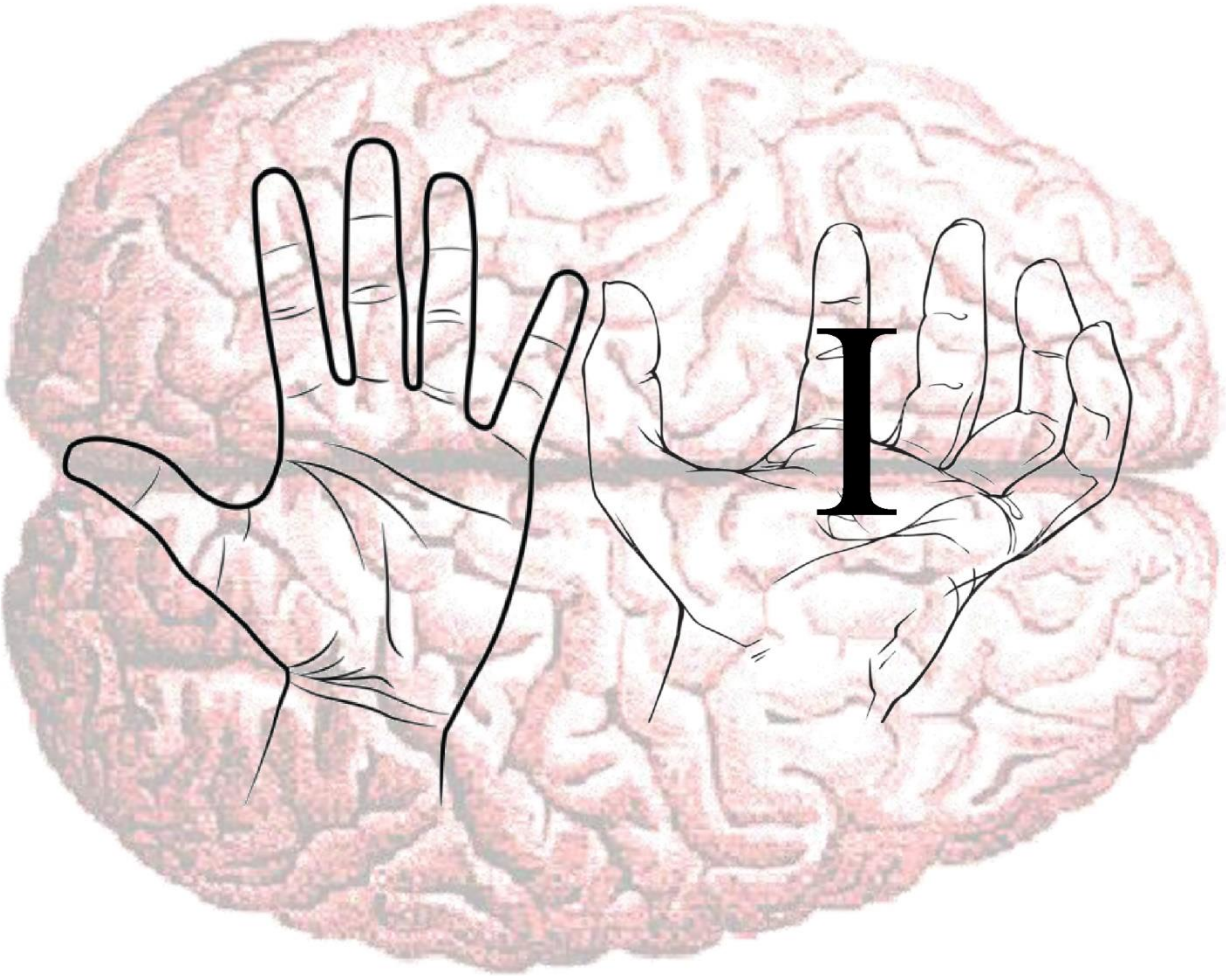

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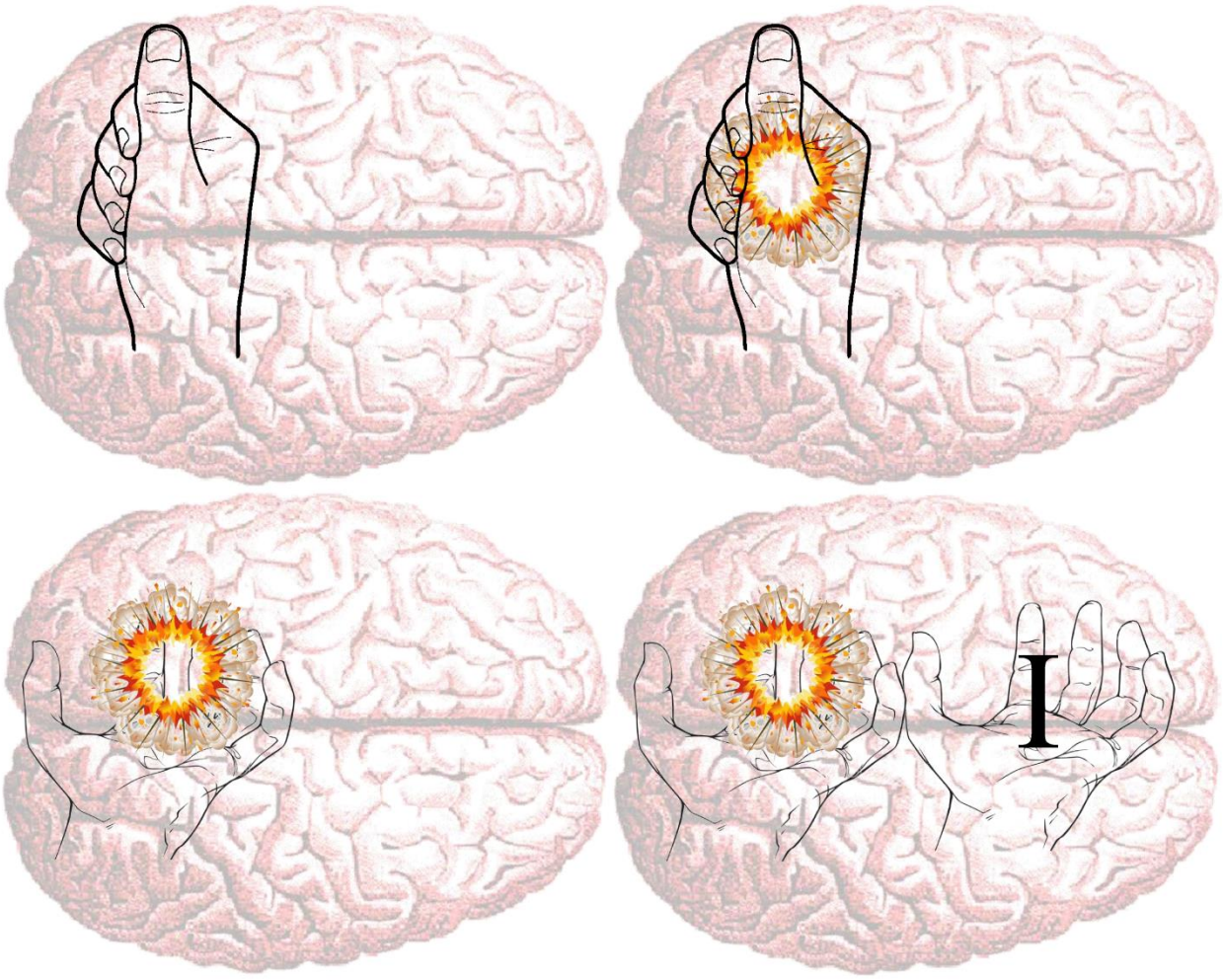

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Three States of Mental Organs in relation to Consciousness?

The primer/probe method separates different elements of psychedelic pharmacology onto different molecules. Thus we can take the primer and probe separately/individually, or together. We can also adjust the relative doses of the primer and probe, combine various primers with various probes, and alter the relative timing of the primer and probe when taken together. Some of these variations have appeared in primer/probe reports in the Shulgin Archive. By teasing

apart the primer/probe components, these experiments are revealing aspects of the psychedelic mechanism that were not previously apparent.

It has been hypothesized that mental organs can be in or out of consciousness (Ray, 2016). But are these discrete states or part of a continuum? The observations we have made so far about 5-HT_2 and breadth of consciousness suggest that there are three steps potentially involved in bringing an affective content mental organ fully into consciousness such that it expands the breadth of consciousness and is experienced as a heart opening:

- Activate probed mental organ
- Activate primer mental organ
- Remove cannabinoid blocks if necessary

These three steps may not be required to occur in any particular order, except that apparently the probe should not follow the primer. Whether cannabis is required appears to depend in part on which primer is used. With DOB or DOET as a primer, the primer and probe together produce a full heart opening without cannabis. With MEM or 2C-B-fly as a primer, the heart opens only after cannabis.

With 2C-B-fly, when the primer and probe were taken together, after reaching the plateau (but before cannabis), subjects experienced an intriguing intermediate state in which the mental effects of the probe were subtly evident, but the heart did not open:

> **8.0 mg 2C-B-fly and 2.0 mg of rilmenidine**: 1:45 hours after taking, I began to feel a lot of empathy for the characters in the documentary video I was watching.… [later] I took cannabis vapor. Within minutes my heart opened and the rilmenidine fully blossomed [more from report above, Pharm 2, p. 26-27]. (Shulgin, 2016) Pharm 2, p. 26

> **8.0 mg 2C-B-fly and 2.0 mg of rilmenidine**: I thought of my father. His expression was extremely vivid, sharp and of high resolution. I could feel his emotion, and the underlying history for the emotion of that moment. However I was not personally attached. I was more an observer. I called it impersonal empathy, in that I felt I could read other (imagined) people's facial history and understand it deeply…
> Then I checked my cell phone, and was attracted by my friend's photo. She smiled so authentically, and I was moved (but still not personally, this was an odd feeling. It was more universal). I was moved, but my heart wasn't open. I was able to feel them on their terms, but not because I was attached. It was as if my observing part was very present and understood many things. I could enter their minds to feel them enjoy the moment, and be happy for them, but it's not personal. I was really observant. I saw the elements of the smile, the life behind the smile, the emotions she had. I was immensely attracted to the real photos, but not staged ones, even the staged photo of children posing; I could not feel things behind the staged photos. It was amazing, the real photos had so many things going on, so vivid, so humane…
> My heart never opened throughout the experience (I did not use cannabis, although my husband did). (Shulgin, 2016) Pharm 2, p. 30-31

When the probe was taken after the primer had cleared the transition, loading of the probed mental organ into consciousness was not possible with or without cannabis, and the intriguing intermediate mental state did not manifest:

> **4.0 mg DOET at 10:30 am; 0.2 mg of clonidine at 1:30 pm; 3:30 pm cannabis vapor**: After 3 hours I took the clonidine. I like clonidine by itself. The first time I took one tablet I described the feeling as relaxed and comfortable. As the clonidine came on I felt better than with the DOET alone. Yes, again, relaxed and comfortable. About 30 minutes after taking the clonidine I sensed a blood pressure drop and a bit of dizziness, so I decided to stay in bed. By an hour after taking the clonidine, I would say that it had reached full effect, but it did not fully bloom as when I had taken it with 2C-B-fly.
> So I waited another hour and took cannabis, as I had when I used the clonidine with 2C-B-fly. This put me into a typical cannabis state, not the beautiful clonidine state that I had experienced … with 2C-B-fly/clonidine taken together at the same time and followed by cannabis. I was having the kinds of thoughts typical of cannabis, and did a bit of writing of the kind that I typically do with cannabis...
> I had previously taken just clonidine and cannabis (no primer) and found it to be a very pleasant state, and this was similar to that. I would say that this combination, DOET/clonidine/cannabis was a bit brighter and more vivid than it would have been without the DOET. But by no means did I experience a heart opening. When I took 2C-B-fly/clonidine/cannabis… the clonidine fully bloomed and I was able to clearly experience and describe the mental effects of clonidine. However today I could not recognize or characterize the mental effects of the clonidine. (Shulgin, 2016) Pharm 2, p. 28

There is a quantum difference between the intermediate state and the full heart opening. In the intermediate state it is as if 5-HT_2 has loaded the probed mental organ subtly into consciousness, but a thin veil separates the mental organ from a full heart opening, and cannabis can dissolve this veil. This suggests that there may be three states of the relationship between mental organs and consciousness:

- **Not loaded into consciousness, heart not opened** – Either when the probe is taken alone; or when the probe is taken after the primer reaches the plateau: the probed mental organ does not enter consciousness or open the heart, but fully manifests its physiological effects (clonidine and rilmenidine are both blood pressure medications and produce reduced blood pressure and drowsiness at the doses used), and cannabis manifests its usual properties.
- **Loaded into consciousness, heart not opened** – When the primer and probe are taken simultaneously, and cannabis is needed to open the heart, but has not yet been taken: the probed mental organ enters consciousness in a subtle way, but the heart does not open.
- **Loaded into consciousness, heart opened** – When the primer and probe are taken simultaneously, followed by cannabis if needed: the probed mental organ is manifest in consciousness in a full heart opening. Once the heart opens, the drowsiness caused by the probe is usually not felt. Although cannabis, if needed, initiates the quantum leap into the heart opening, the characteristic effects of the cannabis are not noted, and the heart opening far outlasts the expected duration of the cannabis.

These three states appear to be discrete states rather than points on a continuum, though more data is needed. It should be noted that the hypothesis that there is an intermediate state, with the mental organ loaded into consciousness but with the heart not opened, is based on very little data, and is thus still a weak hypothesis, though quite intriguing.

Depth of Consciousness – 5-HT_7

Consciousness Itself & Creativity – "Serotonin-7ization"

Much of this section is adapted from (Ray, 2012).

The hypothesis is that 5-HT_7 mediates consciousness and creativity. Consciousness holds what we are aware of: the present scene, fantasy, imagination, feeling, idea, theory, memory. Rather than creating a central theater of consciousness, 5-HT_7 may bestow the property of consciousness on other mental organs. With mild stimulation of 5-HT_7, the subject feels a profound lucidity and clarity, which feels like consciousness itself. It may feel like genius. It may lift the spirits. It may be the seat of the intellect, or a core element of it.

Another way of putting it is that with increased activation of 5-HT_7, qualia become more vivid, or the contents of consciousness are rendered at higher resolution. The reference to higher resolution is a computer metaphor suggesting more pixels in an image. However in the context of 5-HT_7 and consciousness, rather than more pixels we find greater subtlety, nuance, depth, complexity, tangibility, vividness, and capacity; to render thought, feelings, and sensory input in conscious awareness.

Consciousness mediated by 5-HT_7 also provides the spark of creativity. As 5-HT_7 is gradually strengthened (as by successively higher doses of a 5-HT_7 drug, or by full doses of a series of drugs with successively higher relative affinities at 5-HT_7), all contents of consciousness are transformed, a creative process I call "serotonin-7ization", Figure 10. There seem to be common themes to these effects: adds a creative exuberance; takes it to a higher level; makes connections; comprehends the bigger picture; creates a sense of sumptuousness, sparkle, sublime, grandeur, majesty, transcendence, something greater, cosmic, divine, or god; intangible becomes tangible; thoughts, feelings, motivations originating from within may be perceived to originate from without.

