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# Constructing the ecstasy of MDMA from its component mental organs: Proposing the primer/probe method ☆

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ABSTRACT

The drug MDMA, commonly known as ecstasy, produces a specific and distinct open hearted mental state, which led to the creation of a new pharmacological class, "entactogens". Extensive literature on its mechanisms of action has come to characterize MDMA as a "messy" drug with multiple mechanisms, but the consensus is that the distinctive entactogenic effects arise from the release of neurotransmitters, primarily serotonin. I propose an alternative hypothesis:

- The entactogenic mental state is due to the simultaneous direct activation of imidazoline-1 ($I_1$) and serotonin-2 (5-$HT_2$) receptors by MDMA.

This hypothesis emerges from "mental organ" theory, which embodies many hypotheses, the most relevant of which are:

- "Mental organs" are populations of neurons that all express their defining metabotropic receptor, and each mental organ plays a distinct role in the mind, a role shaped by evolution as mental organs evolve by duplication and divergence. Mental organs are the mechanism by which evolution sculpts the *mind*.
- Mental organs can be in or out of consciousness.
- In order for a mental organ to enter consciousness, three things must happen:
  - The mental organ must be activated directly at its defining receptor.
  - 5-$HT_2$ must be simultaneously activated. One of the functions of activated 5-$HT_2$ is to load other simultaneously activated mental organs fully into consciousness.
  - In some cases THC must be introduced to remove long-term blocks mediated by the cannabinoid system.

I propose the "primer/probe" method to test these hypotheses. A "primer" is a drug that selectively activates 5-$HT_2$ (e.g. DOB or MEM) or serotonin-1 (5-$HT_1$) and 5-$HT_2$ (e.g. DOET or 2C-B-fly). A "probe" is a drug that activates a receptor whose corresponding mental organ we wish to load into consciousness in order to understand its role in the *mind*. The mental organ is loaded into consciousness when the primer and probe are taken together, but not when taken separately. For example, the blood pressure medications rilmenidine and moxonidine are selective for imidazoline-1 and can be used to test the hypothesis that the entactogenic mental effects of MDMA are due to loading the imidazoline-1 mental organ into consciousness. The primer/probe method is not limited to testing the specific hypothesis about MDMA and imidazoline, but is a general method for studying the role of mental organs in the *mind*. For example, the role of dopamine mental organs can be studied by using Parkinson's drugs such as ropinirole or pramipexole as probes.


## Mental organs

Theodosius Dobzhansky said "Nothing in biology makes sense, except in the light of evolution" [1]. The mind emerges from biology, so this must apply to the mind as well. Human research with psychedelic drugs has suggested what appears to be a mechanism by which evolution sculpts the *mind*, which must be a fundamental organizing principle. I call it "mental organs": populations of neurons that share a common receptor, such as serotonin-7, histamine-1, or alpha-2C. Some mental organs provide consciousness (in separate adult and childhood forms); some function as the "hands" of the mind, dexterously giving shape to

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consciousness, determining what is shut out and what is brought in, and expressing volition; some function as gatekeepers to consciousness in long and short time frames; some give salience, meaning or significance to the contents of consciousness, while some provide content to consciousness. Some mental organs support the facilities of language, logic, and reason, which appear to be fully developed only in adult humans. A very diverse set of mental organs provide affective "ways of knowing" the world, through feeling alone, which provide the complete archaic mind in our developmental and evolutionary antecedents [2].

The mental organs described by [2] are defined by "metabotropic" receptors (mostly G-protein coupled receptors, GPCR), which do not have fast excitatory or inhibitory effects on neurons, but rather have relatively slow effects through second messengers. Second messenger pathways are often branching, such that activation of a single receptor can have many different effects on a cell simultaneously. These effects might include (but are not limited to) alterations in: membrane conductance (both increases and decreases), the properties of transmitter release, the properties of other membrane receptors and transporters, synaptic strength upon repeated firing, biasing the membrane potential towards or away from the spike threshold, pattern of neuronal firing (bursts or constant firing), basal firing rate [3]. In this way, metabotropic receptors can potentially control most of the important parameters of the behavior of neurons. A single metabotropic receptor can initiate a branching second messenger pathway, potentially resulting in any suite of settings for the tunable parameters of the neuron. A mental organ then, is a population of neurons that share a common pattern of settings for the parameters of neuronal behavior. Operating through metabotropic receptors, evolution is able to shape a population of neurons that can function as a whole, a mental organ, with a common set of behavioral parameters tuned by evolution to a common function.

The new hypotheses that will be introduced here flow from mental organ theory which was elaborated by [2]. Ray synthesized broad receptor affinity data for thirty-five psychoactive drugs (mostly assayed by the NIMH-PDSP against fifty-one sites, [4]) together with existing literature on the mental effects of the same drugs. This work showed that each of the dozens of receptors that psychedelics interact with produce perceptible effects, revealing their individual roles in the tapestry of the human mind. Yet in most cases the effects of a receptor are not apparent when it alone is pharmacologically activated. The coherence and distinctiveness of the mental effects associated with each receptor suggested the concept of mental organs. Ray [2] defines and describes mental organs, presents hypotheses for thirteen specific mental organs (serotonin-1, serotonin-2, serotonin-7, dopamine, alpha-1, alpha-2, beta, histamine-1, sigma, mu, kappa, imidazoline, cannabinoid-1), describes some apparent interactions between mental organs, and discusses some of the implications of the theory.

Most of the drugs studied interact with multiple receptors, and most of the receptors studied interact with multiple drugs (similar to what we see in the interactions between odorant molecules and odor receptors, also metabotropic receptors). Thus most of the thirteen mental organs characterized are activated by multiple drugs, in each drug in a different pharmacological context (together with a different set of mental organs). The characteristic effects of each mental organ [2] can be seen across the multiple drugs and pharmacological contexts in which they are expressed, providing strong support for the specific individual mental organ hypotheses, as well as a broader view of each mental organ's various facets and contours, depending on its expression in different mental contexts.

There are many mental organs that provide ways of knowing, each of which paints a distinct facet of the world in consciousness. Collectively, the various ways of knowing provide a multifaceted representation of reality in consciousness. These represent a set of natural ontological categories, discovered and refined through evolution [2] over long time frames, to represent the world most fully in consciousness for the good fitness of the being. Many of these ways of knowing in humans render social aspects of the world. The mental organs that provide ways of knowing have coevolved in the mind by having each mental organ evolve to represent a different and complementary facet of reality. Yet the collective is evolved to blend together into the experience of reality as a perceptual whole.

Thus when we see a mental organ expressed in multiple drugs, we see its characteristic mental effects, its specific flavor, blended into different sets of mental organs. Each drug has a distinct flavor, resulting from its blending in consciousness of different sets of mental organs in different proportions. This is what I call "full-flavor psychopharmacology". Many mental organs are based on GPCR, the gene family that also includes the odor receptors, which operate on much the same principles: the experience of odor/flavor depends on the blend of odor and taste receptors, in the different proportions that the odorant/tasteants molecule(s) interact with them [5]. This produces the sensation of odor/flavor as a perceptual whole, although the trained gourmet can detect the individual components that contribute to the odor/flavor (e.g. the different spices in a fine curry). The same is true for detecting the contributions of individual mental organs to the flavor of a drug that awakens multiple mental organs.

