Methods

The method involves assaying a large and diverse set of psychoactive drugs against a large number of receptors, transporters and ion channels, and then synthesizing the molecular affinity data together with pre-existing data on the subjective effects of the drugs in humans. This method represents a full realization of de Wit's suggestion that "it may be time now to recognize these extraordinary subjective experiences... It is time for psychopharmacologists to open their minds and their laboratories to the full domain of human drug experience. We would do well to be wary of our own preconceptions and prejudgments, and to be prepared to consider the entire scope of human experience and behavior as legitimate targets for systematic and ethical scientific investigation" (de Wit 2006), and Coyle, Presti, and Baggott's suggestion that "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). In fact the results of this work take the form of a series of just such novel hypotheses.

The efficacy of this method relies entirely on the ability to do a comparative study across a large and diverse set of psychoactive drugs. It must be acknowledged that at the outset of the study, this was a kind of shot in the dark, with no assurance that anything significant would come of it: an untried method. Under the circumstances, an ethical argument could not be made for conducting clinical studies with so many powerful yet poorly understood drugs. Thus the ideal human data (double-blind controlled clinical studies conducted for the purpose of this study) could not be used. In fact human data could not be generated for this study. The study had to rely on data generated for other purposes. In order to be able to include data on so many drugs, it was necessary to work with an exceedingly heterogeneous set of data, with wildly varying sample sizes between drugs, with different drugs explored to different extents over their dose ranges, mixing data from scientific sources with data from guerilla psychopharmacology. This broad comparative method must of necessity work with such heterogeneous data. Only strong patterns can emerge from such data.

Affinity Assays

The NIMH-PDSP assayed twenty-five drugs for this study, each against fifty-one sites, and comparable data for ten others (mostly assayed by NIMH-PDSP) was gathered from the literature (Ray 2010). All the assays performed by the NIMH-PDSP are in transfected immortalized human cells (see ethics statement below). For this manuscript, the drugs must have been assayed at 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{7}, and human data must be 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). This study includes only the phenethylamine, tryptamine, and ergoline psychedelics which roughly correspond to classic hallucinogens. There are a wide variety of other compounds that are excluded from this study that have been described as hallucinogens and may produce similar psychedelic effects, but which operate through substantially different mechanisms, such as ketamine, PCP, cannabis, muscimole, salvinorin A, scopolamine and chronic amphetamine.