In this passage from "Jane Eyre", Charlotte Brontë captures what I believe is the natural role of modest serotonin-7ization in the healthy un-medicated mind, interpreted as religion by the character St. John:

> Won in youth to religion, she [religion] has cultivated my original qualities thus:—From the minute germ, natural affection, she has developed the overshadowing tree, philanthropy. From the wild stringy root of human uprightness, she has reared a due sense of the Divine justice. Of the ambition to win power and renown for my wretched self, she has formed the ambition to spread my Master's kingdom; to achieve victories for the standard of the cross. So much has religion done for me; turning the original materials to the best account; pruning and training nature. (Bronte, 2009)

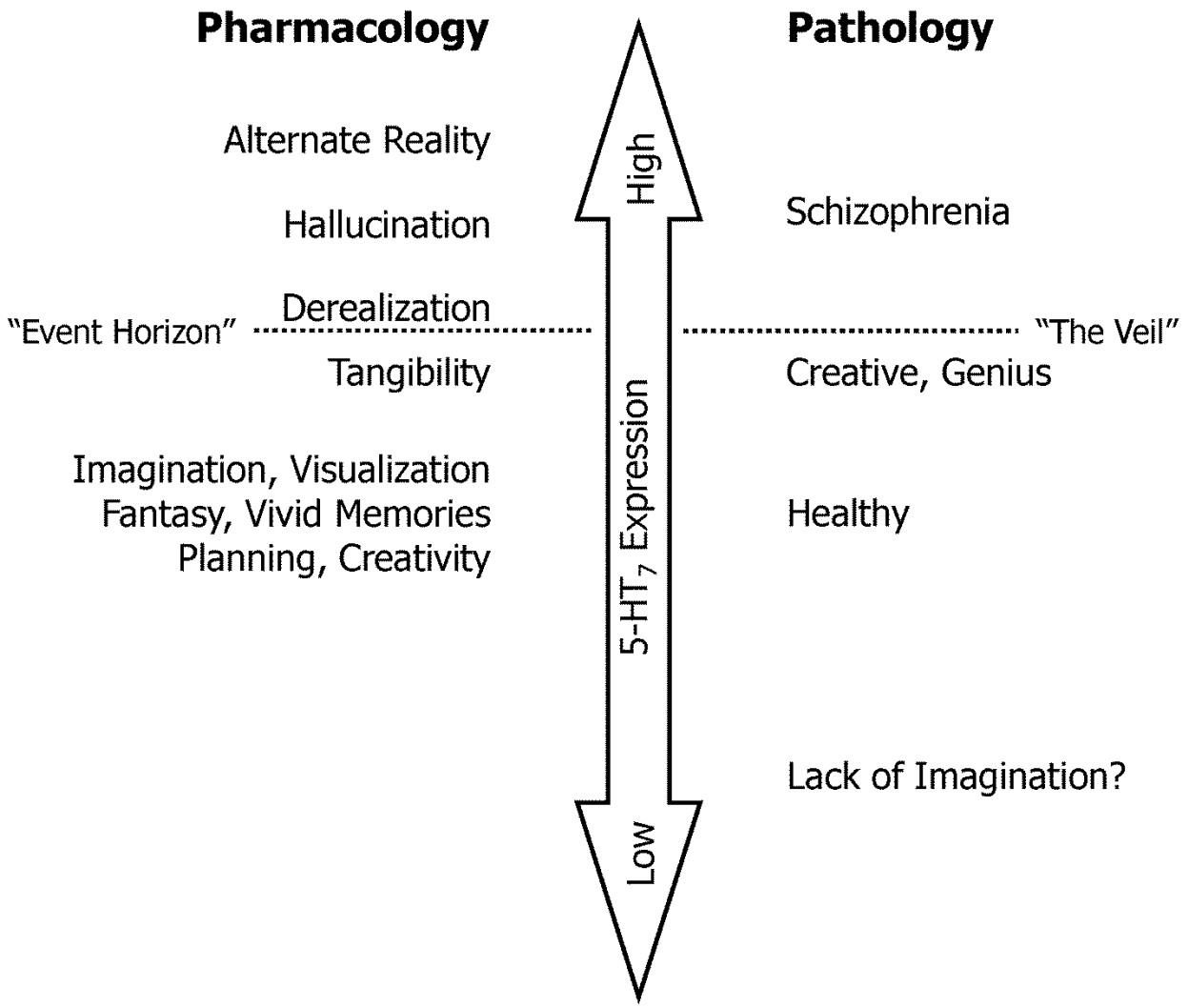

Figure 10: Hypothesized spectrum of 5-HT_7 expression (see also (Ray, 2012) figure 11)

As 5-HT_7 is strengthened further, the contents of consciousness become more tangible, and begin to be perceived as if through the five senses. For example, space, thought, and music, can all take on a tangible quality. One may feel that space has a tactile quality, or that they can see or touch thought or music. Fantasy and imagination become so vivid that they can be seen, touched, heard, smelt, or tasted. Thoughts, feelings, or motivations originating from within may become so tangible that they are felt as if experienced through the senses, and thus may be interpreted as originating from without. External sense perception held in consciousness may become blended with creative internal fantasy to produce dramatic creative alterations of sense perception, some of which I will refer to as "creative visuals".

At a critical point along the spectrum of 5-HT_7 activation we pass through a mental event horizon, as the creative contents of consciousness become more salient than actual reality. When crossing the event horizon we lose contact with actual reality, and may find ourselves in a formless void, or in an alternate reality that is fully visually rendered (creative visuals). This is

what (Strassman, Wojtowicz, Luna, & Frecska, 2008) have referred to as "beyond the veil." We mentally exit the actual space and time and enter a space and time created by the mind, within which the mind is able to create an alternate reality. At this point a mental big bang may occur; consciousness is a generative system, capable of creating worlds, universes. In addition, under certain conditions when consciousness is strongly expanded, the sense of self can be lost, ego-loss.

Interactions between 5-HT_7 and Other Mental Organs

This manuscript will advance the hypothesis that 5-HT_7 directly mediates three specific dramatic mental effects of psychedelics: creative open-eyed Visuals, Ego-loss, and loss of contact with Reality (VER). Yet among the twenty-two drugs of this study there is no drug for which 5-HT_7 is the only perceptible mental organ, and among these drugs, 5-HT_7 manifests in varying combinations with a wide variety of other mental organs. Mental organs do not exist or function in isolation. 5-HT_7 plays a central role in the mind, interacting intimately with other mental organs. In order to identify and understand the role of 5-HT_7, we cannot ignore these interactions. I will now present an overview, and follow with an in-depth discussion of the role of other mental organs in the occurrence of the three most dramatic psychedelic phenomena, VER.

I hypothesize that while loss of contact with reality appears to depend only on the strength of activation of 5-HT_7, whether this manifests as a richly detailed alternate reality or an empty void, depends on what other mental organs are also activated.

I hypothesize that ego-loss depends on the balance between 5-HT_7 and 5-HT_2, occurring principally when 5-HT_7 is strongly activated while 5-HT_2 is either inhibited by a weak partial agonist (LSD, psilocin) or not perceptibly activated (5-MeO-DMT). However in most psychedelics 5-HT_2 is perceptibly activated, preventing ego-loss.

Creative visuals represent a subset of a wide variety of visual effects produced by psychedelics (see below). I hypothesize that while creative visuals require 5-HT_7, they do not appear as a result of 5-HT_7 alone, but require the simultaneous participation of non-serotonin mental organs, as we see in the case of a richly detailed alternate reality (DMT). While it appears that 5-HT_7 is necessary for the production of creative visuals, there are other dramatic visual effects that do not require 5-HT_7.

We will now examine in more depth, the conditions under which VER arise, beginning with loss of contact with reality for which the conditions are the simplest. Then we will examine the conditions for ego-loss. Finally we will examine the conditions for creative visuals, which requires that we first learn to distinguish creative visuals from simple visuals.

Crossing-Over into Loss of Contact with Reality

I hypothesize that there is a discontinuity in the spectrum of 5-HT_7 activation (Figure 10), as described above. As 5-HT_7 is strengthened, at a critical point, the creations of the mind replace actual reality, and the subject "crosses over" "beyond the veil". Nichols' description of the

effects of psychedelic drugs is a clear reference to the cross-over experience: "The user may feel transported to an alternate time or place, another dimension, or another plane of existence that may seem completely real" (Nichols, 2004). Pinchbeck has beautifully articulated the approach to and crossing of this mental event horizon:

> I believe that psychedelic drugs, used carefully, are profound tools for self-exploration. The forbidden substances can be a precision technology for revealing the interstitial processes of thinking, the flickering candle sputters of emotion, the fine-tuned machinery of sense perceptions. The unfolding of the self through an increase in perception, cognition, and feeling is one level of the trip. On low doses, that is all you get, and often it is enough.
> The next level begins where consciousness, suddenly able to go beyond its normal boundaries, bursts open on the nonordinary world. It fascinates me that these two levels are so closely related. It is as if the mind were a rocket, gathering force as it speeds along a runway until it finally lifts into space, beyond the tug of gravity, where all the rules are different. Why should a process that begins by sharpening normal perceptions – making colors brighter, enhancing awareness of patterns in nature – lead seamlessly into "abnormal" perceptions, into paintings that breathe, statues that dance, trees that writhe with faces and limbs? Not to mention, as yet, those geometric and hallucinatory vistas of unleashed Otherness, revealed to the closed eyes. (Pinchbeck, 2002), p. 3

This cross-over phenomena does not appear to depend on any mental organs other than 5-HT_7, however, other mental organs modulate the qualities of the loss of contact with reality. In Figure 2, examine the group of five drugs in the upper (strong 5-HT_7) portion: 5-MeO-DMT, 5-MeO-MIPT, TMA, LSD, DMT (in order from least to greatest breadth). We get a formless void when only serotonin mental organs are activated (e.g., 5-MeO-DMT, examples cited below). We may get an alternate reality when non-serotonin mental organs are also activated, and the greater the number of non-serotonin mental organs activated the more richly detailed, multifaceted, and realistic is the alternate reality (e.g., DMT, examples cited below). While 5-HT_7 provides a mental space, the content comes from other mental organs. Crossing over may or may not be visually rendered, but always involves loss of contact with the present reality.

When a subject is on the threshold of crossing over, they may have a foot in both worlds, and experience derealization (Figure 10), in which the actual reality seems artificial, as if constructed of paper or plastic, and peoples' faces may appear as masks:

> **DMT**: the experience settled into a comic book kind of reality in which my surroundings turned into very cheap plastic (the kind that kewpie dolls are made of). (DeKorne, 1997) p. 12

> **DMT 75 mg, intramuscularly**: The faces of people seemed to be masks. (Shulgin & Shulgin, 1997) p. 416

Although alternate reality is generally experienced and interpreted as being completely independent from our familiar reality, there is evidence that the alternate reality can be strongly influenced by the set and setting under which the drug is taken. Strassman noted:

> **DMT**: There are surprising and remarkable consistencies among volunteers' reports of contact with nonmaterial beings…. Volunteers find themselves on a bed or in a landing bay, research environment, or high-technology room. The highly intelligent beings of this "other" world are interested in the subject, seemingly ready for his or her arrival and wasting no time in "getting to work." There might be one particular being clearly in charge, directing the others. Volunteers frequently comment about the emotional quality of the relationships: loving, caring, or professionally detached.
> Their "business" appeared to be testing, examining, probing, and even modifying the volunteer's mind and body. Sometimes testing came first, and after results were satisfactory, further interactions took place. They also communicated with the volunteers, attempting to convey information by gestures, telepathy, or visual imagery. The purpose of contact was uncertain, but several subjects felt a benevolent attempt on the beings' part to improve us individually or as a race. (Strassman, 2001) p. 199

This could be interpreted as a highly psychedelicized (serotonin-7ized) representation of the situation that the subjects actually find themselves in: The studies took place in a hospital environment. During the experiment, the subject was in a bed, fitted with black eyeshades, a catheter in one arm for administering drug, another catheter in the other arm for withdrawing blood, an automatic blood pressure cuff, and a thermistor probe inserted into the rectum. During the experiment the subjects were closely attended by Strassman and other members of his staff (Strassman, Qualls, & Berg, 1996; Strassman, Qualls, Uhlenhuth, & Kellner, 1994). Due to extreme serotonin-7ization, the relationship between the actual setting and the psychedelicized version of it that appears in an alternate reality can be easily missed.

Ego-loss

Ego-loss is defined as the dissolution of the sense of self, and the feeling of merging with one's surroundings, or with the universe, "the boundary between self and environment may dissolve so completely that the drug user feels at one with other people, animals, inanimate objects, or the universe as a whole" (Grinspoon & Bakalar, 1997). One can feel as a drop in the ocean. This is the effect referred to by Snyder (Snyder, 2006): "the extraordinary change in the sense of self, a feeling of communion with the infinite, a dissolution of ego boundaries with the self, seeming to merge with environment".

I hypothesize that ego-loss occurs when 5-HT_7 is activated much more strongly than 5-HT_2, and that ego-loss is likely to occur in only three of the drugs of this study: LSD, psilocin, and 5-MeO-DMT. What sets these three drugs apart in terms of receptor interactions, is their relationship to the 5-HT_2 receptors: LSD and psilocin are the only drugs of this study that are weak partial agonists at 5-HT_2 (the remainder are full or nearly full agonists (Ray, 2010)), while 5-MeO-DMT is the only drug of the study that has no perceptible affinity for any of the three 5-HT_2 receptors (the concept of perceptibility is described in S02Methods.pdf).

It has been convincingly argued that LSD is an antagonist at 5-HT_2, with no intrinsic activity (Norman, Nash, & Sanberg, 1989; Pierce & Peroutka, 1988, 1990). It has also been argued that LSD is a weak partial agonist at 5-HT_2, producing an activity of about 25% of that produced by

serotonin (Kurrasch-Orbaugh, Watts, Barker, & Nichols, 2003; Pierce & Peroutka, 1990; Sanders-Bush, Burris, & Knoth, 1988), although (Pierce & Peroutka, 1988) suggested that this weak partial agonism measured in brain slices occurred "via a non-5-HT2 receptor-mediated mechanism". It has been shown that when LSD and serotonin are both present, the resulting activity is the low activity (~25%) of LSD alone rather than the full activity (100%) of serotonin (Pierce & Peroutka, 1988; Sanders-Bush et al., 1988). This low level of activity at 5-HT_2 is not typical of psychedelics, and is a feature that sets LSD apart (Kurrasch-Orbaugh et al., 2003; Nichols, 2004; Norman et al., 1989; Pierce & Peroutka, 1988, 1990; Ray, 2010; Sanders-Bush et al., 1988).

The relevant question for the present argument is whether when LSD is given to a human, the 5-HT_2 system is excited or inhibited relative to the un-medicated state. Whether a weak partial agonist excites or inhibits "depends upon the level of ongoing activity within the particular system" (Sanders-Bush et al., 1988) when the drug is applied:

> Thus, depending on the concentration of 5-HT, LSD will have apparently opposite effects on 5-HT-2 receptors, *i.e.*, with a low level of 5-HT, LSD will function as an agonist, because it gives weak, but detectable, receptor stimulation; at higher concentrations of 5-HT, LSD would function as an antagonist because it blocks the effect of 5-HT. (Sanders-Bush et al., 1988)

A series of in vivo assays have shown LSD to be inhibitory to responses understood to be mediated by 5-HT_2: guinea pig trachea contraction, rat uterus smooth muscle contraction, rat paw edema, tryptamine seizures, and head-twitch (reviewed in (Pierce & Peroutka, 1988, 1990)); and human platelet shape change (McClue, Brazell, & Stahl, 1989). There is ample reason to believe that LSD inhibits the 5-HT_2 system in humans relative to the un-medicated state, and this analysis will make that assumption.

Psilocin has also been shown to produce low levels of activity at 5-HT_2 receptors (Table 2):

	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}
psilocybin	31 ± 8%	24%	51 ± 3%
psilocin	43 ± 17%	45%	51 ± 37%

> **Table 2**: Data represent mean functional assay values for activation of phosphoinositide hydrolysis in cells expressing human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptors, relative to serotonin at 100%. When SD is given $N \geq 3$. From (Sard et al., 2005).