Because they are based on individual genes, mental organs can evolve by duplication and divergence. They provide a direct linkage from genes, to proteins, to neural populations, to psychology; providing a missing link between biology and psychology [6]. When seen from the perspective of mental organs, the mind comes into focus. The mind has structure, function, process, genetics, development, and evolution. Mental organ theory has explanatory and predictive power. It provides new approaches to understanding the etiology and treatment of mental disorders. It provides understanding of psychoactive drugs, both psychiatric and recreational. It helps us to understand ourselves and others. The interested reader is invited to read [2] which is available from the author (tray@ou.edu).

## Mental organs in and out of consciousness

Here I will define "psychedelic" as expansion of consciousness. Although this occurs by multiple mechanisms, here I will speak only of expansion of breadth of consciousness, which I will define as bringing more mental organs into consciousness. This is consistent with [7] who 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" [7] p. 90.

There are many mental organs whose mental effects, in the absence of psychoactive drugs, do not enter consciousness, but in the presence of psychoactive drugs are experienced in consciousness (e.g. alpha-1, alpha-2, beta, histamine-1, mu, imidazoline). Psychedelic drugs make it apparent that the mental effects produced by mental organs can be in consciousness, or not in 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. For the remainder of this manuscript, when I use the word "psychedelic", it will refer to mental organs being brought into consciousness. However, I will continue to use the phrase "psychedelic drug(s)" or its synonym "psychedelics" in a broader sense to refer to drugs

that expand consciousness by any mechanism, not just by breadth. This manuscript is about one psychedelic mechanism that causes mental organs to enter consciousness: simultaneous activation of 5-$HT_2$ and the mental organ(s) entering consciousness (there appear to be other mechanisms).

In light of both the 5-$HT_2$ paradigm of psychedelic drug action [8] and the mental organs hypotheses of [2], I would like to highlight some observations relevant to the current manuscript:

- Drugs selective for 5-$HT_2$ alone (DOB or MEM) or selective for 5-$HT_1$ and 5-$HT_2$ together (2C-B-fly, DOET) are not psychedelic in the sense that they do not bring additional mental organs into consciousness and they do not expand consciousness by any mechanism. Based on examination of DOB and MEM, [2] characterized 5-$HT_2$ as gatekeepers to consciousness, hypothesizing that higher levels of activation of 5-$HT_2$ produces consciousness closing effects, shutting thoughts and feelings out from consciousness. I will use the phrase "non-5-$HT_{1/2}$" to refer to receptors other than 5-$HT_1$ and 5-$HT_2$.
- Through the synthesis of broad receptor profiles with data on subjective effects of thirty-five drugs, [2] found that
  - the specific subjective mental effects of psychedelic drugs are due to their action at non-5-$HT_{1/2}$ receptors
  - action at different non-5-$HT_{1/2}$ receptors produces different specific subjective qualitative mental effects

These observations would seem to place the views of [8] and [2] in direct conflict. These observations and the apparent conflict arise from the examination of only psychedelic drugs. The resolution comes from additional observations on non-psychoactive drugs.

The primer/probe hypotheses emerged recently while contemplating together the receptor affinity profiles of clonidine and mescaline. Both drugs have alpha-2 as their primary affinity, with lesser affinity at imidazoline-1. Ray [2] had previously proposed hypotheses for the mental effects mediated by the alpha-2 and imidazoline-1 mental organs. Based on a simple interpretation of these hypotheses, it would be expected that clonidine would have psychedelic effects overlapping with those of mescaline, however clonidine is not psychoactive, apart from causing sedation. Clonidine is a medication used for its physiological effects, primarily in treating high blood pressure. Yet a clear difference between clonidine and the psychedelic mescaline, is that only mescaline has measurable affinity at the paradigmatic psychedelic 5-$HT_2$ receptors.

Comparison of pairs of drugs with similar receptor profiles, yet differing in the presence or absence of affinity at 5-$HT_2$ (e.g. mescaline and clonidine, MDMA and rilmenidine) clarified the psychedelic mechanism:

- Activation of 5-$HT_2$ alone is not psychedelic (e.g. MEM or DOB)
- Activation of the defining receptors of mental organs alone is not psychedelic (e.g. clonidine at alpha-2, imidazoline-1, and alpha-1; rilmenidine or moxonidine at imidazoline-1)
- Simultaneous activation of 5-$HT_2$ and the defining receptors of mental organs *is* psychedelic (e.g. mescaline at alpha-2, 5-$HT_2$, and imidazoline-1; MDMA at imidazoline-1, 5-$HT_2$, and alpha-2)

We might suppose that all mental organs capable of entering consciousness are in fact always in consciousness, but do not stand out individually, as they are lightly activated and blend together with the full bouquet of mental organs; yet, when we strongly activate specific mental organs with drugs, those mental organs stand out against the tapestry of the mind, revealing themselves. If this supposition were true, then any drug that strongly activates a mental organ should make it stand out in the mind, including drugs such as clonidine and rilmenidine. That such drugs are not psychoactive is strong evidence that the corresponding mental organs are not normally in consciousness at all, no matter how strongly activated, and enter consciousness only in the presence of a psychedelic drug that loads activated mental organs into consciousness.

These observations led to the origin of the primer/probe hypotheses which provide a resolution of the apparent conflicts between [8] and [2]. It is now apparent that 5-$HT_2$ has a critical psychedelic property that was not recognized by either [8] or [2]: it can load activated mental organs into consciousness.

The concept of mental organs as elaborated here still stands as a set of hypotheses and a conceptual framework, which have not been put to the test by the machinery of science. However, the primer/probe method proposed here would test the most fundamental aspects of the theory, as well as many of its particulars.

## MDMA mechanisms

There is a ubiquitous but unstated pragmatic principle of psychopharmacology: we interpret the mechanism of action of drugs through their interaction with receptors that we think we understand, while we ignore the interactions that the same drugs also have with other receptors whose mental effects we don't understand. For a class of drugs that interacts with dozens of receptors, such as psychedelics or antipsychotics, this practice can create blind spots. Although psychedelics are believed to act through 5-$HT_2$ receptors [8], they are also known to have measurable affinity at many other receptors. Ray [4] reported that individual psychedelic drugs may have measurable affinity at as many as twenty-four receptors, and likely perceptible affinity at as many as twenty-one receptors.

Here I will illustrate the operation of this unstated principle for the case of MDMA, which produces a specific and distinct, profoundly open hearted mental state [9–23]:

> "... with MDMA also: the specific insights, feelings, and resolution 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. Individuals are able, if their intention in taking the substance is serious and therapeutic, to use the state to resolve long-standing intrapsychic conflicts or interpersonal problems in relationships...
>
> "People feel they have true compassion, forgiveness, and understanding for those with whom they have important relationships. Most importantly, in terms of the therapeutic implications, they have empathy and compassion for themselves, for their ordinary, neurotic, childish, struggling persona or ego. The relative absence or attenuation of normal anxiety and fear in these states is perhaps the single most important feature in regard to their therapeutic value. People report being able to think about, talk about, and deal with inner or outer issues that are otherwise avoided because of the anxiety levels normally associated with those issues.
>
> "Feelings of being returned to a natural state of innocence before guilt, shame, and unworthiness arose are common in these Adamic ecstasies; and so are feelings of connectedness and bonding with fellow human beings, animals, plants, and all the forms and energies of the natural world." [12], p. 59–60.