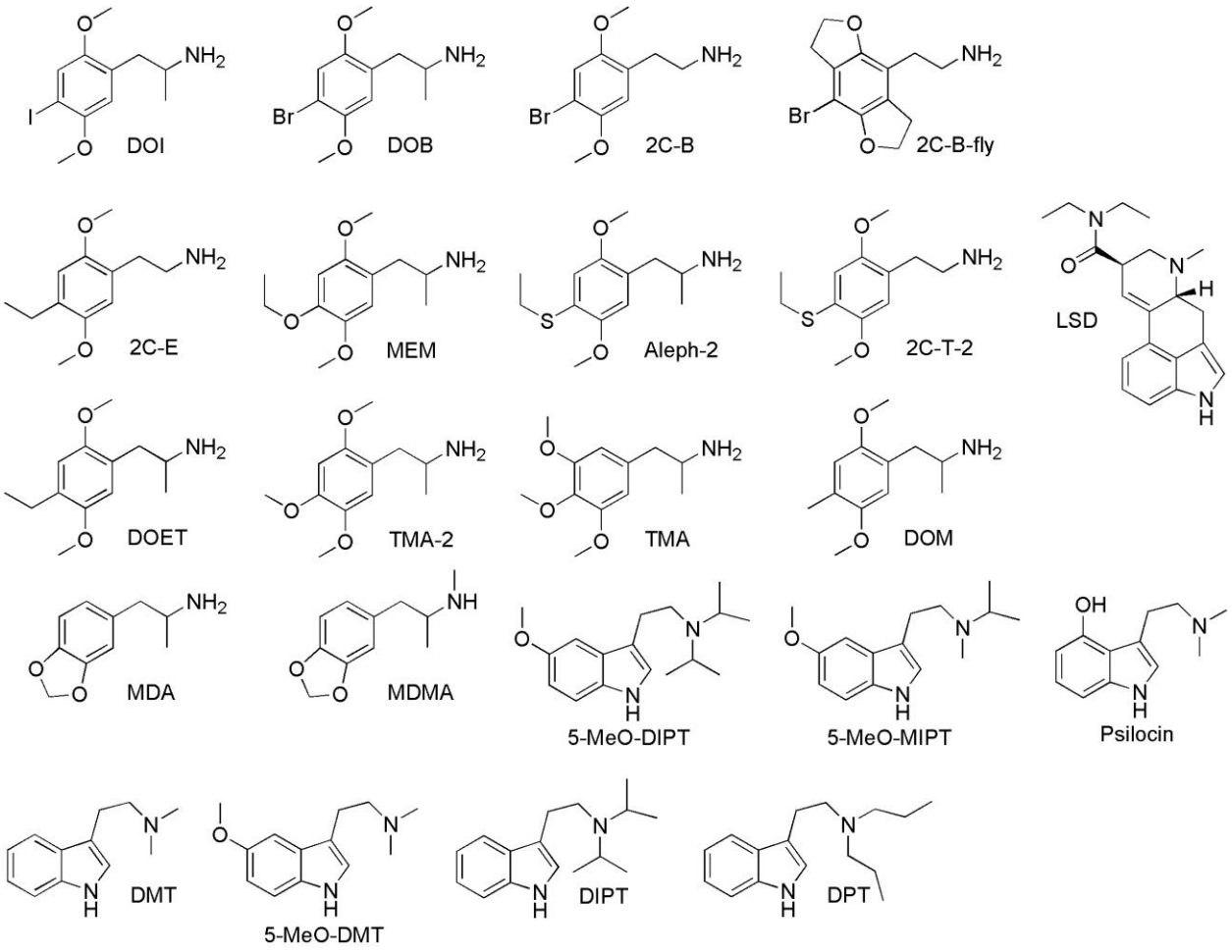

Figure 1: The twenty-two drugs of this study

Normalization

(Ray 2010) introduced a normalization of affinity data for multiple drugs at multiple receptors that effectively factors out the absolute potency of each drug, and allows us to focus on the relative affinities of each drug at each receptor. The description of normalization presented here is an update of that presented in (Ray 2010).

When the primary assay did not produce >50% inhibition, the K_i value is treated as >10,000. When the primary assay hit, but the secondary assay was not performed, the K_i value is also treated as >10,000. The lowest K_i value in the data set of this study (the thirty-five drugs discussed in (Ray 2010)) is 0.3 (lisuride at 5-HT_{1A}) and the highest value is 9,780 (DOET at Sigma-1), thus collectively, the data in this study cover nearly five orders of magnitude of K_i values. However, ignoring values reported as >10,000, the K_i values for a single drug in this study never exceed four orders of magnitude in range.

Raw K_i values are distributed over several orders of magnitude thus a log transform is a good first step. In addition, higher affinities produce lower K_i values, thus a change of sign producing pK_i is also standard practice: $pK_i = -\log_{10}(K_i)$. pK_i has the advantage that higher affinities have higher pK_i values, and each unit of pK_i value corresponds to one order of magnitude of K_i value. Generally, the highest K_i value generated by NIMH-PDSP is 10,000, which produces a pK_i value of -4.

Up to this point, the transformations have been applied equally to all K_i values across all receptors and all drugs. The next step is to bring the relative affinities for each drug into register at their highest values by subtracting a value pK_{iMax} from pK_i: $pK_i - pK_{iMax}$. pK_{iMax} is the maximum pK_i value for each drug, thus the value of pK_{iMax} is different for each drug. For each drug, the highest value of $pK_i - pK_{iMax}$ will be zero.

The vast majority of values of $pK_i - pK_{iMax}$ are negative. In some applications, it is convenient to transform the data such that all values are positive. This can be accomplished by adding an integer to all values of $pK_i - pK_{iMax}$. We can use the smallest integer, P, that makes all values positive: $P + pK_i - pK_{iMax}$ (known as "npK_i" or "relative affinity"). In this study, the value of the integer P is 4.