The activity of psilocin is higher than that of LSD, but lower than most other psychedelics. We can expect that psilocin may also have an inhibitory effect on 5-HT_2 in humans, but not as strongly as LSD.

Table 3 illustrates that 5-MeO-DMT is in a pharmacological class all by itself, in that it is the only one of the twenty-two drugs to have no perceptible affinity at any of the three 5-HT_2 receptors. Although 5-MeO-DMT has been shown to be a full agonist at 5-HT_{2A} and 5-HT_{2C}

(Ray, 2010), its affinity for all three 5-HT_2 receptors should be imperceptible, and 5-MeO-DMT is the only drug of the study with this quality.

Drug	5ht2max	5ht2a	5ht2c	5ht2b
5-MeO-DMT	1.5480	0.9753	1.5480	0.6895
5-MeO-MIPT	3.3227	2.4383	1.7503	3.3227
DIPT	3.4806	–	–	3.4806
LSD	3.5380	3.5380	3.1053	3.1139
MDMA	3.6429	–	–	3.6429
DOET	3.7222	3.7222	3.1282	3.6990
DPT	3.8792	2.0910	2.3074	3.8792
5-MeO-DIPT	3.9097	–	–	3.9097
DMT	3.9102	2.5760	3.4175	3.9102
MDA	4.0000	–	2.1516	4.0000
TMA	4.0000	–	3.0154	4.0000
Psilocin	4.0000	2.1411	2.5223	4.0000
MEM	4.0000	2.2132	–	4.0000
DOM	4.0000	2.3628	1.4683	4.0000
Aleph-2	4.0000	2.4231	2.5026	4.0000
2C-B-fly	4.0000	2.8898	2.9289	4.0000
2C-T-2	4.0000	3.1772	3.0466	4.0000
DOB	4.0000	3.2275	2.9730	4.0000
TMA-2	4.0000	3.4221	2.5799	4.0000
DOI	4.0000	3.4423	4.0000	3.1347
2C-B	4.0000	3.6894	3.1785	4.0000
2C-E	4.0000	3.7572	3.3822	4.0000

Table 3: The relative affinity at 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}, for the twenty-two drugs assayed at all three. 5ht2max is the maximum value of the relative affinities at the three receptors. Relative affinities below 2 should be imperceptible (the concept of perceptibility is discussed in S02Methods.pdf available with the supporting information). A dash (–) means that the affinity was below the limit of measurement.

LSD and psilocin are outstanding among psychedelics in their low level of activation of the 5-HT_2 receptors (LSD more so than psilocin), and 5-MeO-DMT is unique in that its affinity at the three 5-HT_2 receptors can be expected to be imperceptible. I hypothesize that these are precisely the reasons why these are the only three drugs of this study that are prone to cause ego-loss. –

Although we have good data about the intrinsic activity of these drugs at the 5-HT_2 receptors, it appears that we have little or no data about the activity of the same drugs at the 5-HT_7 receptor. The ego-loss hypothesis suggests that 5-HT_7 is strengthened by these drugs, and I will assume here that these drugs are agonists at 5-HT_7. Thus it is supposed that LSD and psilocin simultaneously strengthen 5-HT_7 while weakening 5-HT_2; and that 5-MeO-DMT strengthens 5-HT_7 while not affecting 5-HT_2.

By considering the 5-HT_2 and 5-HT_7 hypotheses together, we can examine how ego function arises from the interaction of the two mental organs. 5-HT_2 is hypothesized to filter, gate, or mediate access to consciousness via the 5-HT_7 system, which may bestow the property of consciousness on other mental organs. Thus the ability of 5-HT_2 to shape 5-HT_7 depends on the relative strengths of the two systems. If 5-HT_7 is strengthened without simultaneously strengthening 5-HT_2, the ability of 5-HT_2 to perform its 5-HT_7-shaping function diminishes, and can reach a point where 5-HT_7 completely overwhelms 5-HT_2 and the shaping fails altogether. It appears that the egoic sense of self emerges from the *act* of 5-HT_2 shaping consciousness (5-HT_7). As the efficacy of this shaping diminishes, so does the sense of self, and the sense of self melts away when the shaping fails altogether (Figure 11).

We can consider 5-HT_7 consciousness and 5-HT_2 hands of the mind to be in a kind of yin-yang relationship where neither organ makes sense without the other, like the heart and the circulatory system. 5-HT_7 provides mental space, and 5-HT_2 shapes that space. Yet neither provides the content; that comes from the content mental organs which are largely non-serotonin. While content mental organs are numerous, providing the multifaceted view of the world that they render in consciousness, they could be viewed as a single component in a functional trinity, a triangular yin-yang. 5-HT_7 provides mental space, the content mental organs fill that space, and 5-HT_2 gives it all shape.

5-MeO-DMT frequently causes ego-loss (M. W. Ball, 2008; Grof, 2005; Oroc, 2009) and appears to be the drug that most reliably produces the non-dual state. It was recently shown in controlled double blind studies (Griffiths, Richards, Johnson, McCann, & Jesse, 2008; Griffiths, Richards, McCann, & Jesse, 2006) that psilocybin commonly causes "a sense of the unity of all things, a separate 'self' ceasing to exist, and merging and/or an encounter with ultimate reality (or God)." LSD has long been known to be capable of producing ego-loss (Chadwick, 2002; KLEE, 1963; Leary et al., 1964; Marrazzi, Meisch, Pew, & Bieter, 1966; McCabe, 1968; SAVAGE, 1955). Examples of ego-loss with LSD, psilocybin, and 5-MeO-DMT follow.

> **LSD 300 µg**: I experienced feelings of basic identity and oneness with the universe; it was the Tao, the Beyond that is Within, the *Tat tvam asi* (Thou art That) of the Upanishads. I lost my sense of individuality; my ego dissolved, and I became all of existence. Sometimes this experience was intangible and contentless, sometimes it was accompanied by many beautiful visions – archetypal images of Paradise, the ultimate cornucopia, golden age, or virginal nature. I became fish swilling in crystal-clear waters, butterflies floating in mountain meadows, and seagulls gliding by the ocean. I *was* the ocean, animals, plants, the clouds – sometimes all these at the same time. (Grof, 1975) p. 114

Verbatim written comments from ten of the 24 psilocybin volunteers who rated the experience at the 14-month follow-up as being among the top five (including the single most) spiritual experiences of their lives, out of a total of 36 volunteers (Griffiths et al., 2008):

> **Psilocybin**:
> Freedom from every conceivable thing including time, space, relationships, self, etc… It was as if the embodied 'me' experienced ultimate transcendence – even of myself.

A non-self self held/suspended in an almost tactile field of light.
The utter joy and freedom of letting go – without anxiety – without direction – beyond ego self
Collapse of ordinary space and time sense. Realization of unity of existence and relativity of ordinary consciousness…
The sense that all is One, that I experienced the essence of the Universe
To cease to 'BE', as I understand it, was not frightening. It was safe and much greater than I have words for or understanding of. Whatever is larger than the state of being is what was holding me.
The feeling of no boundaries – where I didn't know where I ended and my surroundings began. Somehow I was able to comprehend what oneness is.
The breath of God/wind/and my breath are all the same…
The part that continues to stick out for me was 'knowing' and 'seeing' and 'experiencing' with every sense and fiber of my being that all things are connected.
The complete and utter loss of self… The sense of unity was awesome…
(Griffiths et al., 2008)

5-MeO-DMT 15-20 mg: the best way that I can describe it would be this ultimate expansion. And in its expansion, there was the dissolution of any sense of past, or future, and these concepts of past and future just dissolved away, into what can only be described as the eternal present, the absolute being of this moment, without any past and without any future. And within that there was also the complete dissolution of any sense of personal ego, or identity, or sense of self, so that there was only the awareness of this pure present moment. There was no self there, it was just the awareness of the moment itself. And that moment, that absolute moment, without any past and without any future, really I can only describe, as, pure consciousness, pure being, pure love, and absolute acceptance of all things. (M.W. Ball, 2008) 26':40"

5-MeO-DMT ~20 mg: It seemed to be pure consciousness, intelligence, and creative energy transcending all polarities. It was infinite and finite, divine and demonic, terrifying and ecstatic, creative and destructive—all that and much more. I had no concept, no categories for what I was witnessing. I could not maintain a sense of separate existence in the face of such a force. My ordinary identity was shattered and dissolved; I became one with the Source. (Grof, 2005) p. 254-255

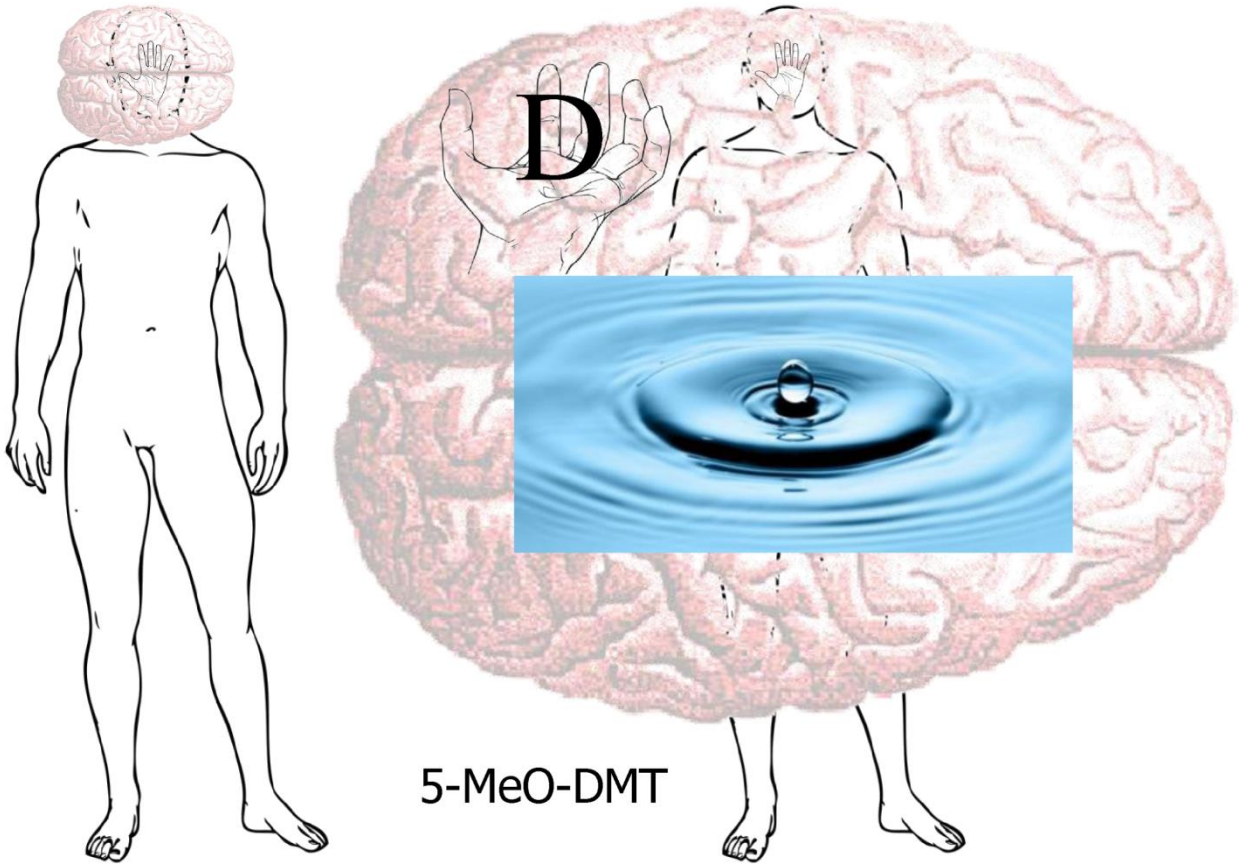

Figure 11: Ego-loss due to 5-MeO-DMT. On the left we see the un-medicated mind represented in its unexpanded state. The hands of the mind mediated by 5-HT_2 are illustrated in the mind icon by the open hand. On the right, 5-MeO-DMT strongly activates 5-HT_7, but does not activate 5-HT_2. Thus we see the mind icon (the pink brain) greatly expanded, yet the open hand representing 5-HT_2 is unchanged. This is likely to produce a state of ego-loss, represented by a drop in the ocean. 5-MeO-DMT weakly activates D_1 (relative affinity of 2.38), thus at very high doses we can expect D_1 to also be loaded into consciousness, represented by the letter D held in the upturned hand. Open hand by PETROO / Shutterstock.com, upturned hand by Luis M. Seco / Shutterstock.com, drop of water by Aleksandra Pikalova / Shutterstock.com.

LSD, psilocin, and 5-MeO-DMT are prone to cause ego-loss, to varying degrees. All the other drugs of this study strengthen 5-HT_2, and thus even those that that simultaneously act at 5-HT_7 strongly enough to cause crossing-over are not likely to cause ego-loss. Consider the case of DMT, which when taken at high doses normally causes the subject to experience a complete alternate reality, yet the ego is retained even under such extreme conditions:

> During a 5-MeO-DMT experience, I am able to experience "consciousness without identity," and I neither remember smoking the 5-MeO-DMT, nor have any sense of who "I" am. The "I" in me ceases to exist, now a part of something greater. With DMT, I generally retain knowledge of who I am and what I have done. (Oroc, 2009) p. 80

> **DMT**: There was no transcendence of the ego, which remained perfectly intact throughout the journey. There was no dissolution. In fact, I was fully "there" and completely "sober" the entire time, despite the overwhelming onslaught of psychedelic energy and visuals. (M. W. Ball, 2008) p. 193

> **DMT**: it has the quality of an event because it does not touch the core observer. You are not changed. What's changed, is the sensory input is changed. You are still who you are. You don't think you're god. You don't feel bad about yourself. You are exactly who you were before you did it, with the same set of concerns, *but* you have been whisked into an alien dimension, one you never had imagined existed, or could have, a moment before have conceived of, and suddenly its one hundred percent in place, three hundred and sixty degrees around you. (McKenna, 2009) 1hr:10':18"

The descriptions in (Strassman, 2001; Strassman et al., 2008) of "entities" clearly show a presence of the subject, who is interacting with the entities. Note the references to "me" and "I":

> **DMT**: There were four to five of them, and they were on me fast. As crazy as this sounds, they looked like saguaro cactuses, flexible, fluid, geometric, green. Not solid. They weren't benevolent, but they weren't nonbenevolent. They probed, really probed. They seemed to know time was limited. They wanted to know what I, this being who had shown up, was doing. I didn't answer. They knew… (Strassman et al., 2008) p. 68

McKenna describes entities who greet *him* when he arrives, encourage *him* to visit more often, offer *him* objects, jump into *his* chest, urge *him* not to be astonished, and encourage *him* to do as they do. All of this clearly indicates the presence of an "I". I have added italics to emphasize references to the presence of the self:

> **DMT**: Self transforming machine elves, I call these things… And they come pounding forward like badly trained dogs, cheering. They say "here *you* are!" … And one of the things they do that's quite disconcerting, is they come jumping up or dribbling up to *you*, and then they will sort of vibrate in place, then they jump into *your* chest, then they jump back out… They will scramble forward, elbowing each other, jumping up and down, very excited, and they say [to *you*] "look at this, look at this", and they pull objects, sing objects into existence, and show them to *you*, and as *your* attention goes into these things, *you* are, it's the emotion is indescribable… And they're pushing each other away, saying [to *you*] "look at this one, look at this one." … Naturally, the fact that *you're* having this experience raises certain fundamental questions, such as "am *I* dead now, is that what's happened?" And the entities say, they say [to *you*], "Don't give way to amazement. Don't flip out about how *you* can't believe it and its impossible and so forth, and so on, don't [*you*] do that. Just [*you*] pay attention, pay attention to what we are doing, and what we are showing *you*." And what they preach is a new dispensation of language. A language that can be beheld. And as *you* sit there *you* feel like a bubble form in *your* stomach and begin to make its way to *your* mouth, and when it comes out as a kind of a glossolalia, *you* discover that in that space *you* too can make jeweled objects with spinning interiors and reflexively rotating sub-themes and so forth and so on. (McKenna, 2008) 57':57"