Although psychedelic drugs are understood to function through activation of the 5-$HT_{2A}$ and/or 5-$HT_{2C}$ receptors [8], a separate pharmacological class, entactogens [24,25], has been created for MDMA, which is understood to operate by a mechanism other than 5-$HT_{2A/C}$ activation. The separate class was justified both on the

grounds of a distinct mechanism of action and of producing a specific and distinct set of qualitative subjective effects (entactogenic).

The receptor affinity profile of MDMA produced by the National Institute of Mental Health – Psychoactive Drug Screening Program (NIMH-PDSP) shows imidazoline-1 as its best hit, followed by 5-$HT_{2B}$, Ca + channel, alpha-2 and muscarinic receptors, in descending order of relative affinity ([4] Figure S2). MDMA was also broadly screened by [26], who reported the following rank order of affinities for MDMA: "5-HT uptake > $\alpha_2$-adrenoceptors = 5-$HT_2$ serotonin = M-1 muscarinic = H-1 histamine > norepinephrine uptake = M-2 muscarinic = $\alpha_1$-adrenoceptors = β-adrenoceptors ⩾ dopamine uptake = 5-$HT_1$ serotonin >> D-2 dopamine > D-1 dopamine". They also reported "negligible affinities (>500 μM) at opioid (μ, δ and κ), central-type benzodiazepine, and corticotropin-releasing factor receptors, and at choline uptake sites and calcium channels".

The two sets of affinity data are very different, and it should be noted that [26] used outdated methods involving brain homogenates, while [4] used modern methods involving cloned receptors in cell culture. The key differences between the two sets of affinity data are that while [26] did not assay at imidazoline-1, [4] found it to be the best hit; while [26] reported 5-HT uptake to be the best hit, [4] reported >10,000 nm affinity at the serotonin, norepinephrine, and dopamine transporters (SERT, NET, DAT); while [26] reported negligible affinity (>500 μM) at calcium channels, [4] reported a $K_i$ of 1198 nm, placing the calcium channel in third place of rank order. These differences in reported pharmacologic profiles lead naturally to very different interpretations of the mechanism of action of MDMA. I will base my hypotheses on the NIMH-PDSP data reported by [4].

The following mechanisms of action of MDMA have been noted:

- Release of neurotransmitters
  - serotonin [24,26–49]
  - norepinephrine [32,35,37,41,44,47–50]
  - dopamine [30–33,35–49,51]
  - acetylcholine [35,52]
  - oxytocin [41,50,53,54]
  - vasopressin [41]
  - monoamines [34,46,55,56]
  - cause efflux of serotonin from vesicular stores [31,46,56]
- Inhibition of reuptake of neurotransmitters
  - serotonin [24,28–30,36,37,40,42,43,46,51,56–59]
  - norepinephrine [24,28,46,57]
  - dopamine [24,28,43,46,57–59]
- Action at transporter
  - serotonin [26,28,31–35,41,42,44,50,56]
  - norepinephrine [32,41,43,44,50]
  - dopamine [31,32,34,36,41,44,50]
  - Carrier-mediated 5-HT release [30,32,33,35,39,41–43,48–50,56,58,60,61]
  - Carrier-mediated norepinephrine release [48,49,60,61]
  - Carrier-mediated dopamine release [48,49,58,60,61]
  - 5-HT-MDMA exchange through the carrier [28,29,32,36,42,44]
  - norepinephrine-MDMA exchange through the carrier [44]
  - dopamine-MDMA exchange through the carrier [44]
  - reversal of 5-HT uptake transporter [35,46,47,50,62]
  - reversal of dopamine uptake carrier [35,42,43]
  - "occupy the 5-HT transporter site and prevent 5-HT from binding" [36]
  - 5-HT release due to interaction with the vesicular monoamine transporter-2 [46,52]
  - MDMA taken up by noradrenaline transporter increasing efflux of dopamine [41]
  - "competitively block the noradrenaline transporter" [41]
- Direct actions
  - serotonin [26,28,32,33,35]
  - 5-$HT_2$ [32,33,35,36,39,41,43,50,58]
  - 5-$HT_{2A}$ [46,63]
  - 5-$HT_1$ [41,43,58]
  - 5-$HT_2$ agonist [41]
  - 5-$HT_{2A}$ agonist [41]
  - 5-$HT_{2C}$ agonist [41]
  - dopamine-2 [35,58]
  - $\alpha_1$ adrenergic [41]
  - $\alpha_2$ adrenergic [30,35,39,41,43]
  - $\alpha_{2AD}$ adrenergic [41]
  - $\alpha_{2C}$ adrenergic [41]
  - β-adrenergic [41]
  - $H_1$ histamine [35,41,43]
  - $M_1$ muscarinic [41,43]
  - $M_2$ muscarinic [41]
  - α7 nAChR [46]
  - "a novel receptor... may be a trace amine such as tyramine" [41]
- Indirect effects
  - 5-HT release leading to stimulation of
    - 5-HT [42]
    - 5-$HT_2$ [34]
    - 5-$HT_{2A}$ [38]
    - 5-$HT_{2C}$ [38]
    - 5-$HT_{1A}$ [30,43]
    - 5-$HT_{1B}$ [35,36,38,50]
    - noradrenergic system [35]
  - 5-HT release activating 5-$HT_{1A}$ which causes release of oxytocin [50,53,54,64,65]
  - 5-HT release leading to dopamine release [30,36]
  - 5-$HT_2$-mediated increase of dopamine activity [28,33–36,41,50,60,66]
  - 5-HT release leading to stimulation of 5-$HT_{2A}$ leading to release of dopamine [31,40,41,56]
  - 5-HT release leading to stimulation of 5-$HT_{2C}$ leading to release of dopamine [38,41]
  - 5-HT mediated secretion of corticosterone, aldosterone and renin [41]
  - $H_1$ histamine interaction leads to acetylcholine release [35,46,52]
  - $\alpha_1$ adrenergic [50,61]
- Mechanisms of specific mental components
  - Serotonin
    - "carrier-mediated serotonin release was mainly responsible for its positive mood and entactogenic properties" [56]
    - "5-HT release primarily mediates the MDMA-typical "empathogenic" mood effects" [60]
    - "overall psychological effects... largely depend on carrier-mediated 5-HT release" [35,40]
    - "SERT-mediated 5-HT release is" important for "positive mood effects" [48]
    - SERT-mediated 5-HT release "is thought to cause the 'positive' effects desired by the user, such as feelings of emotional warmth, empathy toward others, enhanced sensory perception, a general sense of wellbeing and decreased anxiety" [67]
    - "increase in the net release of serotonin (and possibly dopamine) is the major mechanism of action underlying the distinctive mental effects" [37]
    - "a primary role for 5-HT in the mediation of all aspects of the subjective effects" [61]