The normalization involves the following steps:

1. Start with raw K_i values
2. Log transform (this produces $\log_{10}(K_i)$)
3. Change sign (this produces $pK_i = -\log_{10}(K_i)$)
4. Subtract pK_{iMax} (this produces $pK_i - pK_{iMax}$); pK_{iMax} is the maximum pK_i value for each drug
5. Add smallest integer (P) that shifts all data into a positive range (this produces $P + pK_i - pK_{iMax}$, known as "npK_i" or "relative affinity")

For each individual drug:

- $npK_i = P + pK_i - pK_{iMax}$
- If K_i treated as >10,000, then $npK_i = 0$

The normalization will set the highest npK_i value for each drug to a value of P (4 in this study), and set all K_i values reported as >10,000 to a value of zero. The value P is not arbitrary, but is set by the range of the K_i data for each drug, which never exceeds four orders of magnitude of values in this data set. If the data ranged over at most three orders of magnitude, P would be set to a value of 3. We will call this normalized value "npK_i" (Ray 2010) or "relative affinity".

With this normalization:

- higher affinities have higher values
- all values are positive
- each unit of npK_i value represents one order of magnitude of K_i value
- affinities too low to be measured will be reported as zero
- for each drug, the highest affinity will be set to a value of P (4 in this study)
- potency is factored out so that drugs of different potencies can be directly compared

This normalization effectively factors out the absolute potency of each drug, and allows us to focus on the relative affinities of each drug at each receptor. This normalization reflects the practical reality that at the time of use, drugs with higher affinities are taken at lower doses than drugs with lower affinities. Active dose ranges of drugs reflect absolute affinity values. In order for a drug to achieve its full action, the drugs must achieve a plasma concentration that produces an effective level of receptor occupancy. The effective level of receptor occupancy can be achieved at a relatively low plasma concentration if the drug has high affinity for the receptor, or for a drug with low affinity for the receptor a higher plasma concentration will be required to achieve the same level of receptor occupancy. Plasma concentrations will correspond to the dose of the drug ingested. The adjustment of drug dose in correspondence to receptor affinity means that the organism effectively experiences the relative affinity profile of the drug, perhaps in a more meaningful sense than it experiences the absolute affinity profile. The correspondence of drug dose with drug receptor affinity effectively creates a biological transformation analogous to the normalization that occurs when pK_{iMax} is subtracted in the transformation leading to relative affinity, npK_i.

Perceptibility of Relative Affinities – likely different for agonists and antagonists

Over a period of years of observing the relationship between the qualitative subjective effects of psychedelics, and their pattern of relative affinities, I came to a rule of thumb that I first heard articulated by Dave Nichols: that a drug with 100-fold or more selectivity for one receptor can be seen as truly selective. Although stated by Nichols in the context of a drug that would be functionally selective for a single receptor, the principle implies that in drugs that act at many receptors, the perceptible receptor interactions would drop off to the imperceptible level when the receptor has at least two orders of magnitude less relative affinity than the best-hit receptor. This view is consistent with my review of the relevant data.

The concept of perceptibility of relative affinities in the context of psychedelic drugs acting at many receptors was introduced in the methods section of Ray 2010 (Ray 2010), and the text from that section as well as Figure 2 (Figure 3 in (Ray 2010)) are used here with some modifications related to its application in this study.

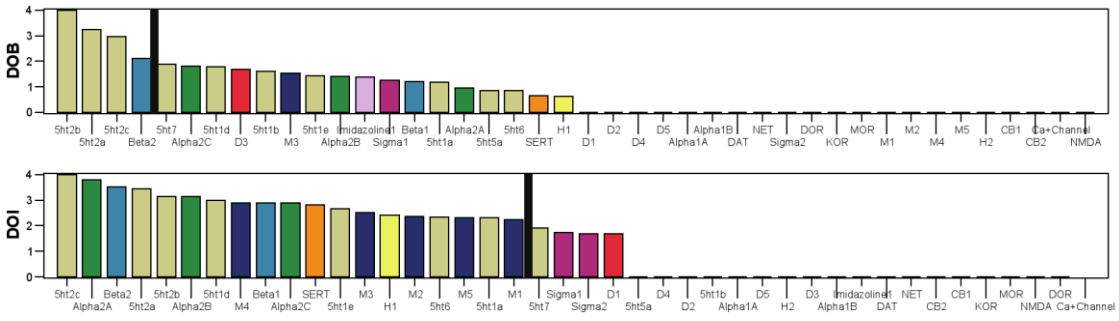

Figure 2. The ranked multi-receptor relative affinity profiles of DOB and DOI. The ranked multi-receptor affinity profiles of DOB and DOI. Not all of these affinities are able to produce perceptible mental effects. A black vertical bar represents a 100-fold

drop in affinity relative to the receptor with the highest affinity, and divides those npK_i values greater than 2.0 (on the left) from those 2.0 or less (on the right). This is presumed to be the limit of perceptible receptor interaction. Receptors to the right of the black bar should be imperceptible, while receptors to the left of the black bar should be perceptible, increasingly so the further left they are. In spite of the long tail of affinities, DOB is effectively selective for the three serotonin-2 receptors (beta-2 falls at the approximate limit of perceptibility), while DOI by contrast has nineteen receptors in the presumed perceptible range, although they should not all be equally perceptible. Previously published in (Ray 2010) as Figure 3.