In his May 25 2015 video Strassman authoritatively states that DMT does not produce a mystical, unitive experience:

> In Zen, the goal of meditation is the enlightenment experience, kensho, or nirvana. This is what I refer to as a mystical, unitive experience. The state attained by the historical Buddha, and the benchmark spiritual experience sought by all serious practitioners, is characterized by the term "emptiness". Although this does not adequately capture all of the nuances involved with the term. Nevertheless, the state can be characterized as being formless, non-verbal, content-free, where personal identity is negated, in a merging with the ground of being. This was the peak experience that I was expecting my volunteers to encounter. And it was also their goal, since the majority were practitioners of various types of meditation…
> A common experience reported by the volunteers was encountering beings. These were more or less recognizable sentient things, with whom the volunteers' awareness interacted. They took the shape of humans, humanoids, machines, mammals, birds, reptiles, insects, plants, and less recognizable objects, such as furniture, or even sensed in the geometric kaleidoscopic patterns that the volunteer beheld.
> Volunteers maintained a sense of their own personal individual consciousness, and willfully interacted with these beings. In the relationship, instances of dialog, healing, threat, education, predicting, and so on took place. Only one typical, formless, enlightenment-like experience happened in the course of my study. Thus the DMT state differed from the unitive mystical state in that it was what I call "interactive relational"…
> Thus the experience of the volunteers was distinct from the formless, ego-free, enlightenment experience that both they and I had expected. It was interactive and relational, not mystical and unitive…
> While Buddhism provided a valuable set of tools for my research, I found it less useful in its approach to the basic unreality of the worlds revealed by DMT, as well as the benchmark experience of Buddhism, the mystical unitive and enlightenment experience, differing so much from the interactive, relational, DMT state. (Strassman, 2015)

Although 5-MeO-DMT is likely the drug that most reliably produces the non-dual state, it is not guaranteed to do so. We can see a clear presence of the self in this report by Ralph Metzner, which illustrates both the subjectively intense energy and brutality that this drug is capable of:

> A shattering annihilation, a feeling of being inside a nuclear explosion, being fragmented into countless tiny shards. I felt as though I was being turned inside out, like my innards were extruding through my mouth. My body was rolling on the ground, coiled into a ball, like the urobouros serpent circle…
> Images of decapitation, dismemberment, disembowelment flashed by, in rapid succession, including an image of being run through the chest with a sword (Metzner, 2004), p. 191-192

In summary, the hypothesis is that ego emerges from the *act* of 5-HT_2 shaping 5-HT_7; the ego is lost when the ability to shape is overwhelmed because 5-HT_7 is strengthened without

strengthening 5-HT_2, which occurs with LSD, psilocin, and 5-MeO-DMT; and the ego is retained when 5-HT_2 is strengthened, as occurs with all other drugs of this study, including DMT.

Beyond the Trinity, the Core

Over the course of discussion of ego-loss, I have made reference to a functional trinity, a triangular yin-yang: 5-HT_7 provides mental space, the content mental organs fill that space, and 5-HT_2 gives it all shape. While these are the three functional groups of mental organs that this manuscript focuses on, it would be misleading not to mention that they do not constitute the whole of the mind, or even all the major components. Cannabis has been mentioned in some experience reports, but I have not explained the important role of the cannabinoid mental organ. Kappa is important but has been mentioned only in passing. I will discuss dopamine near the end of the manuscript. There are many mental organs whose roles remain unknown.

I must at least briefly discuss sigma, which appears to be the core of our being, around which all other mental organs constellate. Sigma may have been the primordial mental organ from which all others differentiated. Various authors have acknowledged this component of the psyche, although they have not associated it with sigma. Sarno (Sarno, 2006) called it the unconscious, Jung (Hall & Nordby, 1973) called it the shadow, Freud (Freud, 1962) called it the id, and Tolle (Tolle, 2005) called it the pain body.

These accounts of facets of sigma are based on introspection or psychological observations of others, a method that involves discerning "components of the psyche whose discreteness is normally obscured by their being embedded in the complete tapestry of the mind" (Ray, 2012). They have made their observation without the benefit of pharmacological probes that, "By activating specific components of the mind, they are made to stand out against the background of the remainder of the psyche. Thus both their discreteness and their specific contribution to the psychic whole can be better appreciated" (Ray, 2012). The drug-free approach to discerning mental architecture is much more difficult, and less likely to clearly distinguish the various components of the psyche and their various facets and interactions.

The introspective/psychological observations often emphasize the dark side of sigma; yet sigma has profoundly positive aspects that are apparent on deeper examination. Jung also makes reference to a "self" which appears to represent a very positive facet of sigma. The preponderance of darkness associated with sigma may flow from its suppression; healing may flow from reintegration with sigma.

Ibogaine is the most revealing sigma drug, and sigma plays a central role in the DMT/ayahuasca experience. Descriptions of experiences of sigma drugs such as ibogaine or DMT commonly make reference to a "plant intelligence" that, among other things, may show the user what they need to see. This plant intelligence is likely sigma. Studies of regular ayahuasca users have shown:

> Ayahuasca users whom UCLA's Grob has researched in other countries "have become better partners to their spouses, better parents to their children, better children to *their*

> parents, better employees, better employers, just more responsible overall, bringing a higher level of ethical integrity to everything they do," he says. (McClelland, 2017)

This ethical integrity likely emerges from reintegration with sigma. It is a central tenet of Jungian psychodynamics, that bringing the shadow/self (sigma) fully into consciousness yields a more healthy state characterized by greater harmony with one's self and other persons, and possessed of greater liveliness, spontaneity, insight, and creativity. This is likely part of the mechanism by which ayahuasca produces the benefits described by Grob.

In the context of ego-loss, I am reminded of these descriptions:

> **LSD overview**: The sense of self or personal ego is utterly lost. Awareness of individual identity evaporates. "I" and "me" are no more. Subject-object relationships dissolve, and the world is simply an extension of the body, or the mind. The world shimmers, as if it were charged with a high-voltage current, and the subject feels he could melt into walls, trees, other persons. It is not that the world lacks substance; it is real, but one is somehow coterminous with it. And it is fluid, shifting. One is keenly aware of the atomic substructure of reality…
> As for identity, it is not really lost. On the contrary, it is found; it is expanded to include all that is seen and all that is not seen. What occurs is simply depersonalization. The subject looks back on his pre-drug existence as some sort of game or make-believe in which, for some reason, he had felt called upon to assume the reduced identity or smaller self called "I." Being had concentrated its attention at a single point in order to create, and play, the game of writer, banker, or cat burglar. Or so it now seems… Home at last, after that dreadful party, Being slips out of her stays, so to speak, and breathes an ontological sigh of celestial relief. Consciousness is allowed to scatter, and the subject at last can be Himself again.
> The subject is somehow united with the Ground of his Being, with the life force that has created the visible world. He *remembers*. And what he remembers is the true identity that underlies all the individual egos of the world. He is one again with the universe, the eternal, the Absolute.
> He has found himself again. He is made whole again. That which he once knew, he has remembered. (Braden, 1967) p. 14-16

> Descriptions of cosmic unity are usually full of paradoxes violating the basic laws and the very essence of Aristotelian logic. An individual can, for example, talk about this experience as being contentless and yet all-containing; everything that he can possibly conceive seems to be included. He refers to a complete loss of his ego and yet states that this consciousness has expanded to encompass the whole universe. He feels awed, humbled, and utterly insignificant but, at the same time, has the feeling of an enormous achievement and experiences himself in cosmic proportions, sometimes to the extent of feeling identified with God. (Grof, 1975) p. 105-106

In this section I have presented various descriptions of the loss of the egoic sense of self, which I associate with 5-HT_2. However, the human sense of self is more complex than the 5-HT_2 ego alone. Sigma appears to provide a more fundamental and archaic sense of self, which may

survive the pharmaceutical manipulations in which 5-HT_7 overwhelms 5-HT_2. This sense of self mediated by sigma may be close to the "ground of being" or "absolute" mentioned in the preceding descriptions of ego-loss. We may retain the sigma self when the 5-HT_2 ego is stripped away.

Anything said about the relationships between sigma and the trinity would be very speculative, but let me start the conversation. It appears that 5-HT_7 unites and energizes the theatre of consciousness, and the 5-HT_2 hands of the mind shape the products of the content mental organs (mostly non-5-HT) in 5-HT_7 consciousness. Sigma then experiences the conscious products of the trinity. The hands of the mind may also have a protective role for sigma, which is quite sensitive to pleasure and pain. When 5-HT_2 is stripped away in ego-loss, the sigma core becomes vulnerable to trauma, whether ecstatic or hideous. This can happen when 5-MeO-DMT is taken at high doses. Masters (Masters, 2005) wrote a book about it, Oroc (Oroc, 2009) devotes an appendix to it, and the Erowids have commented:

> The primary health risks associated with the use of 5-MeO-DMT are mental health problems, like lasting Post Traumatic Stress Disorder (PTSD)-type reactions where people feel shocked for days, weeks, months, or years after their last use. (Erowid, 2016)

Open Eyed Visuals

There are a wide range of effects produced by 5-HT_7 (serotonin-7ization), but most of them tend not to be consistently well articulated in subjective reports. Visual effects are the most likely to be well represented in reports, and they can be used as a primary means of discriminating breadth from depth. The easiest way to detect expansion of depth of consciousness from subjective reports is through its distinctive creative open-eyed visual effects. But there are also dramatic visual effects that emerge from expansion of breadth of consciousness, and it is essential to be able to distinguish the two. Drugs acting through many mental organs cause closed-eyed visuals, and I have not sorted out how these vary depending on mental organs. Here we will only consider open-eyed visuals:

- Simple Visuals: apparently through non-5-HT_7 mental organs
    - Clarity of vision
    - Heightening of colors
    - Enhanced perception of shades of color
    - Objects seen to be glowing with an inner light
    - Profound sense of beauty
    - A sense of movement in objects
    - Simple distortion
- Creative Visuals: apparently through 5-HT_7 combined with non-5-HT mental organs
    - Patterning laid over the visual field
    - Creative transformation of objects in the visual field
    - Seeing objects or scenes that are not there
    - Seeing a completely constructed world, an alternate reality

Creative Visuals through Expansion of Breadth and Depth

We will look at a series of examples of visual effects from drugs with moderate or strong relative affinities for 5-HT_7 (DMT, TMA, 5-MeO-MIPT, LSD, 5-MeO-DMT, DPT, 5-MeO-DIPT, Psilocin, 2C-B, 2C-E; listed in order of decreasing relative affinity for 5-HT_7), beginning with 2C-E. 2C-E combines moderate affinity for 5-HT_7 with strong and moderate affinity at the three alpha-2 receptors, as well as weak relative affinity at D_3 which should be perceptible only at higher doses:

> **2C-E 20 mg**: When I lay on my bed, I saw myself as an old, old man, many years in the future. I was appalled to see my forearm as a withered, dry-skinned, almost-bone which could only be that of someone dying. I looked down at the rest of me, and I was thin, emaciated, brittle, shallow. (Shulgin & Shulgin, 1991) p. 94

> **2C-E 25 mg**: I have a picture in my living room that is a stylized German scene with a man on horseback riding through the woods, and a young girl coming out to meet him from the nearby trees. But she was not just 'coming out.' He was not just riding through the woods. The wind was blowing, and his horse was at full gallop, and his cape was flapping in the storm, and she was bearing down upon him at full bore. The action never ceased. I became exhausted. (Shulgin & Shulgin, 1991) p. 518

We can see this creative extension of reality taken even further with LSD which has strong relative affinity for 5-HT_7, as well as moderate affinity at alpha-2A, and moderate and weak relative affinity at the five dopamine receptors:

> **LSD 225 µg**, subject on the street in Greenwich Village, NYC: People continued to stream towards us and past us. I focused on an old lady in her late seventies, a dowdy pathetic creature dressed in shabby black and carrying impossibly huge shopping bags. As she made her way heavily towards us I saw, no longer much to my astonishment, that she began to lose years. I saw her as an Italian matriarch in her sixties, then in her fifties. As she continued to bloom backwards in time, she entered her portly forties and, after that, her housewifely thirties. Her face softened, her body grew more shapely, and still the years kept on dropping away. In her twenties she was carrying a child, and then she was a bride and carried orange blossoms. A moment later and she was a child who, in turn, shrank into a newborn baby carried by a midwife. The baby's umbilical cord was still intact and it let out a howl of awakening life. But then the process was reversed and the baby grew back into childhood, became again a bride, passed through her thirties, forties, fifties, sixties, and was the old lady in her seventies I had seen at the beginning. The old woman blinked, her eyes closed for a fraction of a second, and in that instant I clearly saw her death mask. She passed us by and had moved a little down the street when I heard from the direction she had come a baby's howl of awakening life. I turned my head, expecting to perceive afresh Our Lady of the Eternal Return, but saw instead the vortex of a crowd. (Masters & Houston, 1966) p. 23

This going beyond reality culminates in DMT which transports the subject to a complete alternate reality. DMT is the only drug of this study for which 5-HT_7 is the best hit. At the same

time, DMT has the greatest breadth of receptor interaction of the drugs of this study. DMT combines the greatest breadth with the greatest depth of consciousness expansion of the drugs of this study, Figure 2, Table 1.