- "increases in emotional excitability and sensitivity... might not involve an action at the 5-HT uptake site" [41]
- "LSD-like hallucinogenic effects, and the subjective feelings of "love, happiness, peace and connection" are probably due to the huge elevation of 5-HT in the extracellular space and the resulting activation of, among others, 5-$HT_{2A}$-receptors" [31]
- Hallucinogenic properties due to 5-$HT_{2A}$ agonism [46]
- "The mild hallucinogen-like perceptual effects... appear to be due to... 5-$HT_2$ receptor stimulation" [35]
- "impairments on verbal memory are in large part caused by direct or indirect stimulation of the 5-$HT_{2A}$ receptor" [63]
- "we can assume that the slight hallucinogen-like effects of MDMA are due to 5-$HT_{2A}$ receptor stimulation" [33]
- enhances prepulse inhibition via a mechanism involving serotonin [40,41,68]
- "prosocial effects and action on OT [oxytocin] are mediated by 5-HT receptors" [65]
- "primary role for serotonin in the effects... on oxytocin release, emotion identification, and... potential prosocial effects" [69]
- "5-$HT_2$ receptors mediate positive moods induced by MDMA but not negative moods or impulsivity" [59]
- "5-$HT_1$ receptors do not appear to be involved in MDMA effects on mood and impulse control" [59]

○ Dopamine
- "dopamine functions underlay the stimulant/elatory properties" [56]
- Positive mood effects, "the more stimulant-like euphoric mood effects... appear to relate, at least in part, to dopamine $D_2$ receptor stimulation" [35,40]
- "increase in the net release of serotonin (and possibly dopamine) is the major mechanism of action underlying the distinctive mental effects" [37]
- "DA-release appears to be responsible for the acute amphetamine like psychostimulatory effects" [31]
- "reinforcing properties... are associated with dopamine release" [41]

○ Norepinephrine
- "NET-mediated NE release primarily mediates the more stimulant-typical emotional excitation and cardiovascular response" [48]
- "NE release may be responsible for the stimulant and cardiovascular effects" [60]
- Noradrenergic signaling contributes to "high", "closeness", "stimulated" interpersonal sensitivity, and anxiety [70]
- "increased release of noradrenaline is mainly responsible for the physical effects that it shares with amphetamine" [37]
- "vesicular release of norepinephrine... does not critically contribute to the effects of MDMA in humans"; "the $\alpha_2$ agonistic effects of MDMA are not relevant for its main action in humans or are outweighed by the transporter-mediated release of NE and other monoamines" [49]
- "a possible role for $\alpha_1$-adrenergic receptors in the mediation of the mood-enhancing and stimulant effects of MDMA in humans" [61]
- "$\alpha_2$-adrenoceptor agonist actions at all three receptor subtypes... may contribute to its abusive potential and cardiovascular and autonomic side effects" [46]
- "we are not aware of any evidence that... $\alpha_1$-adrenergic receptor stimulation has appreciable mind-altering effects in humans comparable to those produced by hallucinogens or psychostimulants" [33]

○ Histamine
- "we are not aware of any evidence that $H_1$ histaminergic... receptor stimulation has appreciable mind-altering effects in humans comparable to those produced by hallucinogens or psychostimulants" [33]

○ Acetylcholine
- α7 nAChR "may account for... neurotoxicity, cholinergic neurotransmission" and "processes related to addiction and dependence" [46]

○ Oxytocin
- prosocial feelings (amicability) are due to release of oxytocin [53,54,64,65]
- "enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions" [65,69]
- "MDMA (75 mg) selectively enhances emotional empathy in humans... it is suggested that peripheral oxytocin does not seem to be the main actor in this" [71]
- "direct receptor interactions of these drugs seem to make no major contribution to their central actions" [31]
  - Inhibition of synthesis of 5-HT [28–30,36,40,41,43,50]
  - Uptake of MDMA into the neuron [72]
  - Act as a monoamine oxidase (MAO) inhibitor [36,41,43,46,50]
  - Effects of MDMA are mediated through multiple sites [35,36,38,43,50]
  - The pharmacology of MDMA is "messy" [29,43,56,62]

Over the span of more than thirty years of literature on the molecular mechanisms of MDMA, we can recognize dramatic advances in methods in neuroscience. In the early years we see vague statements about release of monoamines or serotonin. As the methodology matures, we see much more specific and diverse information reporting the consequences in vitro, in animal models, and in humans of the effects of MDMA through almost every molecular site that the drug interacts with, as well as secondary indirect downstream actions resulting from the interactions of those direct sites with other sites. It appears now that we can observe and measure most of these processes, and hence MDMA has become the most thoroughly examined psychedelic drug, using modern techniques. There may still be a larger literature on LSD, but most of it predates the prohibition, and is thus based on much older methodologies.

Researchers have come to characterize MDMA as "messy", due to its many receptor interactions. Yet complex interactions are characteristic of psychedelics and antipsychotics. MDMA is not unusual in this respect. Ray [4] ranked thirty-five drugs in order of decreasing breadth of interaction (Table 3, column "$B_{sq}$"). MDMA ranked 18th on the list, placing it among relatively less-messy psychedelic drugs. Ray [4] reported that individual psychedelic drugs may have measurable affinity at as many as twenty-four sites, yet MDMA had measurable affinity at only nine sites (partly due to its low potency). On the other hand, MDMA appears distinctive in that of the eighteen psychedelic drugs assayed at the calcium channel, it was the only drug with measurable affinity, and the calcium channel is third in MDMA's rank order of affinity. It is possible that action at the calcium channel could potentially cause any neuron to release its neurotransmitters, thus making MDMA messy

indeed. Affinity for the calcium channel may also be responsible for MDMA's toxicity:

> "... if too much calcium enters the cell through open channels, it would poison the cell.... A limited form of excitotoxicity may be useful as a 'pruning' mechanism for normal maintenance of the dendritic tree (see Figs. 1–23), getting rid of cerebral 'dead wood' like a good gardener; however, excitotoxicity to an excess is hypothesized to cause various forms of neu rodegeneration..." [73], p. 392.

## New hypotheses

If our goal is to understand the properties of a drug that millions of people use, then it is important to consider all of the effects reviewed above. However the focus of this paper is much narrower. I want to ask: what specific molecular mechanisms result in the manifestation of the specific entactogenic effects characteristic of MDMA? The answer I propose here is: none of the above. I propose instead that we invoke Occam's razor and suppose that the specific distinctive entactogenic effects are due to action at the site of highest affinity of MDMA, the imidazoline-1 receptor. I propose to test this hypothesis through the primer/probe method, in which we attempt to load the imidazoline-1 mental organ fully into consciousness with the use of a selective 5-$HT_2$ primer and a selective imidazoline-1 probe.