Many psychedelic drugs interact with a large number of receptors (Ray 2010). For potent compounds like DOB and DOI, it is possible to measure K_i values over nearly a full four orders of magnitude range of affinity (Figure 2). However, not all of these affinities are able to produce perceptible mental effects. As a rule of thumb, 100-fold relative affinity is considered truly selective. Thus, receptors with npK_i values below about 2.0 should not have perceptible mental effects. In Figure 2 above, and Figures 2, 12, 14, and 15 of the main manuscript, a heavy black vertical or horizontal bar represents a 100-fold drop in affinity relative to the receptor with the highest affinity, and divides those perceptible npK_i values greater than 2.0 from those imperceptible npK_i values of 2.0 or less. This is presumed to be the limit of perceptible receptor interaction. The value 2.0 is an arbitrary round number. Careful observation of the data in this study suggests that a more accurate limit of perceptibility is closer to 2.15. Values to the right of or below the black bar should be imperceptible, while values to the left of or above the black bar should be perceptible, increasingly so the further left or above they are. Figure 2 above shows the ranked distributions of npK_i values for DOB and DOI. In spite of the long tail of affinities, DOB is effectively selective for the three serotonin-2 receptors (beta-2 falls at the approximate limit of perceptibility), while DOI by contrast has nineteen receptors in the presumed perceptible range, although they should not all be equally perceptible. The perceptibility of a receptor when activated by the full dose of a drug can be considered to be a continuum from the maximum possible effect at an npK_i value of 4.0, fading gradually as npK_i values decrease, until perceptibility vanishes before the npK_i value drops to 2.0 and below.

This principle of perceptibility of relative affinities however does not appear to apply to antagonist drugs, with antipsychotics being a good example. Seroquel is prescribed as a sleeping medication at 50 mg doses (Stahl 2013). Seroquel's best hit is histamine-1. This is the same best hit as diphenhydramine which is also sold for sleep in 50 mg doses (or for allergy in 25 mg doses). However, when used as an antipsychotic Seroquel is sold in 800 mg doses, sixteen times the dose used for sleep in the same dug. This means slamming the histamine-1 receptor very hard. Imagine taking sixteen 50 mg doses of diphenhydramine! In the case of Seroquel, there are many other receptors being hit along a spectrum of strength, in proportion to their relative affinity at the various receptors. This amazingly high dosing is explained theoretically on the grounds that the intent is to bring the dopamine-2 receptors up to a certain threshold of Seroquel occupancy. If this were the true mechanism of action, a much cleaner dopamine-2 antagonist drug should be safer and more effective. But it is not.

It appears that for agonists more than antagonists, taking a drug to higher doses eventually becomes uncomfortable, and the tendency is to settle on a moderate dose. Generally speaking,

for psychedelics I have not been able to detect the effects of receptors whose relative affinities (npK_i) are less than about 2.16. This specific principle likely does not apply to all classes of drugs.

Relative Affinity (npK_i), Selectivity (X-fold), and Perceptibility

To my knowledge, this formulation of relative affinity was first introduced by Ray 2010 (Ray 2010) who associated it with the symbol "npK_i", and the more descriptive phrase of "relative affinity" is being introduced here for the first time. However, relative affinity is essentially not new and is equivalent to one of the most widely used concepts in pharmacology: selectivity. Selectivity is widely used by medicinal chemists when developing ligands selective for a specific target. For example, Glennon et al. 2000 (Glennon *et al.* 2000) developed the agonist EMDT (2-ethyl-5-MeO-DMT) with "10-fold" greater affinity at the best-hit 5-HT_6, relative to the second best hit 5-HT_{1A}.

This standard formulation of selectivity is calculated as a simple ratio of K_i values, which I will call "X-fold". For EMDT with K_i values of 16 at 5-HT_6 and 170 at 5-HT_{1A}, we find X-fold = 170/16 = 10.6. X-fold is related to npK_i through a simple transformation (below). Thus EMDT has a relative affinity of 4 (P) at 5-HT_6 and 2.97 at 5-HT_{1A}.