> **DMT**: … an infinite hive. There were insectlike intelligences everywhere, in a hypertechnological space. I felt wet stuff hitting me all over my body. They were dripping stuff on me. They wanted me to join them, to stay with them. I was tempted. I was looking down a corridor that was stretching out forever. I lost awareness for a moment, then I found myself in that hive. There was another one helping me—different from the previous helper. It was very intelligent. It wasn't at all humanoid. It wasn't a bee, but it seemed like one. It was showing me around the hive. It was extremely friendly and I felt a warm, sensual energy radiating throughout the hive. It said to me [that] this was where our future lay. (Strassman et al., 2008) pp. 70

The visual effects of full doses of 2C-E, LSD, and DMT cited above, represent moderate to strong activation of 5-HT_7 together with other (non-serotonin) receptors. At lower doses, such drugs produce less dramatic visuals, such as patterning laid over the visual field. The following quote describes how the visual effects increase with dose for psilocybin mushrooms, which combines moderate relative affinity at 5-HT_7 and D_3 with strong relative affinity at D_1:

> **Psilocybin mushrooms**: At very low doses, the visual effects of mushrooms are very subtle. Colors become more vivid and light takes on a luminous, ethereal quality. Slight distortions in the visual field present themselves, but only subtly.
> As the dosage and strength of the mushrooms increase, so do the visual effects. At slightly higher doses, patterns begin to appear on the surface of objects. When these effects first start to come on, I usually find myself thinking that the "mystic lizards" are here, given that the patterns the visuals create are very similar to M. C. Escher artwork of entwined lizards or other repeating patterns. Objects also begin to visually flow and melt with movement being the most defining characteristic of these visuals. All the world becomes movement, change, and flow. Light becomes extremely beautiful at this point and can be endlessly engrossing.
> At still higher doses and potency the visuals become even stronger. Patterns of flow, movement, and change are no longer confined to the surface of objects, but can fill all of the visual space of a person's perception. Empty rooms become filled with intricate lattices of undulating geometric patterns. The sky appears filled with energy currents and the depths of the heavens take on the appearance of magnificent architecture. Kaleidoscopic and Mandala-like images abound.
> At these doses, it is common to perceive oneself as embodied in these different patterns as the normal sense of one's physical body is transcended. Spiritual explorers may feel themselves as geometric shapes filling a room or extending on out into space. Scenes may also begin to unfold in these visions, complete with characters, architecture, and other places and other times. The geometric forms can also coalesce into definite figures or personas that may interact with the visionary or may present a form of communication.
> At the highest doses, the physical world melts away and one becomes completely immersed in the visionary world of the mushrooms. Profound states of consciousness are reached therein and revelations and awakenings are common. Deep levels of

> synaesthesia are also reached where sounds, colors, smells, movements, and all the senses cross over into each other, opening the visionary up to radically altered ways of experiencing and appreciating the senses and their methods of processing information. The visual aspects of mushrooms are beautiful and can be infinitely engrossing. They fill the world with a profound sense of wonder and awe, revealing the magic and mystery that embraces all things. Nature takes on a deep living quality and all things are perceived as expressive, alive, and intelligent. It is a true opening to the mystical powers of the mind and human awareness. (Ball, 2006) p. 31-33

Seeing objects or scenes that are not there normally occurs with eyes closed, in the dark, in loss of contact with reality, or on a blank canvas such as an undecorated ceiling or wall:

> **LSD 225 µg**: I lay on my back and looked up at the ceiling where a kaleidoscope of images from ancient civilizations flickered rapidly before my eyes. Egypt and Greece, Assyria and old China sped across the ceiling. Flickering pharaohs, fluttering parthenons and palpitating Nebuchadnezzar – all contributed to this panoramic, historical agitation. (Masters & Houston, 1966) p. 20

It may also occur as a transformation of a patterned surface:

> **LSD 250 µg**: S is told to look at the flowered fabric of the couch on which he is sitting and to relate what he sees there. He perceives a great number of faces and scenes, each of them belonging to a different environment and to a variety of times: some to the American Gay Nineties, some to the nineteen twenties, some later. There are Tolouse Lautrec café figures, Berlin nightlife scenes and German art from the late twenties and mid thirties. Here and there, a "Black Art" appears and he recognizes the work of Felicien Rops and drawings like those of the artist who has illustrated Michelet's *Satanism and Witchcraft*. There are various Modigliani figures, a woman carrying a harpoon, and persons such as appear in the classical Spanish art of the seventeenth century. Most interesting to him are "paintings" like those of Hieronymus Bosch, and he describes a great complex of sprawling yet minutely detailed figures which combine to make up a larger complex of a mountain scene of trees and snow. In another variation, this same complex consists of "a great face with the trunk of an elephant that is blowing liquid on the face of a demon whose body has been trampled into the ground. The elephant is blowing liquid on the face of the demon either in an attempt to revive him or as a gesture of contempt. A Herculean male figure rises next to the elephantine face. He is trapped to the waist in stone and this marbled stone looks like sea foam, it is so delicate and lacy. Everything blends into everything else. The Herculean figure is also the ear of a face and the elephant-like trunk is the bridge of the nose of another larger, still more complicated figure. (Masters & Houston, 1966) p. 27-28

Seeing objects that are not there with open eyes, woven into a well-lit complex visual scene is extremely rare. One convincing example involves a four year old boy who ate a sugar cube he found in the refrigerator:

> **LSD 250 µg**: S continued intermittently to see crabs and lobsters coming out of the walls and crawling across the floor towards him…
> S also hallucinated a whole array of "monsters" – apparently creatures such as elves, dwarfs, and other small, deformed human-like beings. Fearful at first, he gained confidence when his mother encouraged him to "make friends with the monsters" … After some of his anxieties were disposed of, several of the "monsters" came and sat on S's knees and in the palm of his hand and he talked with them. Others danced around him and made faces. (Masters & Houston, 1966) p. 172-173

Simple Visuals without Depth

Now that we have seen the dramatic visual effects associated with simultaneous expansion of both breadth and depth of consciousness, we will contrast those effects with drugs that have weak or imperceptible relative affinity for 5-HT_7 (DIPT, MDA, DOET, MEM, DOI, DOB, DOM, 2C-T-2, 2C-B-fly, Aleph-2, MDMA, TMA-2; listed in order of decreasing relative affinity for 5-HT_7), and thus do not expand depth of consciousness. Most but not all of these drugs expand breadth of consciousness. The visual effects produced by non-5-HT_7 mental organs consist either of a profound visual experience of the world as it is, or minor visual distortions such as a sense of movement or changes of perspective or proportion. I will cite examples of each of these effects:

- Clarity of vision
- Heightening of colors

> **MEM 30 mg**: There were visual phenomena, with some color enhancement and especially a considerable enhancement of brights and darks. (Shulgin & Shulgin, 1991) p. 767
>
> **MEM**: In a study employing nine subjects with dosages ranging from 15 to 40 mg, there were consistent reports of color intensification... (Shulgin, 1978) p. 300
>
> **DOB 0.4 mg**: There was a distinct enhancement of visual perception, and some strengthening of colors. (Shulgin & Shulgin, 1991) p. 620
>
> **DOET 2 mg**: There seemed to be more definition and more distinctness about things in my visual field. Lights seemed to be brighter. (Snyder et al., 1974)
>
> **DOET 6 mg**: Everything I smelled was vivid, as are all the colors and shapes; they are clean, beautiful, serenely self-contained. No visual movement. (Shulgin & Shulgin, 1991) p. 632

- Enhanced perception of shades of color
- Objects seen to be glowing with an inner light
- Profound sense of beauty

MDMA 120 mg: The woodpile is so beautiful, about all the joy and beauty that I can stand. I am afraid to turn around and face the mountains, for fear they will overpower me. But I did look, and I am astounded. Everyone must get to experience a profound state like this. I feel totally peaceful. I have lived all my life to get here, and I feel I have come home. I am complete. (Shulgin & Shulgin, 1991) p. 737

TMA-2: The central, sensory changes appear in the second hour and are characterized by some exaggeration of visual input (especially in the appreciation of colors and contrasts of lighting) and of empathy with irrational objects in one's environment. These preludes lead to a plateau, from three to about six hours following administration, which is an impressive altered state of consciousness virtually free of the distortions and portentousness so common with LSD. (Shulgin, 1976)

TMA-2, 27 mg: Then we saw flowers. The flowers have amazing beauty and presence. They were very gentle. I could connect with them very easily, feeling the flowers and the flowerness, the being. (Shulgin, 2016) Pharm 1, p. 199

TMA-2, 32 mg: I looked at flowers, and saw them with all the beauty and connection that comes with mescaline, DOM, or DOI, though it seemed to have a more earthy quality. (Shulgin, 2016) Pharm 1, p. 199

DOM 4 mg: I saw the clouds towards the west. THE CLOUDS!!! No visual experience has ever been like this. The meaning of color has just changed completely, there are pulsations, and pastels are extremely pastel. And now the oranges are coming into play. It is a beautiful experience. (Shulgin & Shulgin, 1991) p. 639

DOM 8 mg: Then I looked at the flowers. The flowers had that inner glow, shimmering, and I could also sense that the fragrance was seeping from their inside. They were so un-intrusive, so modest. As long as we paid attention to them, they showed their beauty and life to us. They were the most beautiful flowers I have ever seen. (Shulgin, 2016) Pharm 1, p. 135

R-DOI 2.2 (±0.2) mg: [cited in the description of alpha-2 in the section **Cognitive & Affective**] (Shulgin, 2016) Pharm 1, p. 40

- A sense of movement in objects

Aleph-2, 4 mg: The usual color perception was not very much increased, and my vision was not sharpened as it was with DOM. Rather, I noticed waves of movement, very smooth and not too busy. Both my tactile perception and auditory acuity were enhanced. (Shulgin & Shulgin, 1991) p. 465

Aleph-2, 5 mg: There's an awful lot of visual stuff; the ivy is wiggling non-stop. I wouldn't mind a five-minute breather from it all… About as plus-three as you can get, and even with eyes closed, I couldn't escape the movement. You know how I love

visuals, usually, but these were so powerful, I was almost seasick! (Shulgin & Shulgin, 1991) p. 210-217

Aleph-2, 5 mg: This turned out to be a day of extraordinary visuals and interpretations. About two hours into it, I felt that the effects were still climbing, but there was a marvelous onset of visual distortions and illusions, right at the edge of hallucination. The logs in the fireplace were in continuous motion. The notepaper I was writing on seemed to scrunch and deform under the pressure of the pen. Nothing would stay still; everything was always moving. (Shulgin & Shulgin, 1991) p. 465

DOET 2.5 mg: There is much, too much, movement with my eyes closed. And an awful lot there with my eyes open. The movement on the concrete floor in the basement when I went downstairs for wood for the fireplace, was too much. I felt almost sea-sick. (Shulgin & Shulgin, 1991) p. 632

DOET 6.0 mg: Rotate K.R. flask without touching it. Hose on patio can be twisted at will, mentally. (Shulgin, 2017) p. 213

MEM: In a study employing nine subjects with dosages ranging from 15 to 40 mg, there were consistent reports of color intensification, wavering and flickering in the visual field, and a relatively long-lasting euphoria. (Shulgin, 1978) p. 300

DOB 3.0 mg: Everything around me was dancing a little at the edges and flowing in the center… (Shulgin & Shulgin, 1991) p. 293

- Simple distortion

R-DOI 2.2 (±0.2) mg: I also feel the space is different. It might be because I have a different sensitivity with the light and shade. The hall felt narrower. The diagonal distance between me standing beside the microwave oven to the far corner of the dining room is longer than usual. When I look at the wall, the wall is actually not totally even, if I looked at it long enough, it began to float, some images would come out, and they are moving. I glanced at a magazine, the characters were higher than the page, they are 3-dimensional with their shade. (Shulgin, 2016) Pharm 1, p. 40

MDMA did not produce hallucinations, but instead, its effects were typically described as an intensification of sensory perception ("colors were more intense," "objects appeared more detailed," etc.) and visual illusions (3-dimensional vision of flat objects, micropsia, and macropsia, etc.). (Vollenweider, Gamma, Liechti, & Huber, 1998)

These are deeply moving, profound, fully psychedelic experiences, resulting from expansion of the breadth of consciousness, without expansion of depth. The visual effects are dramatic, but they are qualitatively very different from the creative visual effects associated with depth of consciousness. Drugs such as mescaline, DOM, and DOI have been universally described as hallucinogenic, but their open eyed visual effects are characteristic of the expansion of breadth,

not depth of consciousness. The term "hallucinogenic" has not historically discriminated between simple and creative visuals.

As stated above, consciousness expansion through breadth (non-5-HT mental organs) can provide a more profound and multifaceted experience of actual reality, that which actually exists, internally or externally; while consciousness expansion through depth (5-HT_7) adds the spark of creativity, and allows us to go beyond actual reality, using our imagination, our creative capacity, to add to actual reality. This distinction underlies the difference between creative visuals and simple visuals.

Creative Visuals Require Breadth and Depth

Among the drugs of this study, the kind of creative embellishment of reality illustrated above for expansion of depth of consciousness does not occur in the absence of moderate to strong affinity for 5-HT_7. However, affinity for 5-HT_7 alone is not sufficient to produce this creative effect: it requires simultaneous affinity for non-serotonin receptors; it requires breadth with depth. The creative embellishment of reality emerges out of the interaction between 5-HT_7 and non-5-HT mental organs.

This can be seen by comparing drugs in the different regions of Figure 2. DMT in the upper right corner has the greatest breadth of interaction with all mental organs, combined with the greatest depth (Figure 2, Table 1) and is wildly visual (examples quoted above from (Strassman, 2001; Strassman et al., 2008) (McKenna, 2008) (McKenna, 2009)). Some have stated that DMT is the most visual psychedelic drug (Turner, 1994) p. 55. DMT is able to create an alternate reality that challenges the subject's concepts of reality (Meyer, 1992) (Rodriguez, 2007) (Strassman, 2007). In order to construct a convincing alternate reality, we need many content mental organs in consciousness, to assemble enough facets to render a credible reality, Figure 12. This alternate reality may seem "realer than real" because our ordinary consciousness is likely assembled from fewer facets (fewer content mental organs). By having the greatest breadth, DMT is the drug of this study that comes closest to manifesting the "full bouquet" of mental organs in consciousness:

> We now have the potential to experience the blooming of the full bouquet of mental organs, resulting in the realization of our full human potential... This full bouquet of mental organs is what is great in us. This is our humanity, this is our evolutionary heritage. This is what makes us rich. It should be cultivated in its wholeness, not only narrowly selected parts of it, chosen by the historical accident of our birth into a particular religious, philosophical, secular, or ethnic tradition.
> Recognizing and valuing the full bouquet has the potential, at least theoretically, to unify the competing traditions, by showing the contribution of each one to the richness of the human spirit. We see how taken together, they form the beautiful bouquet of the human heart, mind, soul, and spirit. Each mental organ is like a unique flower, contributing to the floral arrangement that evolution has left us, here a rose, there an iris, and there a daisy… Only when all are taken together are we *fully* human. (Ray, 2012)

This fully human state should be found this side of the veil.

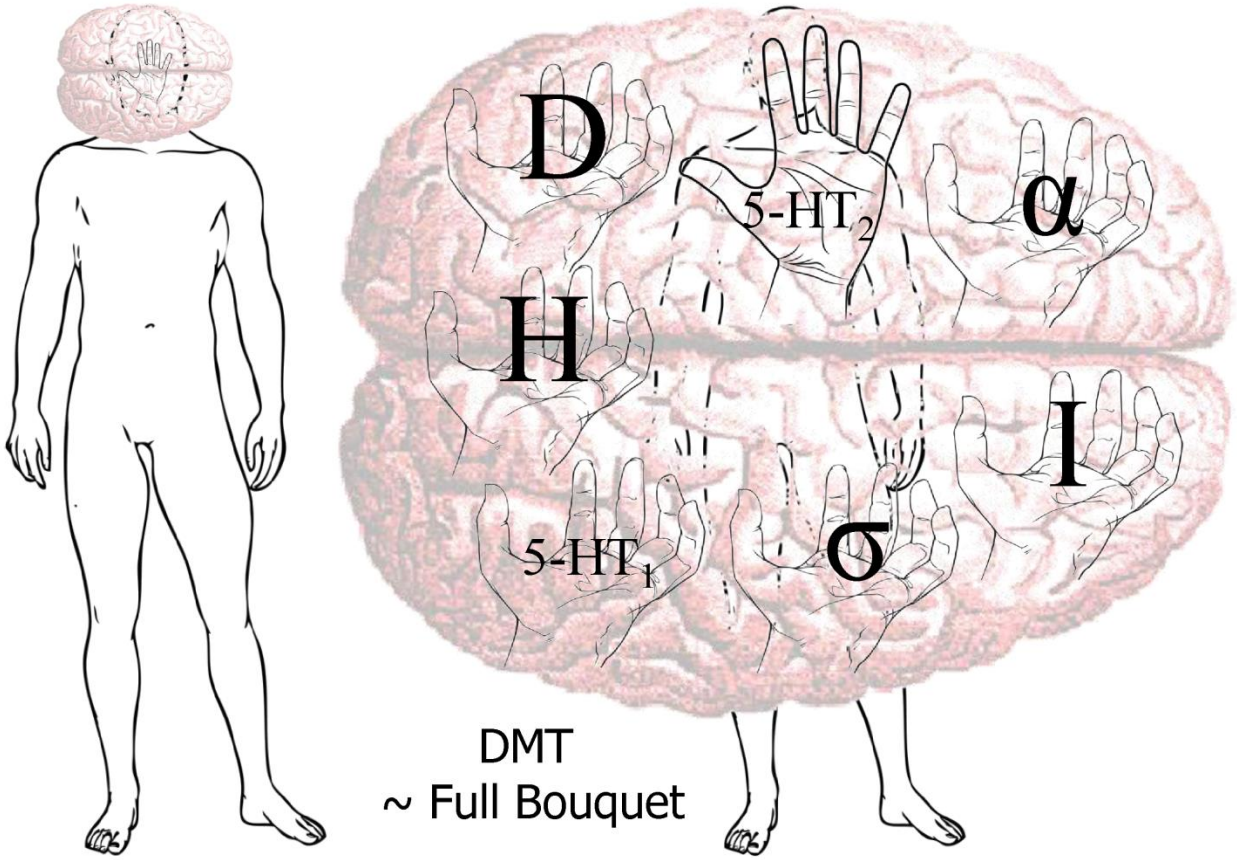

Figure 12. DMT and the full bouquet – DMT is the drug of the study that simultaneously produces the greatest expansion of both breadth and depth of consciousness. DMT most fully interacts with the greatest number of mental organs. On the left, the un-medicated state, manifesting the gatekeeper. On the right, expansion of depth of consciousness, 5-HT_7, represented by enlargement of the mind icon (pink brain) relative to the body. DMT has perceptible affinity for: 5-HT_7, 5-HT_{1D}, 5-HT_{2B}, alpha-2B, alpha-2C, D_1, 5-HT_{2C}, 5-HT_{1E}, Imidazoline-1, alpha1B, alpha2A, alpha1A, 5-HT_{2A}, and sigma-1 (in decreasing order of relative affinity), and likely histamine-1 (which was not assayed). The gatekeeper hand, 5-HT_2, is drawn as enlarged, and prevents ego-loss. The activation of the various categories of mental organs is illustrated by their corresponding icons being held in consciousness in upturned hands (D = dopamine, H = histamine, I = imidazoline, α = alpha-1 and alpha-2, σ = sigma). This is the closest that any drug of this study comes to bringing the "full bouquet" of mental organs into consciousness. Open 5-HT_2 hand by PETROO / Shutterstock.com, upturned hands by Luis M. Seco / Shutterstock.com.