Mental organ theory [2] suggests these hypotheses:

- Expression of specific metabotropic receptor genes define "mental organs" (populations of neurons that all express the defining receptor), and each mental organ plays a distinct role in the mind, a role shaped by evolution as mental organs evolve by duplication and divergence. Mental organs are the mechanism by which evolution sculpts the *mind* [2].
- Mental organs can be in or out of consciousness, and their presence or absence in consciousness is mediated by complex processes, some of which involve drugs, neurotransmitter systems, or other mental organs.
- Drugs can be "mind manifesting" or "psychedelic" in the sense that they bring fully into consciousness, mental organs that normally do not enter consciousness.
- Drugs that are truly selective for 5-$HT_2$ receptors, or selective for 5-$HT_2$ and 5-$HT_1$ receptors, are not psychedelic in this sense, on the contrary they tend to close the gates to consciousness at increasing doses [2].
- The specific qualitative subjective effects of psychedelic drugs are predominantly due to their bringing into consciousness of mental organs other than 5-$HT_1$ and 5-$HT_2$ ("non-5-$HT_{1/2}$ mental organs").
- The flavor of a psychedelic drug is dominated by the non-5-$HT_{1/2}$ mental organs corresponding to the receptors at which the drug has the highest affinity, in descending order of dominance/affinity.
  - The mental state produced by a psychedelic drug emerges as a perceptual whole, as a blend of the various mental organs that the drug brings into consciousness, in varying proportions determined by the drug molecule's relative affinities at the corresponding receptors ("full-flavor psychopharmacology")
  - This is similar to the mechanism by which odor emerges as a perceptual whole as a result of the interaction of odorant molecules with various strengths at various odor receptors, which are also metabotropic receptors [5].
- However, for many non-5-$HT_{1/2}$ mental organs, activation alone does not bring the mental organ into consciousness and thus does not produce a psychedelic effect.
- In order for such a non-5-$HT_{1/2}$ mental organ to enter consciousness, three things must happen (yet there may be other mechanisms for loading mental organs into consciousness):
  - The mental organ must be activated directly at its defining receptor
  - 5-$HT_2$ must be simultaneously activated. It appears that one of the functions of activated 5-$HT_2$ is to load other simultaneously activated mental organs fully into consciousness.
  - In some cases THC must be introduced to remove long-term blocks mediated by the cannabinoid system [2].
- The specific entactogenic state produced by MDMA is due to the imidazoline-1 mental organ [2] being loaded into consciousness due to simultaneous activation of imidazoline-1 and 5-$HT_2$ receptors.
- Hypotheses of the mental functions associated with thirteen mental organs and some of their interactions are described in [2].

Psychedelic drugs have special value in revealing the structure of the human mind, in part precisely because they are "mind manifesting", in the sense that they are able to load mental organs into consciousness. When mental organs are loaded into consciousness, their role in the mind can be discerned, as well as some of the mechanisms of consciousness.

## Primer/probe method

I will use the word "primer" to refer to a drug that can load activated mental organs into consciousness. Within the scope of this manuscript, primers will be drugs that are selective for 5-$HT_2$ (DOB, MEM), or selective for 5-$HT_2$ and 5-$HT_1$ (DOET, or 2C-B-fly) [4]. Careful review of the descriptions of the subjective effects of these four drugs show that they are not psychedelic, by themselves they do not load mental organs into consciousness, they are subtle, and at higher doses tend to close off consciousness: DOB [9,74–76]; MEM [9,13,76]; DOET [9,11,13,77–83]; 2C-B-fly [76,84–87]. I will use the word "probe" to refer to a drug that does not act at 5-$HT_2$, but does act at non-5-$HT_{1/2}$ mental organs (e.g. dopamine, norepinephrine, imidazoline). I will refer to the receptor(s) activated by the probe as the "probed" receptor(s).

The primer/probe method consists of using a primer to load the mental organs activated through the probed receptors into consciousness, and is a proposed new method of studying the mind which consists of a double-blind controlled clinical experiment, which has three treatments:

- The probe taken alone
- The primer taken alone
- The primer and probe taken together

For the specific case of constructing the entactogenic mental state of MDMA, the experiment can take this form

- The primer taken alone (DOB, MEM, DOET, or 2C-B-fly)
- The probe taken alone: selective imidazoline-1 agonist (rilmenidine or moxonidine)
- MDMA taken alone
- The primer and probe taken together

The last two, but not the first two treatments, should produce the entactogenic state characteristic of MDMA. This experiment is a test whose results may disprove, support, or refine the imidazoline hypothesis proposed by [2]. To be clear, the claim is not that the last treatment would recreate the MDMA experience. The claim is only that the primer/probe combination would create the distinctive entactogenic state characteristic of MDMA. If the primer/

probe method is validated, then primed rilmenidine or moxonidine will be the purest known imidazoline-1 psychedelics, much cleaner (more selective) than MDMA. However they might not produce some other effects of MDMA such as stimulation or toxicity. If so, the primer/probe combo might be more suitable for therapeutic applications than is MDMA itself.

A dose of a medication that is adequate to produce a physiological effect (e.g. reduce blood pressure or reduce Parkinson's symptoms) should also be adequate to manifest a mental organ in consciousness when primed by 5-$HT_2$. Thus when this experiment is first attempted, it should be done with a dose of the probe that is in the normal range of doses used in the medical application. Similarly, a modest dose in the normal dose range of the primer should be used as well.

In this context, we can provide a new explanation for observations made by [88], who noted the "disconcerting absence of additivity between the component isomers in comparison with the activity of the racemate" for MDMA. While most phenylisopropylamine psychedelics are more active in the R isomer than the S isomer, in MDMA the characteristic entactogenic effect is found with the S isomer. Given that the racemate is active in doses of 100–160 mg, we would expect the S isomer to be active at half this dose, 50–80 mg. Yet the S isomer is active in the 80–120 mg range, much higher than expected. While the authors do not provide an explanation for these observations, they close with this thought: "Perhaps there is a stimulant action from one of the isomers which enhances or potentiates the (otherwise) dormant potential of the other." Yes, mental organ theory suggests that racemic MDMA is actually a primer/probe pair of drugs, with the R isomer acting as the primer at the 5-$HT_2$ receptors, and the S isomer acting as the probe at the imidazoline-1 receptor. The relative affinity of the two isomers at imidazoline-1 and 5-$HT_2$ could be examined to test this hypothesis. It has already been shown that "R(−)-MDMA possesses about a 3-fold greater affinity [at 5-$HT_2$] than does its S(+)-enantiomer" [89]. Mental organ theory has explanatory and predictive power.

A way of further corroborating that the MDMA mental state is due to the combination of imidazoline-1 and 5-$HT_2$ is to make a list of drugs known to produce the MDMA entactogenic mental state, and assay them broadly to see if they all have moderate to strong relative affinity for both receptors. Imidazoline-1 is likely to be the dominant flavor for all of these drugs.