- npKi = P – log(X-fold)

In every meaningful sense, npK_i and X-fold are completely equivalent, yet they tend to differ in the perspective from which they are used. The most common perspective for the use of X-fold is in relation to a key receptor, usually the best-hit receptor. In contrast, relative affinity is generally used to look at all the receptors that a drug interacts with, without preference for a key receptor. This broader perspective is also taken with X-fold when looking at the side effects produced by drugs that act a multiple sites, not just the intended target.

An excellent example of the use of X-fold from the broad perspective is the case of erectile dysfunction (ED) drugs whose target site is the phosphodiesterase PDE5. However, there are many phosphodiesterases, and ED drugs interact with several of these. Thus Bischoff (Bischoff 2004) has calculated X-fold for the interaction of three ED drugs with various phosphodiesterases. Setting P = 4, for all three drugs the best-hit is PDE5 (X-fold = 1, npK_i = 4), but the focus is really on the other phosphodiesterases, in relation to the side-effects caused by action there. The most interesting case in relation to the present study is PDE6 which is expressed in the retina. Action at PDE6 produces clearly perceptible visual effects in the form of a bluish tinge. This allows us to see the principle of perceptibility of relative affinities exhibited in a well understood system.

The first row of Table 1 shows the X-fold values reported by Bischoff (Bischoff 2004) for three drugs at PDE6, and the second row shows the corresponding npK_i values calculated from them (P = 4). Bischoff reports: "Inhibition of this enzyme can induce visual disturbances, which have occurred at the highest clinically applied dose of sildenafil and to a lesser extent with vardenafil. No visual disturbances have been reported with tadalafil use." This is consistent with the

suggestion above that npK_i values below 2 are imperceptible, while those above 2 are perceptible, increasingly so as we approach P.

	sildenafil	vardenafil	tadalafil
X-fold	7.4	15	780
npK_i	3.13	2.82	1.11

Table 1. Relative affinity and X-fold of ED drugs at PDE6 Selectivity (X-fold) values and relative affinity (npK_i) values at PDE6 for three erectile dysfunction drugs. The three X-fold values are taken directly from Bischoff (Bischoff 2004). npK_i values are calculated from X-fold as: $npK_i = P - \log(\text{X-fold})$, $P = 4$.

Given that X-fold and npK_i are essentially equivalent, and that X-fold has a long history of use in pharmacology, X-fold should continue to be the preferred index for most conventional work in pharmacology. I believe however that npK_i has advantages in studies that look at multiple drugs that act at many receptors, and when we are not focused on a key receptor.

Qualitative Dose Response

When studying the qualitative subjective effects of drugs that act at multiple receptors, it is important to recognize that quality can vary with the dose, as larger doses bring more receptors into perceptible levels of activation. Figure 3 illustrates two hypothetical drugs with the same quality but different potencies. Drug A has an order of magnitude higher receptor affinities than drug B, and both drugs have an order of magnitude higher affinity for 5-HT_{2A} than for 5-HT_7. Let us suppose that drug A is active in the 10-20 mg range, while drug B is active in the 40-80 mg range. At their lowest active doses (10 mg of A, 40 mg of B), each drug will cause perceptible activation of only the 5-HT_{2A} receptor, thus exhibiting only the mental qualities associated with 5-HT_{2A} activation.