DPT is also found in the upper right quadrant of Figure 2. Although it has an order of magnitude lower relative affinity for 5-HT_7 than DMT, it has the second highest breadth of interaction with all mental organs. DPT has also been noted to be exceptionally visual:

> **DPT**: The graphics of this vision were high-res and hyperperfect… Like DMT, the level of visual organization of the DPT realm was far beyond anything that the synaptical wiring of my brain could create – it was, in its own peacock-feathery way, not just as real as this reality, but far more real, crackling with power… etched in perfect solid-state reality – more than photographic. The sleekness of the DPT dimension was beyond belief. (Pinchbeck, 2002) p. 265-266

We find DOI in the middle right of Figure 2 with the third greatest breadth of the twenty-two drugs, but imperceptible 5-HT_7. DOI does not produce creative visuals. None of the drugs below the heavy horizontal line (2 on the vertical axis) produce creative visuals. Comparing DOI and DMT raises an interesting question: Can DOI load so many mental organs into consciousness, without expanding its depth, as DMT does?

5-MeO-DMT has the lowest breadth of mental organ interaction of the drugs of this study that have strong or moderate relative affinity for 5-HT_7. The only perceptible non-serotonin affinity of 5-MeO-DMT is D_1 with a weak npK_i of 2.38, which should be perceptible only at high doses. Although wildly consciousness expanding, 5-MeO-DMT typically produces very little visual effect or content of any kind:

> **5-MeO-DMT ~20 mg smoked**: In all my previous psychedelic sessions there always had been some rich specific content. The experiences were related to my present lifetime—the story of my childhood, infancy, birth, and embryonal life—or to various themes from the transpersonal domain—my past life experiences, images from human history, archetypal visions of deities and demons, or visits to various mythological domains. This time, none of these dimensions even seemed to exist, let alone manifest. My only reality was a mass of radiant swirling energy of immense proportions that seemed to contain all Existence in a condensed and entirely abstract form. I became Consciousness facing the Absolute. (Grof, 2005) p. 254

This illustrates that neither breadth nor depth alone produce creative visual effects. Creative visual effects occur only when breadth and depth are combined. When combined with non-serotonin mental organs, the visual effects produced by 5-HT_7 have the quality of taking actual objects in the visual scene, and transforming them according to the imagination of the subject. Even this side of the veil, these transformations can be quite dramatic. Once the veil is crossed, entire visual worlds can spring from the imagination of the subject.

The VER Hypothesis – creative open-eyed Visuals, Ego-loss, loss of contact with Reality

The hypothesis that 5-HT_7 mediates depth of consciousness and is responsible for the most dramatic effects of psychedelics, VER, is in direct conflict with the current 5-HT_2 paradigm. For this reason I would like to motivate this hypothesis by presenting more of the empirical evidence from which it arose. The first step in motivating the hypothesis is to learn to discriminate the qualitative effects of consciousness expansion through breadth and depth. In the preceding sections I have described each of the three components of VER (creative open-eyed Visuals,

Ego-loss, loss of contact with Reality), including how to distinguish simple visuals from creative visuals.

With knowledge of these distinctions, it becomes possible to examine subjective descriptions of the effects of the twenty-two drugs of this study to determine the extent to which VER is manifest in each report, and the extent to which each drug produces VER. This allows the demonstration that the tendency to produce VER correlates cleanly and without exception with the gradient in relative 5-HT_7 affinity among the twenty-two drugs of this study, and provides strong motivation for the hypothesis that 5-HT_7 is responsible for VER. However, the review of the literature on the relevant subjective effects of the twenty-two drugs presents more than two-hundred-fifty reports and runs more than a hundred pages in length. For this reason, and with great reluctance, the 5-HT_7 gradient review has been moved to the supporting information in the document S05GradientReview.pdf. I encourage interested readers to treat that document as an integral part of this manuscript, these are a large portion of the raw natural history observations on which this work is built. Here I will summarize the results of the gradient review.

Students in my psychopharmacology class were trained (before being introduced to the concepts of depth and breadth) to distinguish the presence or absence of VER in published descriptions of subjective drug experiences by reading the document S06Training.pdf which is available with the supporting information. These raters who were blind to the dose, identity of the drugs, or literature source of the subjective reports, rated the presence or absence of VER in each of 250 reports representing 22 drugs, and this rating provides a convenient way of quantifying, visualizing, and summarizing the verbose subjective reports. Figure 13 presents the blind rating data for 5-HT_7 and 5-HT_{2A}, showing that while 5-HT_7 cleanly separates high from low VER drugs, 5-HT_{2A} provides no separation.

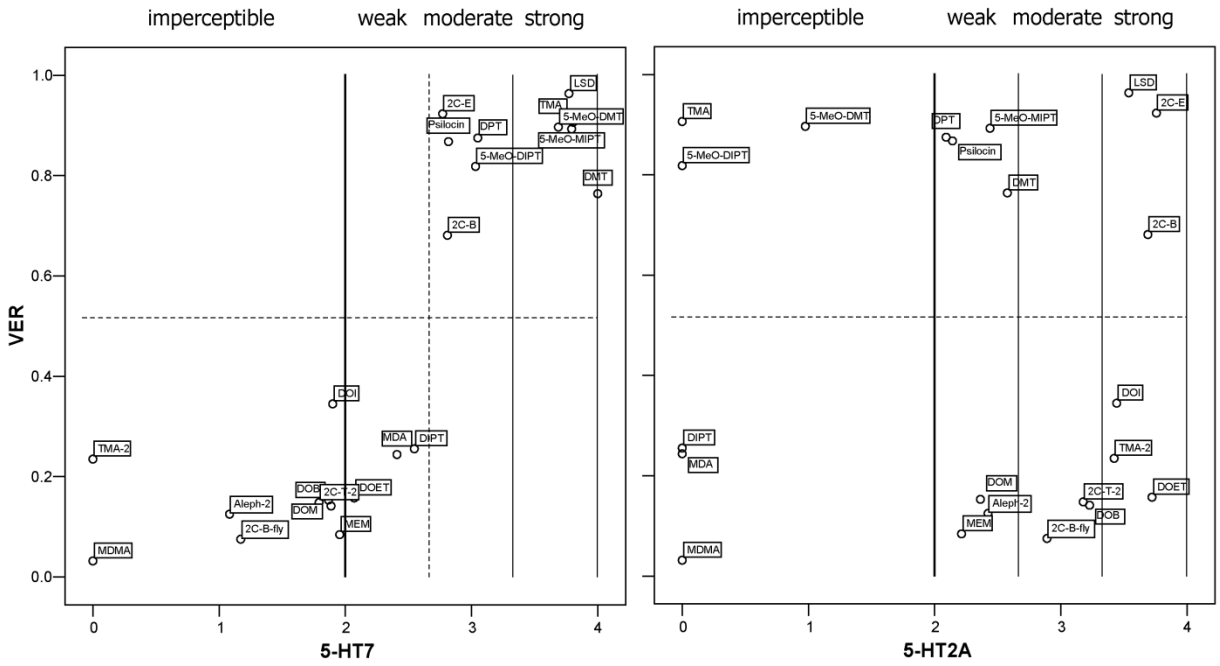

Figure 13. VER plotted against relative affinity of 5-HT_7 and 5-HT_{2A}. Blind rating results (VER) plotted against relative affinity at 5-HT_7 and 5-HT_{2A}. Dashed lines cleanly separate high from low VER drugs.

The VER blind ratings for the twenty-two drugs are strongly bimodal (data ranges from 0 to 1 with no values between .35 and .65). For all of the ten drugs with high (strong and moderate, $npK_i > 2.66$) relative affinities for 5-HT_7 (DMT, TMA, 5-MeO-MIPT, LSD, 5-MeO-DMT, DPT, 5-MeO-DIPT, Psilocin, 2C-B, 2C-E), there are abundant and readily available reports providing vivid and detailed descriptions of VER. Vivid and detailed descriptions of these three phenomena are completely lacking for the remaining twelve drugs with low (weak and imperceptible, $npK_i \leq 2.66$) relative affinity at 5-HT_7 (DIPT, MDA, DOET, MEM, DOI, DOB, DOM, 2C-T-2, 2C-B-fly, Aleph-2, MDMA, TMA-2), with two exceptions (one report each for MDA and DOM; both reports are acknowledged in peer-reviewed journals to be anomalous for these drugs).

While the initial gradient review focused on 5-HT_7, the ten drugs that produce VER act at many receptors. The common denominator method (Glennon, 1990) was used to choose prospective VER producing receptors that should be examined. I searched for common receptors in the high (strong and moderate) relative affinity range among the ten drugs that typically produce VER. There are two absolute common denominators: 5-HT_7 and 5-HT_{1D}. However Glennon did not speak of an absolute common denominator, but rather "the majority of the agents". Table 4 is a frequency distribution of the occurrence of high relative affinity ($npK_i > 2.66$) receptors among the ten drugs with high VER.

Freq	Receptor		Freq	Receptor
10	5-HT_7		3	5-HT_{5A}
10	5-HT_{1D}		3	Alpha-2B
9	5-HT_{1A}		3	Imidazoline-1
9	5-HT_{2B}		2	Alpha-1B
6	Alpha-2A		2	D_1
5	5-HT_6		2	D_3
5	5-HT_{2C}		2	SERT
5	Alpha-2C		2	Sigma-1
4	5-HT_{1B}		1	Sigma-2
4	5-HT_{1E}		1	H_1
3	5-HT_{2A}		1	Alpha-1A

Table 4: Frequency distribution of high relative affinity ($npK_i > 2.66$) receptors across the ten drugs that produce high VER

The frequency distribution suggests four strong candidates: 5-HT_7, 5-HT_{1D}, 5-HT_{1A}, and 5-HT_{2B}, as well as a distant fifth: $alpha_{2A}$ which qualifies with a bare majority of six out of ten drugs.

Figure 13 illustrates that relative affinity at 5-HT_7 cleanly separates drugs that show VER from drugs that do not, whereas relative affinity at 5-HT_{2A} does not. This analysis has also been made for relative affinity at: 5-HT_{2B}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, alpha-2A, and alpha-2C. In addition the analysis was made for a number of composite statistics grouping closely related receptors that may have similar functions:

- 5-$HT_{2[AC]}$ – square root of the sum of squares of the two relative affinities: 5-HT_{2A}, 5-HT_{2C}
- 5-$HT_{2[AC]max}$ – maximum of the two relative affinities: 5-HT_{2A}, 5-HT_{2C}
- 5-HT1 – Square root of the sum of squares of the four relative affinities: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1E}. The 5-HT1 index represents a hypothesis whose biological meaning is that when a drug acts at multiple 5-HT_1 receptors, each individual 5-HT_1 receptor contributes to the behavioral effect (e.g., VER), and that the contributions of the individual receptors add, in proportion to their relative affinity (squared).
- 5-HT_{1max} – maximum of the four relative affinities: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1E}
- Alpha2 – the square root of the sum of the squares of the relative affinity at the three Alpha2 receptors (Alpha-2A, Alpha-2B, Alpha-2C)
- Alpha2max – maximum relative affinity at any of the three $Alpha_2$ receptors assayed (Alpha-2A, Alpha-2B, Alpha-2C)

The full analysis is presented in the document S04ProspectiveReceptors.pdf. Neither 5-HT_2 receptors nor alpha-2 receptors provide any separation of high from low VER drugs. Thus this analysis does not provide any support for a role of any of the three 5-HT_2 receptors or three alpha-2 receptors in mediating VER. It should also be noted that relative affinities at 5-HT_2 and alpha-2 do not correlate with relative affinities at 5-HT_7.

On the other hand, both 5-HT_7 and the composite statistic 5-HT1 cleanly separate high from low VER drugs. This might be taken to indicate that 5-HT1 is as likely a causative mechanism for VER as is 5-HT_7. However, there is also a strong correlation between the 5-HT1 index and relative affinity for 5-HT_7. This opens the possibility that one of the two indices (5-HT1 or 5-HT_7) is a spurious correlation.

When we examine each of the four 5-HT_1 receptors individually, we find that 5-HT_{1E} is not able to separate high from low VER drugs, while for the other three, relative affinity provides good separation between high and low VER drugs, and correlates with relative affinity at 5-HT_7, with the exception of some outliers: 2C-B-fly, 2C-T-2, DOM, and DOI at 5-HT_{1D}; DOET, DIPT, and DMT at 5-HT_{1A}; DMT at 5-HT_{1B}. In all eight cases, without exception, the outlier drugs are the same drugs that violate the correlation between 5-HT_1 and 5-HT_7 affinity. In every case of a violation of the correlation between relative affinity at 5-HT_7 and any 5-HT_1 receptor, the ability to separate high from low VER follows 5-HT_7, not 5-HT_1. The most parsimonious interpretation is that 5-HT_7, not 5-HT_1, mediates VER.

This View as Illustrated by the Case of Psilocin – the Dopamine Hypothesis

The view of psychedelic drugs presented here suggests that the mystical-type experiences of substantial personal meaning and spiritual significance produced by psilocybin are not "mediated primarily at serotonin 5-$HT_{2A/C}$ receptor sites" (Griffiths et al., 2006). Nor are they mediated

primarily at 5-HT_7 sites. The view presented here is that the specific full-flavor of psilocin emerges from a specific pattern of interaction with multiple mental organs (Figure 14).