## Imidazoline-1

This is not really a paper about MDMA/imidazoline. I have simply chosen that as the best experiment to illustrate a larger issue: a mechanism that manages access to consciousness. MDMA/imidazoline is the best choice because:

- MDMA is the most thoroughly studied psychedelic drug with modern methods
- MDMA produces distinct and characteristic qualitative entactogenic subjective effects
- several psychometric tests have been developed to detect these effects
- several laboratories around the world are practiced at clinical studies with MDMA
- despite its placement in a separate pharmacological class for both qualitative and mechanistic reasons, MDMA operates by the same primer/probe mechanism as other psychedelics ("classical hallucinogens" [8])
- the existing voluminous literature on MDMA mechanisms has not recognized the role of the primer/probe mechanism in its actions

The imidazoline-1 receptor (NISCH – nischarin, or IRAS – Imidazoline Receptor Antisera-Selected) is not a GPCR. GPCR are characterized by seven transmembrane segments, and signal by coupling to G-proteins. The NISCH receptor has no transmembrane segments, and signals through pathways not known to be linked to heterotrimeric G-proteins. NISCH appears to be a cytosolic protein that is anchored to the intracellular side of the plasma membranes by a POX domain [90,91].

There are several excellent reviews of imidazoline biology [91–96], so here I will only focus on issues relevant to the current manuscript. Several functions of the imidazoline receptors or imidazoline agonists have been observed:

- Physical
  - Metabolic syndrome [95]
    - Hypertension [91,93–97]
    - Insulin resistance [94,95]
    - Glucose intolerance [94,95]
    - Dyslipidemia [95]
    - Hyperinsulinemia [95]
  - Cardiovascular regulation [95]
  - "regress left ventricular hypertrophy" [94]
  - "reduction of atrial natriuretic peptide levels" [94]
  - "treatment of renovascular hypertension" [94]
  - Treatment of obesity [94]
  - Reduce high cholesterol [94]
  - "central imidazoline actions may regulate water and sodium balance" [94]
  - Possible treatment for congestive heart failure [94,95]
  - Anti-apoptotic [90,91,94–96]
  - "inhibits LIM kinase, and may play a role in inhibiting the metastasis of cancer cells" [91]
  - Insulin
    - "insulin and growth-factor mediated cell growth" [94]
    - Associate with insulin receptor substrates [90,91,95,96]
- which results in phosphorylation of extracellular receptor kinase (ERK) [95,96]
- leading to "insulin sensitizing effect of imidazoline agonists" [91]
  - "improvement in endothelial dysfunction" [95]
  - reduction in inflammatory cytokine TNF-α [95]
  - "reduced fasting triglycerides, total cholesterol, glucose and urinary albumin excretion while increasing the anti-inflammatory mediator adiponectin" [95]
  - Integrin
    - Bind to fibronectin receptors [90]
    - bind to integrin, a component of the fibronectin receptor [91,95]
    - "work through the integrin signaling complex and bind to a tyrosine kinase stimulating a cascade of events leading to activation of phospholipase C" [96]
    - "integrin mediated cell-shape" [94]
  - Inhibits cell migration [91,95,96]
  - "mediate cell growth and differentiation" [90]
  - "neurite outgrowth mediator" [90]
  - "could be pivotal in regulating processes such as neuronal cell division, axonal sprouting, and neuroplasticity" [90]
  - Toxicity: "CNS depression, bradycardia,... hypotension, respiratory depression, miosis,... hypothermia", and hypertension (early and transient) [96]
  - "Imidazolines have been shown to inhibit platelet aggregation in a dose-dependent manner" [96]
  - Involved in the neuronal modulation of contractions in the ocular nictitating membrane [96,98]

- Mental
  - "elevation in platelet $I_1$ sites... in untreated... dysphoric premenstrual syndrome" [92]
  - "elevation in platelet $I_1$ sites" in "newly post-menopausal women", "and estrogen replacement therapy down-regulated them" [92]
  - "properties in mice consistent with anxiolysis" [92]
  - Depression
    - Depression is associated with dysregulation or overexpression of imidazoline receptor binding sites [92,96,97,99–103]
    - Antidepressant treatment normalized imidazoline receptor function [92,96,97,99,101–103]
    - Imidazoline receptors involved in antidepressant-like effect of agmatine in forced swimming test [97]
    - Effects of SSRIs involve modulation of imidazoline receptors by agmatine [102]
    - Imidazoline involved in "antidepressant-like effect of tramadol in mice" [103]
    - Lower levels of $I_1$ receptors in brains of depressed suicide victims [92]
    - Platelet $I_1$ receptor density may represent a state marker for depression [92,96,99,101]

The imidazoline-1 literature reviewed above does not discuss psychedelic drugs, but only considers non-psychoactive drugs, whose primary application is in the treatment of high blood pressure. There is also some discussion of an association between imidazoline-1 receptors and depression, at least as a marker for depression. However, the imidazoline-1 literature never suggests an acute psychoactive effect through action of a ligand at imidazoline-1 receptors. As predicted by the primer/probe hypotheses, we find no evidence of psychoactive, and much less of entactogenic effects from imidazoline-1 drugs that do not also act at 5-$HT_2$. The primer/probe hypotheses suggest that activation of 5-$HT_2$ alone is not psychedelic, and the activation of imidazoline-1 alone is not psychedelic, but that 5-$HT_2$ and imidazoline-1 are psychedelic when they are activated together. The imidazoline-1 literature is consistent with these hypotheses.

The entactogenic effects attributed by [2] to imidazoline are not found in imidazoline-1 selective drugs that do not also act at 5-$HT_2$, such as rilmenidine, moxonidine, and clonidine which are primarily used to treat high blood pressure. The three drugs MDMA, rilmenidine, and moxonidine all have their primary affinity at imidazoline-1, with lesser affinity at alpha-2. Yet of the three, only the psychedelic MDMA also has affinity at 5-$HT_2$. This is consistent with the pattern we see with clonidine and mescaline.

The drugs that are known to act at both imidazoline-1 and 5-$HT_2$ are MDMA, DIPT, mescaline, 5-MeO-DIPT, DMT, and DPT, in order of decreasing relative affinity at imidazoline-1 ([4] Figure S3, Table S2, Table S4, Table S6). I believe that it should be possible to discern the entactogenic effects of imidazoline-1 in all six drugs, but of these drugs, currently only MDMA, mescaline, and DMT have adequate literature describing subjective effects. Of these three drugs, MDMA is the only one to have its primary site of affinity at imidazoline-1, and its subjective effects are the archetypical entactogenic effects, described above in the introduction [12]. In mescaline and DMT, imidazoline-1 is not the dominant flavor, and is blended together with the mental effects mediated by other mental organs, yet the entactogenic effects of imidazoline-1 can be recognized in these more complex drugs: mescaline ([104–108]); DMT ([109–111]).

Imidazoline-1 receptors are capable of producing both physical and mental effects, a pattern that is likely typical of all mental organs. While the mental effects manifest only when the defining receptor is activated *and* the mental organ is loaded into consciousness, the physical effects presumably manifest any time the receptors are activated. It is not clear if there is any coherence between the mental and physical effects associated with activation of receptors defining mental organs.