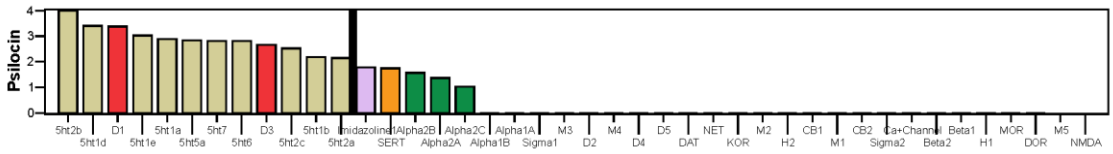

Figure 14. Relative affinity profile for psilocin. Vertical axis are npK_i values. Previously published in the supporting information of (Ray, 2010) as one of thirty-five drugs profiled in Figure S2.

Of all the drugs in this study, DMT has the highest relative affinity at any one dopamine receptor (D_1), and LSD has the highest combined relative affinity for the five dopamine receptors, yet psilocin makes the cleanest presentation of any dopamine mental organ (D_1). What is more, D_1 and to a lesser extent D_3, are the only known content mental organs to add flavor to psilocin. Thus psilocin is the cleanest dopamine psychedelic known, and the flavor of psilocin is dominated by D_1. Psilocin is the only drug of the study whose perceptible relative affinity at any dopamine receptor is significantly higher than its relative affinity at 5-HT_7 (Figure 15):

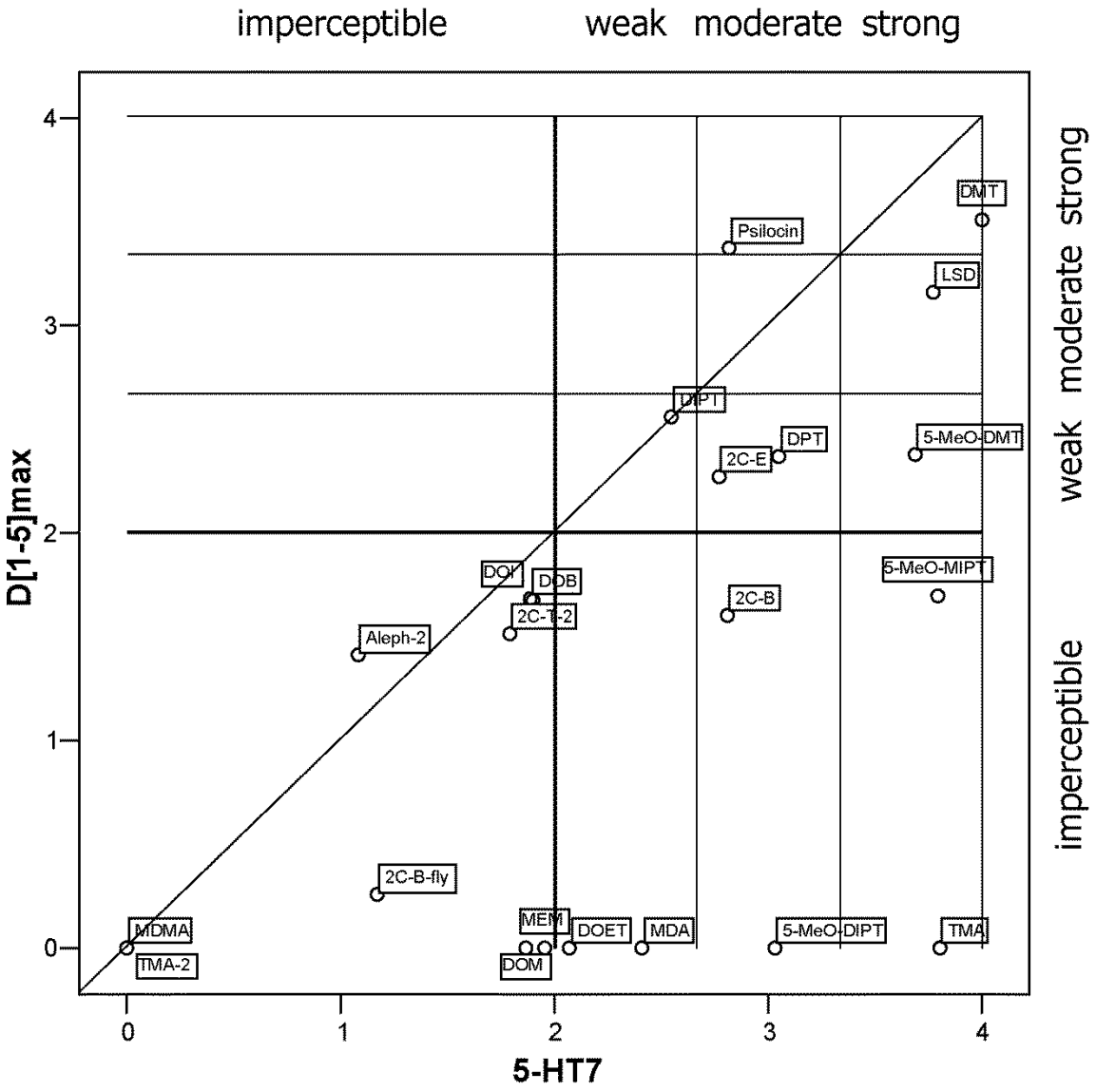

Figure 15. Relative affinity at 5-HT$_7$ and D$_{[1\text{-}5]max}$. Axes are relative affinity (npK$_i$) values. The diagonal line represents equal values of relative affinities at 5-HT$_7$ and D$_{[1\text{-}5]max}$. Drugs above the line have higher relative affinity at dopamine than at 5-HT$_7$. Relative affinity values below 2 should be imperceptible. D$_{[1\text{-}5]max}$ is the maximum relative affinity of any one of the five dopamine receptors.

In order to understand psilocin/psilocybin, we must understand dopamine. At the same time, psilocin is the drug best positioned to be used to characterize the effects of any dopamine mental organ, relatively free of the dramatic effects of 5-HT$_7$. At low doses of psilocin, the properties of D$_1$ should be clear, and may be free of the dramatic effects of 5-HT$_7$. At higher doses, the effects of 5-HT$_7$ should become strong and dramatically influence the quality of the experience. Characterizing the D$_1$ mental organ alone from existing literature is made difficult by the fact that subjects usually choose large enough doses for the effects of 5-HT$_7$ to overwhelm and alter the effects of D$_1$. There is relatively little literature on low doses of psilocin/psilocybin.

The primer/probe method offers a possible solution to the dilemma of characterizing the properties of the dopamine mental organs free from the effects of 5-HT_7. It should be possible to cleanly load dopamine mental organs into consciousness by taking a primer (DOET, DOB, 2C-B-fly, MEM) together with a dopamine selective probe such as the Parkinson's medications ropinirole or pramipexole. Such an experiment should be approached with caution, as there is a tentative hypothesis (mentioned below), that in the absence of 5-HT_7 activation, loading dopamine fully into consciousness might cause thought disorders.

Psilocybin has long been used as a religious sacrament by the indigenous peoples of Central America, and clinical studies have confirmed the ability of psilocybin to provoke mystical experiences of sustained personal meaning and spiritual significance:

> 67% of the volunteers rated the experience with psilocybin to be either the single most meaningful experience of his or her life or among the top five most meaningful experiences of his or her life … similar, for example, to the birth of a first child or death of a parent. Thirty-three percent of the volunteers rated the psilocybin experience as being the single most spiritually significant experience of his or her life, with an additional 38% rating it to be among the top five most spiritually significant experiences. (Griffiths et al., 2006)

The religious scholar Huston Smith characterized two qualities of the psilocybin experience:

> The dominant effects of the experience were two: awe (which I had known conceptually as the distinctive religious emotion but had never before experienced so intensely) and certainty. There was no doubting that the Reality I experienced was ultimate. The conviction has remained. (Smith, 2001) p. 15.

Griffiths *et al.* showed that psilocybin commonly causes

> … a sense of the unity of all things, a separate 'self' ceasing to exist, and merging and/or an encounter with ultimate reality (or God). (Griffiths et al., 2008)

A cinematic rendition of what appears to be a dopamine-like state can be found in the movie "Perfume: The Story of a Murderer" (Tykwer, 2006). Near the end, the orphan Grenouille makes the public debut of his masterpiece perfume, and a state of uncritical awe, certainty, worship, and love washes through the crowd gathered to witness his execution:

> If he wanted, he could... write the pope a perfumed letter and reveal himself as the new Messiah; be anointed in Notre-Dame as Supreme Emperor before kings and emperors, or even as God come to earth... He possessed the power... A power stronger than the power of money or the power of terror or the power of death: the invincible power to command the love of mankind. (Suskind, 2014) p. 259

The flavor of psilocin is essentially serotonin-7ized dopamine in the context of a weakened or absent sense of self. While there is little data on what dopamine looks like without serotonin-

7ization, we get a good glimpse of how it serotonin-7izes. The character St. John described natural un-medicated mild serotonin-7ization in this way:

> Of the ambition to win power and renown for my wretched self, she has formed the ambition to spread my Master's kingdom; to achieve victories for the standard of the cross. (Bronte, 2009)

In these terms, the strong serotonin-7ization of D_1 by psilocin suggests:

- Of the hedonistic desire for reward for my wretched self, she has formed
  - the single most spiritually significant experience of my life or among the top five most spiritually significant experiences
  - the single most meaningful experience of my life or among the top five most meaningful experiences of my life
  - awe and certainty, there was no doubting that the Reality I experienced was ultimate. That conviction has remained.

The extremely strong serotonin-7ization of D_1 by high doses of 5-MeO-DMT could be described as:

> Of the hedonistic desire for reward for my wretched self, she has formed the realization that this is god, I am god, all is god

These characterizations give us a glimpse of two different levels of serotonin-7ization of D_1 (and sample (Smith, 2001) (Griffiths et al., 2006) (Bronte, 2009) (Gura & Actualized.org, 2016), and popular conceptions of dopamine as a "reward" or "pleasure" transmitter).

The association of dopamine with reward may be true, but not uniquely so. In humans, expansion of consciousness through pretty much any means is experienced as rewarding, whether dopamine is involved or not. Furthermore, while "reward" may adequately capture the character of dopamine in animals, reward is a very crude term for the role that dopamine plays in humans. In humans dopamine can be much more. It can allow us to organize our life in part, around religious or political ideology, or any kind of social constructs. Also, dopamine has no particular valence in its "reward", so it may punish as well.

Dopamine is difficult to interpret from subjective reports, perhaps because it is not an ordinary content mental organ, in as much as it does not seem to represent a facet of reality in consciousness. Rather it marks conscious experience, giving it salience, significance, and leaving a lasting trace in our biographical memory. It appears to be able to mark both cognitive and affective content. It appears to mark us at such a deep level that it can imprint upon us, memories, ideologies, and even complex social constructs. It appears that when dopamine is activated by psychedelic drugs, it is able to allow the user to integrate new social constructs, which may take precedent over those adopted in the past. Thus it can facilitate deep change in our beliefs, ideologies, and behaviors (UNGER, 1963) (Mogar & Savage, 1964) (Leary, 1964) (Unger, 1964) (Fadiman, 1965) (Ward, 1967) (Prince, 1967) (Bottrill, 1969) (Downing, 1969) (Soskin, 1970) (Walsh, 2001) (Stolaroff, 2005) (House, 2007).

> In a series of LSD sessions… changes of the personality structure, emotional sets, values, attitudes, belief systems, and often the entire world view. (Grof, 1975), p. 237

This makes dopamine a powerful mental organ that when manipulated pharmaceutically should be used with great care. Healing end-of-life anxiety (Grob, 2007) (Grob et al., 2011) is an example of a good use of this capability. Imprinting ego-loss with dopamine, in which at a gut level we experience oneness with all, is a healthy way to confront the end of life.

Alpha-2 is a prominent mental organ in the LSD state (Watts, 1965). When LSD is experienced without loss of ego or loss of contact with reality, dopamine can imprint on the alpha-2 facet of reality in connection to our surroundings. In the 1960s many who imprinted on alpha-2 through LSD exited industrial civilization and went to live closer to the Earth.

Dopamine may have potential for abuse, in the form of manipulating the beliefs and behavior of people, either intentionally or not. In this context, it is worth considering possible unanticipated effects of the ADHD drugs methylphenidate and Adderall which are believed to operate through dopamine mechanisms. The ability of dopamine to facilitate deep and lasting memory traces could partially explain its ability to enhance academic performance. Yet academic learning (which did not exist when dopamine evolved) may not be the domain of primary effects. Might dopamine enhancement also cause people to more deeply integrate ideologies and social constructs?

Hypothesis: It is the serotonin-7ized dopamine signal that provides the deep sense of personal meaning and spiritual significance in the psilocybin experience. This hypothesis can be tested by repeating the experiments of Griffiths et al. (Griffiths et al., 2006) using 5-MeO-MIPT as the control drug. 5-MeO-MIPT closely matches the receptor affinity profile of psilocin, minus the dopamine, Table 5 (although this does not control for the propensity of psilocin to cause ego-loss). The prediction is that the deep sense of personal meaning or spiritual significance will manifest with psilocybin but not 5-MeO-MIPT.

	psilocin	5-MeO-MIPT
5-HT2B	**4.00**	**3.32**
5-HT1D	**3.40**	**3.74**
D1	**3.37**	*1.70*
5-HT1E	**3.03**	*1.55*
5-HT1A	**2.88**	**4.00**
5-HT5A	**2.83**	*2.11*
5-HT7	**2.82**	**3.79**
5-HT6	**2.82**	**2.98**
D3	**2.67**	*1.70*
5-HT2C	**2.52**	*1.75*
5-HT1B	**2.19**	**2.61**
5-HT2A	*2.14*	**2.44**
Imidazoline1	*1.77*	*2.15*
Alpha2A	*1.36*	**2.85**
Alpha2C	*1.03*	**2.29**
Sigma2	*0.00*	*2.13*

Table 5, Psilocin vs. 5-MeO-MIPT: Relative affinity profiles of psilocin and 5-MeO-MIPT compared. Relative affinities below 2 are likely imperceptible. Values from 2 to 2.15 are likely to be imperceptible but may be weakly felt at high doses or in sensitive subjects. Vales that are likely perceptible are in bold, those likely not perceptible are in light italics.

The key features of psilocybin are the inhibition of 5-HT_2 (weak partial agonism) which can weaken or dissolve the sense of self, strong activation of D_1, and moderate activation of 5-HT_7 and D_3. Without this combination of elements, the specific effects reported by Griffiths et al. (Griffiths et al., 2006) (Griffiths et al., 2008) would not emerge.

It would be a mistake to alter the current paradigm by replacing the subscript 2 with the subscript 7. Full-flavor psychopharmacology implies that there is no key psychedelic receptor.

Discussion

In the natural history approach to the human mind, subjective reports of psychedelic drug experiences are primary data. Viewing the subjective data in light of the molecular affinity data brings many patterns into focus, revealing a variety of mechanisms in the psychedelic process.

These observations have helped to clarify the mechanism by which 5-HT_2 is psychedelic: 5-HT_2 can load content mental organs into consciousness. Because there are many distinct content mental organs, the subjective qualitative experience that emerges from this loading will vary from one drug to another, depending on what combination of mental organs are loaded into consciousness. This is "full-flavor psychopharmacology", and it accounts for much of the qualitative diversity among psychedelics.

5-HT_7 clearly stands out as the most psychedelic of the mental organs, and appears to be responsible for what has been called the "divine spark":

> …whatever divine spark led our ancestors to start creating art *caused* all the other changes as well. In other words, if we can explain the art, we can explain the origins of modern humanity. (Hancock, 2015) p. 6

5-HT_7 appears to interact intimately with all other mental organs, and may be the seat of adult human consciousness and provide the spark of creativity. The grace of the spark of creativity emerging from 5-HT_7 makes each human mind an original source of novelty in the cosmic flow. Our sense of self and volition appear to emerge from the *act* of 5-HT_2 (the hands of the mind) shaping the creative consciousness of 5-HT_7.

Yet neither 5-HT_2 nor 5-HT_7 provides the contents of consciousness. Content comes from a large set of content mental organs associated with diverse neurotransmitter systems, predominantly non-5-HT. Each content mental organ renders a different facet of reality in consciousness. Collectively they render a multifaceted representation of reality. The more facets held in consciousness, the more complete our experience of reality.

5-HT_7 and VER

A clear pattern emerges from the data: drugs with high relative affinity for 5-HT_7 typically produce VER (creative open-eyed Visuals, Ego-loss, loss of contact with Reality) while those with low relative affinity for 5-HT_7 do not. No such association between relative affinity and VER is found for the 5-HT_2 receptors. This pattern shows through clearly in spite of the extremely heterogeneous nature of the data. The clean separation of high from low VER drugs was provided by relative affinity at 5-HT_7 alone, without any consideration of activity, metabolites, or agonist-directed trafficking, implying that at least for VER in this set of drugs, such considerations are not needed.

This pattern could not be detected through animal studies, or through human studies with one or a few drugs. The pattern can only be detected through a broad comparison of many drugs that vary widely in relative affinity for the relevant receptors. A clinical study with so many powerful yet poorly understood drugs would not be ethical and could not be justified. Thus the pattern likely can only be detected through a meta-analysis of existing subjective human data from whatever sources exist, as performed here. This result illustrates that a careful reading of qualitative descriptions of subjective human drug experiences in light of broad receptor affinity profiles can lead to new insights into the molecular pharmacology of psychoactive drugs.

This pattern could not have been detected in the 1970s and 1980s when the 5-HT_2 paradigm emerged, because at that time the 5-HT_7 receptor (and many others) had not been discovered, reliable affinity screening at a broad panel of receptors was not possible, relatively few psychedelic drugs were known, and an adequate body of subjective human data could not be assembled.

The belief that the effects of these drugs are "mediated primarily at serotonin 5-$HT_{2A/C}$ receptor sites" (Griffiths et al., 2006) originated thirty years ago, when our knowledge of neurotransmitter diversity was dramatically incomplete, when most of the drugs of this study had not been invented, and during a period in which prohibition led to the study of psychedelic drugs in rodents. The predominant training drugs used in these animal studies, DOM and DOI, are psychedelic drugs that do not produce VER. Furthermore, "DOI … is typically the drug of choice for studies of hallucinogens... Thus, virtually all of the recent studies on the mechanism of action of hallucinogens in rodents have employed only DOI" (Nichols, 2004). These studies were conducted with the belief in DOI's "relative pharmacological specificity for binding only at 5-$HT_{2A/2C}$ receptors" (Nichols, 2004). Later it was determined that DOI is one of the least selective drugs, its breadth of receptor interaction (Figure 2, Table 1) exceeded only by DMT and DPT, among psychedelics that have been broadly assayed ((Ray, 2010) Table 3). This combination of factors appears to have led to a premature convergence on 5-HT_2 a decade before 5-HT_7 was discovered. The prohibition of human research bears significant responsibility.

Testing the hypotheses

The clear 5-HT_7 pattern that emerged in this study must be balanced against a large body of literature supporting the 5-HT_2 paradigm. Different methods should reinforce the same paradigm, but in this case have produced conflicting results.

I do not claim that this manuscript settles the issue, but I believe that the evidence presented here is strong enough to warrant more research directed at resolving the conflict. Recent years have seen a resurgence of once prohibited human studies with psychedelic drugs, which virtually all cite the 5-HT_2 paradigm as a given. I believe that the 5-HT_7 vs. 5-HT_2 issue is important enough to justify human studies for its resolution. I recommend a direct comparison of relatively 5-HT_2 selective DOB, MEM, 2C-B-fly, or DOET with any of several 5-HT_7 drugs that strongly produce VER, such as psilocybin, LSD, DMT, or 5-MeO-MIPT. DOET may be a good choice as extensive clinical studies have already been conducted (Snyder, Faillace, & Weingartner, 1968; Snyder et al., 1969; Snyder et al., 1974; Snyder, Weingartner, et al., 1970; Snyder et al., 1971; Weingartner et al., 1971; Weingartner et al., 1970). The study could be conducted in much the same way as a recent study of psilocybin (Griffiths et al., 2006), by replacing the active placebo with any one of the relatively 5-HT_2 selective drugs.

Human studies are called for not just to resolve the 5-HT_2 vs. 5-HT_7 issue, but also to test the broader hypothesis of the existence of mental organs, the numerous specific hypotheses about the individual mental organs, and the implications of mental organs in mental health (Ray, 2012).

Limbs of the mind

Modern psychopharmacology textbooks treat receptors as buttons or circuit elements connecting series of neurons into Rube Goldberg devices. Each receptor excites or inhibits the neuron it is found on, in a chain leading to an effect whose nature ultimately only depends on if the final connection is excitatory or inhibitory. This is a proposed mechanism by which 5-HT_{1A} partial agonism in atypical antipsychotics can reduce extrapyramidal symptoms:

> Serotonin binding to $5HT_{1A}$ receptors in the raphe nucleus inhibits serotonin release (indicated by the dotted outline of the serotonin neurons). (1) In the striatum, reduced serotonin release means that $5HT_{2A}$ receptors on GABAergic and dopaminergic neurons are not stimulated, which in turn means that dopamine release is not inhibited. (2) Similarly, in the brainstem, reduced serotonin release means that $5HT_{2A}$ receptors on GABAergic interneurons are not stimulated and therefore GABA is not released (indicated by the dotted outline of the GABAergic neuron). Thus, dopamine can be released into the striatum. (Stahl, 2013) Figure 5-16C

Our metaphors for natural systems are often based on our current dominant technology, thus today we have brain circuits. Let me offer a more biological perspective: The human mind emerges from the interactions of a small population of mental organs (likely somewhere between a couple of dozen, and a couple of hundred). Each mental organ is highly sophisticated, comprising a significant fraction of our human mind. We should not think of mental organs as mere receptors, or neurons, or circuits, or as components of a computing machine. Individual mental organs have sophisticated human qualities.

Let me suggest this metaphor: The mind emerges from mental organs as locomotion emerges from limbs. The behaviors of limbs give rise to the properties of locomotion: gait, kinematics, stance, symmetry/asymmetry, phase, movement. The behaviors of mental organs give rise to the properties of mind: self-awareness, volition, language, biographical memory, compassion, joy, consciousness.

Attempting to understand the mind in terms of receptors is like trying to understand locomotion in terms of muscle fibers. The relevant object is not the receptor, nor the neuron, but the tissues defined by specific types of receptors which form the mental organs, the limbs of the mind. Mental organs have much more complex and sophisticated, higher order behavior than can be understood by analysis of receptors as circuit elements.

Mental Health

A practical prediction that emerges from the $5\text{-}HT_2$ paradigm is embodied in the title of Roth et al. 1999 (Roth, Willins, Kristiansen, & Kroeze, 1999): “Activation is Hallucinogenic and Antagonism is Therapeutic: Role of 5-HT2a Receptors in atypical Antipsychotic Drug actions.” The corresponding prediction to emerge from the $5\text{-}HT_7$ results presented here (assuming psychedelics are agonists at $5\text{-}HT_7$) is that strengthening of $5\text{-}HT_7$ is hallucinogenic, and weakening (partial agonism) may be therapeutic for some forms of schizophrenia.

Many atypical antipsychotics interact with $5\text{-}HT_7$ (PDSP, 2010; Roth et al., 1994), Figure 16. Roth et al. 1999 (Roth et al., 1999) indicate that both clozapine and fluperlapine have been shown to be effective against treatment-resistant schizophrenia. Note that fluperlapine is the only one of the twenty-two drugs in Figure 16 to have its best hit at $5\text{-}HT_7$, and clozapine has a robust npK_i of 2.95.

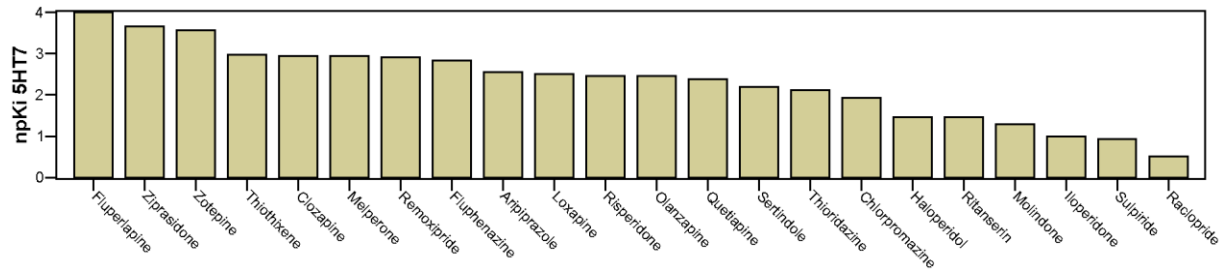

Figure 16. Relative affinities of antipsychotics for 5HT$_7$. Bar plot showing the relative affinity (npK$_i$) of twenty-two antipsychotic drugs for 5-HT$_7$. Data from the NIMH-PDSP web site (PDSP, 2010).

With respect to atypical antipsychotics, "rational" drug design has turned into a shotgun approach embodied in the title of Roth et al. 2004 (Roth, Sheffler, & Kroeze, 2004): "Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia." When we don't know what target to aim for, a magic bullet cannot hit, while a shotgun can. Many of these shotguns hit 5-HT$_7$. Yet I fully agree that many mood disorders and forms of schizophrenia can likely be best treated on an individualized basis by action at a carefully selected combination of sites, rather than a single site. The concept of selective shotguns embraces the spirit of full-flavor psychopharmacology.

While it is clear that strong activation of 5-HT$_7$ can cause hallucination or loss of contact with reality, it does not normally cause disordered thought. Thus 5-HT$_7$ can be only one central axis of schizophrenia. I speculate that disordered thought arises from an imbalance between 5-HT$_7$ and dopamine, in which dopamine is relatively strong, though the support for this hypothesis is thin. To probe into a possible source of disordered thought, I would suggest a broad PDSP screening of thiomescaline "which disorganizes the logical patterning of thought processes, with surprisingly little visual or sensory modification" (Shulgin, 1983). Thiomescaline may point to an additional central axis of schizophrenia.

Current psychiatric practice is based on trial and error. There is no rational method to map from the presenting symptoms of a patient, to the correct profile of receptor affinities and activities for treatment (apart from the broad assignment of antidepressants to the depressed, and antipsychotics to the psychotic). A thorough knowledge of the full complement of human mental organs could provide a solid conceptual framework for understanding the etiology of, for diagnosing, and for rationally designing treatments for a wide variety of mental disorders.

Implicit in the full-flavor/mental organs paradigm is the concept that the overall configuration and proportioning of the full set of mental organs, what I call the "modulatory personality" (Ray, 2012), has a great impact on mental state, and that badly proportioned modulatory personalities can provide the underlying etiology for a wide variety mental disorders. The full-flavor/mental organs paradigm can provide a conceptual framework in which presenting symptoms of some psychiatric patients are recognized as over or under-expressions of specific mental organs. This then translates into a specific hypothesis of a therapeutic drug profile of receptor affinities and activities, allowing a rational practice of psychiatry tailored to the individual patient (although

re-regulations of receptors resulting from chronic treatment may defeat the obvious approach of using agonists or antagonist).

Individualized Treatment of Schizophrenia

I would like to illustrate with the case of schizophrenia-related disorders, how understanding of mental organs could lead to individualized treatments. This manuscript suggests hypotheses relating specific mental states to specific patterns of activation of mental organs. Some of these mental states may appear among the presenting symptoms of psychiatric patients. The bullet list below illustrates some of these relationships:

- From presenting symptoms to expected underlying mental organ deviation
    - Subject is hallucinating or has lost touch with reality
        - 5-HT_7 is too high
    - Subject exhibits a mania with reduction of volitional control resulting in excessive behaviors
        - 5-HT_7 is high relative to 5-HT_2
    - Subject exhibits strong religious ideation mixed into their mania or psychosis
        - Dopamine is too high (and likely 5-HT_7 as well)
    - Subject exhibits thought disorder or word salad
        - Tentative hypothesis: dopamine is high relative to 5-HT_7

The bullet list below contains each of the hypothesized deviations of mental organ expression from the list above, and suggests possible pharmacological interventions:

- From mental organ deviation to pharmacological response
    - 5-HT_7 is too high
        - Use 5-HT_7 partial agonists
    - 5-HT_7 is high relative to 5-HT_2
        - Shift balance either with 5-HT_7 partial agonist, or 5-HT_2 agonist or strong partial agonist, or both
    - Dopamine is too high
        - Use dopamine antagonist or partial agonist
    - Dopamine is high relative to 5-HT_7
        - Shift balance either with 5-HT_7 agonist or strong partial agonist, or more likely dopamine antagonist or partial agonist, or both

Note that it is to be expected that subjects may present with symptoms from more than one of the categories in the first bullet list. Each symptom needs treatment, and this suggests multi-pronged pharmacological responses. A multi-pronged response could be achieved either through a single molecule with all of the desired properties, or through the use of more than one molecule which in combination provide the desired properties. The latter should be more practical to achieve, and allows for individualized fine tuning of the proportion of intervention at each receptor site. An analogous multi-drug approach may be appropriate for symptoms in the first bullet list that are interpreted as arising from an imbalance between two mental organs.

An important practical step in this approach is to develop a set of partial agonists selective for each of the three target receptors (5-HT_7, 5-HT_2, dopamine). We want sets of selective partial agonists sampling over the range of degree of activity (from full antagonist, to weak partial agonist, to partial agonist, to strong partial agonist, to full agonist) at each target receptor. These three sets of compounds can then be combined in various combinations and proportions, depending on the specific presenting symptoms of the individual patient. A key feature of the individualization of treatment would be finding the appropriate level of activation (partial agonism) that provides relief, at each implicated receptor. When multiple receptors are implicated, it is likely that this kind of fine tuning could more practically be achieved through combinations of separate sets of selective partial agonists; rather than through a set of single molecules, each with all of the desired properties.

In treatment it would generally be best not to use full agonists or antagonists in order to avoid pushing mental organ expression to extremes. For example, 5-HT_7 is hypothesized to be the seat of consciousness, creativity, and the intellect. While over-expression of 5-HT_7 may result in psychosis, moderate expression should be very healthy. Extinguishing 5-HT_7 may extinguish creativity and intellect. Treatments should respect these subtleties.

The Hard Problem and AI

If we want to solve the hard problem, then I say "look here": the mechanisms by which mental organs regulate and mediate consciousness are coming into view. Individual mental organs are brought in and out of consciousness through interactions with other mental organs that provide the mechanisms and medium of consciousness. By having a more detailed understanding of these structures and processes in the biological system, we place ourselves in a better position to understand the root of consciousness. Consciousness is not an amorphous phenomenon. It has components, interactions, dimensions, structures, processes, development, genetics, and evolution. When we understand all of this we are in a better position to gain insights about or intuit its ultimate origin.

By having a more detailed understanding of these structures and processes in the biological system, we place ourselves in a better position to conceptualize and design an artificial system with analogous phenomena. To the extent that we can better develop artificial intelligence by understanding biological intelligence, the work presented in this manuscript is relevant. If we want machines to have subjective experience, then we need to understand how subjective experience arises in biological systems, currently the only examples of consciousness that we have. But do we want machines to have these properties?

Acknowledgements I thank Katsunori Shimohara for supporting my work when I initiated this new research direction. I thank Matthew Baggott for suggesting blind rating of the subjective human data. I thank Chenmei Xu for her assistance in every phase of this project. I thank Alexander Shulgin and the Shulgin Archive (Team-Shulgin, 2016), without whom this work would not have been possible.

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