## Chronic tolerance

It is widely reported that MDMA produces a distinctive form of tolerance often called "chronic tolerance" [14,18,29,37,41,43,52,56,58,62,112–127], whose nuances are vividly described in [118]:

> "Ecstasy shows tolerance, but in a rather extreme and unusual way. With most drugs, increased dosage is needed to maintain the same effect. But with ecstasy, increased dosage produces a more speedy and less empathic effect. In fact, frequent heavy users often give up and take amphetamine instead as it provides a similar effect for less money.
>
> "There is another unusual effect that applies even to moderate users: the euphoric quality is nearly always limited to the first few occasions. Later experiences lack the first wonder, and it may never be experienced again even after a long break." – P. 59–61 [118]
>
> "The experience of the 'love effect' from ecstasy rapidly fades with repeated use, and the effects become increasingly like those of amphetamine.[57,1] This may partially explain some of the escalation in dose levels seen in recent years, as some users will be vainly attempting to recover the mental state which they experienced initially – now impossible due to neurochemical and psychological changes in the brain and mind resulting from repeated use...
>
> "It was once believed that ecstasy would be free of any dependency risk because of the rapid loss of the empathogenic 'loved up' effect with repeated use.[57] However, while loss of this effect may lead to declining use in an older group who take ecstasy for its empathogenic properties, younger users in the dance culture may come to appreciate the more amphetamine-like qualities, and have different expectations." – P. 124–126 [117]

The large literature on this subject is generally in agreement with [118] that this peculiar form of tolerance is a distinctive property of MDMA. However, I have found evidence in the literature for the widespread occurrence of this specific form of tolerance among psychedelic drugs, specifically MDMA, DIPT, mescaline, 5-MeO-DIPT, DMT, and DOM [14,76,128], listed in decreasing order of relative affinity for imidazoline-1. However, among these six drugs we find that all but DOM have a high relative affinity for imidazoline-1([4] Figure S3). The five imidazoline-1 drugs that show chronic tolerance are also the five drugs with the highest relative affinity for imidazoline-1. It may be that among mental organs, imidazoline-1 is more prone to this kind of chronic tolerance. The beautiful imidazoline-1 mental state is ephemeral and elusive and cannot be conjured repeatedly at will, without limit. This observation is relevant to the design of the primer probe experiment, especially as it applies to constructing the mental state of MDMA. An above stated hypothesis is relevant here:

- In some cases THC must be introduced to remove long-term blocks (chronic tolerance) mediated by the cannabinoid system [2]

Survey studies have shown that cannabis is used to enhance the effects of MDMA [129], and controlled clinical studies have shown that THC enhances the effects of MDMA [47,130]. Studies have

shown that more than 90% of MDMA users also use cannabis, and the two drugs are often taken together [56,115,122,124,131–134].

The degree of chronic tolerance to imidazoline-1 will depend, at least in part, on a subject's degree of prior exposure to imidazoline-1 drugs, and the elapsed time since exposure. There are gradations of chronic tolerance:

- Full effects of imidazoline-1 without simultaneous use of THC (e.g. first experience)
- Partial effects of imidazoline-1 without THC, and full effects with THC
- No effects of imidazoline-1 without THC, and full effects with THC
- No effects of imidazoline-1 without THC, and partial effects with THC
- No effects of imidazoline-1 with or without THC (e.g. recent heavy MDMA users)

Given the possible need for THC in the proposed primer/probe construction of the MDMA entactogenic mental state, a more complex set of conditions would be needed for a fully controlled experiment:

- The probe taken alone
- The primer taken alone
- THC taken alone
- The primer and probe taken together
- THC and the primer taken together
- THC and the probe taken together
- The primer, the probe, and THC taken together
- MDMA taken alone
- MDMA taken with THC

Pragmatically speaking, it is likely to be more feasible to use the simpler set of three or four conditions described in the previous section, but have THC available if the imidazoline-1 effects do not fully develop within a few hours. Even for subjects who do experience the effects of imidazoline-1 without THC, inclusion of THC can deepen the imidazoline-1 experience. The primer/probe experiments are likely to be long lasting, thus it would be possible to measure the state both before and after the application of THC, in the same experiment. It is also critical to consider that repeated exposures of the same subject to imidazoline-1 drugs will not be comparable, due to the rapid development of chronic tolerance.

## Constructing mental states

Nichols [135] has said:

> "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." [135]

In 1998 it was true that medicinal chemistry could not design mental states. But today the theory of mental organs should make it possible to construct specific mental states by assembling drugs that load the relevant mental organs into consciousness, either through conventional drug design (based on synthetic chemistry and broad receptor assays) or through the primer/probe method.

A good theory has explanatory and predictive power. For mental organ theory, the bullet list of hypotheses above embeds the explanation, and the proposed primer/probe experiment embeds some predictions as well as the method of their testing. If we understand a mental state, and the biological mechanisms by which it arises, then we should be able to engineer the state; construct it from its component elements. In order to advance the project of constructing the MDMA entactogenic mental state from its component parts, I will claim the set of hypotheses stated in the bullet list above as an example of "understand a mental state, and the biological mechanisms by which it arises". For the specific case of MDMA, this understanding suggests an approach to engineering the state: activate imidazoline-1 and load it into consciousness by simultaneously activating 5-$HT_2$.

Constructing the mental state of MDMA is just one illustrative example of a more general approach of constructing mental states that is made possible by the primer/probe method. It should also work in principle for constructing the mental states produced by a wide variety of psychedelic drugs. A code to this enterprise can be found in [4] and [2]. The discussion of [4] states: "If we acknowledge the pervasiveness of the 5-$HT_1$ and 5-$HT_2$ receptors, and then look past them, we find that the set of thirty-five drugs emphasize a wide variety of receptors". This statement is then followed by a list of the drugs that most prominently present each of eighteen mental organs. The intention was to draw attention to the mental organs that are responsible for the qualitative properties, the dominant flavors, of the corresponding drugs. The bullet list in the opening of [2] describes the hypothesized mental states associated with each of thirteen mental organs. These two lists taken together form a key to the primary mental organs at which each drug acts. This information can be used to construct the mental states associated with specific drugs. This process of construction is a test of the series of hypotheses presented in the bullet list of [2], which can either disprove, support, or refine each hypothesis.

MDMA, rilmenidine, and moxonidine all have imidazoline-1 as their best hit. Thus when rilmenidine or moxonidine are used as a probe, they should manifest the dominant flavor of the MDMA (entactogenic) state when combined with a primer. Constructing a close approximation of the mental state of an existing drug is the most feasible when the drug activates only a single non-5-$HT_{1/2}$ mental organ. For example, the DOM mental state could be constructed with a probe that activates the beta-2 receptor, and the TMA-2 mental state could be constructed with a probe that activates the histamine-1 receptor. For drugs that activate multiple non-5-$HT_{1/2}$ mental organs, it would be difficult to find a single probe that would closely match the pattern of affinities found in the target drug; however it should be feasible to find a probe that would provide the dominant flavor, as suggested for MDMA (rilmenidine or moxonidine to activate imidazoline-1). Yet the primer/probe method is not restricted to constructing an approximation of an existing drug. It may be used simply to design a particular mental state.

It is also not necessary to restrict the primer to 5-$HT_{1/2}$ selective agents (DOB, MEM, DOET, 2C-B-fly). For example, [2] hypothesized that both the imidazoline-1 and histamine-1 mental organs mediate empathy, each in a distinct way. These two facets of empathy could be blended into a perceptual whole by using TMA-2 as a primer and rilmenidine or moxonidine as a probe.

Another use of the primer method could be to produce cocktails that bring together more than one class of probed receptor. For example, the combination of imidazoline-1 with dopamine may have applications in healing certain conditions, but the only drug examined by [2,4] that brings these two classes of receptor together is DMT, which also interacts strongly with many other receptors. By combining an imidazoline-1 agonist (e.g. rilmenidine or moxonidine) with a dopamine agonist (e.g. ropinirole or pramipexole) and a primer, a psychedelic cocktail could be constructed that manifests imidazoline-1 and dopamine together.

An interesting aspect of this approach is that we are then in a position to have full control over the effective relative affinities of the two classes of probed receptors, by controlling the relative doses of the two probes. Thus we could for example vary the relative doses of rilmenidine and ropinirole to produce a cocktail with either imidazoline-1 stronger than dopamine, or dopamine stronger than imidazoline-1. This kind of subtle pharmacological manipulation would likely forever remain out of reach through conventional drug design methodology.

This amounts to mental engineering, or pharmaceutical designer minds. More importantly, probes selective for a wide variety of receptors, including receptors not discussed in [2], can be primed in order to elaborate our understanding of their role in the mind.

## Characterizing mental organs

Using the primer/probe method to construct the mental state of existing drugs is of little real value other than as a validation of mental organ hypotheses. Although in the case of MDMA it can also be of value in producing a safer and longer lasting drug, "pharmaecstasy", that might be used in treating PTSD and other disorders, as well as in psychotherapy.

I believe the greatest scientific value of the primer/probe method is that it could be used to characterize mental organs and clarify their interactions. Ray [2] has provided hypotheses characterizing thirteen mental organs, yet there must be many more. The primer/probe method should greatly ease and accelerate the process of testing the thirteen hypotheses proposed by [2], and in characterizing additional mental organs.

For example, [2] presented a hypothesis for the mental state mediated by the alpha-1 mental organ. However, among the thirty-two active drugs studied by [4], perceptible alpha-1 is found only in DMT and DPT, the two drugs with the greatest breath of interaction with multiple receptors ([4] Table 3, column "$B_{sq}$"). Thus the alpha-1 hypothesis was interpreted from DMT and DPT, which have measurable affinity at 17 and 24 receptors respectively. It is difficult for the mental effects of a single mental organ to be interpreted from such complex drugs, thus the alpha-1 hypothesis is weak. We need a more selective alpha-1 psychedelic. Clonidine interacts with alpha-1, alpha-2, and imidazoline. Furthermore, clonidine is a weak partial agonist at alpha-2 and has much higher efficacy at alpha-1 [95]. Thus clonidine is a much better candidate for characterizing the alpha-1 mental organ. Thus a clonidine probe can be used to test, and either disprove, support, or refine the alpha-1 hypothesis proposed by [2].

As another example, among the psychedelic drugs broadly assayed and examined by [2,4], LSD has the broadest interaction with the five dopamine receptors ([4] Table S5, column "$D_1$, $D_2$, $D_3$, $D_4$, $D_5$"), DMT has the highest relative affinity for any one of the five dopamine receptors (D1) ([4] Table S5, column "$D_{max}$"), and psilocin makes the cleanest presentation of dopamine (D1 is the dominant flavor of psilocin ([4] Discussion)). However, there is no drug with a high relative affinity for dopamine that does not also have a high relative affinity for 5-$HT_7$. When activated together with 5-$HT_2$ and 5-$HT_7$, dopamine-1 manifests mystical/spiritual [136] and religious [137] sentiments. 5-$HT_7$ has a very strong flavor [2], thereby making it difficult to separately characterize the dopamine mental organs. Thus existing psychedelic drugs do not provide a clear picture of the role of dopamine in the mind without strong 5-$HT_7$. Using the primer/probe method, we can create clean dopamine psychedelics by using probes, such as any of several drugs used to treat Parkinson's and restless leg syndrome that are selective for various dopamine receptors (e.g. ropinirole or pramipexole). However, caution should be used in clean dopamine primer/probe experiments, as dopamine has been implicated in schizophrenia and addiction.

In this way, the primer/probe method can be used to bring almost any chosen selective receptor agonist together with 5-$HT_2$, to observe the role of its corresponding mental organ in the life of the mind.

## Clarity

One potential advantage of the primer/probe method, should it be validated, is the clarity that it could bring to the roles that the various receptors play in the psychedelic experience. One unfortunate consequence of the current narrow 5-$HT_2$ paradigm [8] is that is has kept research attention focused on the 5-$HT_2$ receptors, and the roles of other receptors in the psychedelic experience have been neglected.

The primer/probe method should highlight what is already obvious from the pharmacology of DOB, MEM, DOET, and 2C-B-fly: that activation of 5-$HT_2$ alone is not psychedelic; and at high doses it tends to be anti-psychedelic, actually constricting consciousness. The primer/probe method also should clearly demonstrate that the specific qualitative subjective psychedelic effects:

- that emerge are mediated by non-5-$HT_{1/2}$ mental organs, which in a primer/probe study will be provided by the probe.
- mediated by the non-5-$HT_{1/2}$ mental organs do not manifest through activation of the corresponding receptors alone, but require the simultaneous activation of 5-$HT_2$, which in a primer/probe study will be provided by the primer.
- experienced will depend on what mental organs are activated by the probe. Activation of different mental organs by different probes should produce qualitatively different effects. This clarity of the association between qualitative subjective experience and receptor activation should dramatically facilitate the mapping of the role that different receptor systems (mental organs) play in the life of the mind and in the psychedelic experience.

## Coda

As discussed above, MDMA appears to be the single most thoroughly studied psychedelic drug, using modern methods of neuroscience. Yet the extensive literature on the mechanisms of action of MDMA appears to never mention imidazoline. If the proposed primer/rilmenidine or moxonidine experiment validates the hypothesis that simultaneous activation of imidazoline-1 and 5-$HT_2$ is responsible for the distinctive and characteristic entactogenic heart-opening of MDMA, this result will vividly illustrate the ubiquitous but unstated pragmatic principle of psychopharmacology.

The primer/probe method will then allow us to deliberately and selectively load the mental organs into consciousness one-by-one, to examine their properties. We can similarly load them in combinations in order to examine their interactions. This will permit the rapid decoding of the *mind*, and the elaboration of many of the missing links between biology and psychology [6]. After this process, there will not be as many "receptors whose mental effects

we don't understand", thus we will be less likely to invoke the unstated principle.

The observation that there are many mental organs that do not normally enter consciousness in adult humans is puzzling. Many of them apparently enter consciousness in childhood, but not adulthood. I suspect that in adulthood they do not simply play their role in the "unconscious", but actually cease to function; and I suspect that this is a pathological state that contributes to the rise of mental illness and destructive/self-destructive behavior in modern humans. I believe that as mental organs become vestigial, we are losing our evolutionary heritage, our humanity. The mental organs that populate the adult human mind are moving in the direction of a cognitive monoculture with a loss of affective diversity, and we are left with a less multifaceted view of reality.

## Conflict of interest

I have no conflict of interest

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