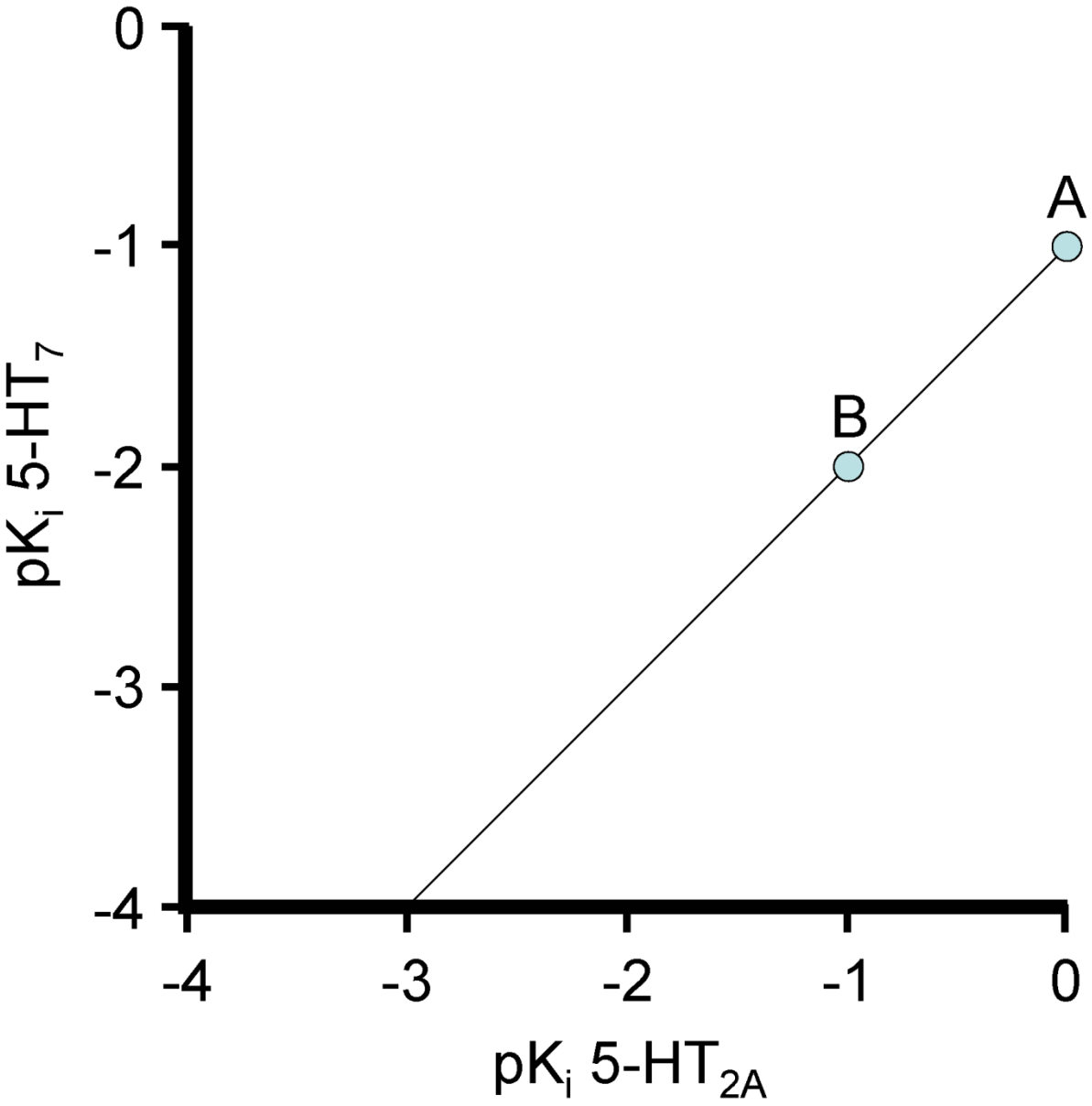

Figure 3 Qualitative Dose Response - Two hypothetical drugs which differ in potency due to having different affinities at the two receptors, but which have the same quality due to having the same relative affinities at the two receptors. For each drug, the lowest perceptible dose will manifest only the qualitative effects of the higher affinity receptor (5-HT$_{2A}$), while the high-end dose will manifest the qualitative effects of both receptors (5-HT$_{2A}$ and 5-HT$_7$), resulting in a gradual change in the quality of the drug across the dose range.

At the maximum dose of each drug (20 mg of A, 80 mg of B), the 5-HT$_{2A}$ receptor population might be saturated and fully activated. In addition, at these higher dose levels, both drugs will also cause perceptible activation of 5-HT$_7$. While their increased expression of 5-HT$_{2A}$ at the higher doses would be felt as a quantitative increase of the qualitative effects of 5-HT$_{2A}$

activation, bringing 5-HT_7 into the mix will cause a qualitative change in the effects of the drug, together with the quantitative changes.

At the low end of the dose ranges, both drugs should act through a single receptor, 5-HT_{2A}, while at the high end of the dose ranges, both drugs should act through two receptors, 5-HT_{2A} and 5-HT_7 (though more strongly through 5-HT_{2A}). 10 mg of drug A should produce qualitatively and quantitatively the same effects as 40 mg of drug B, while 20 mg of drug A should produce qualitatively and quantitatively the same effects as 80 mg of drug B. However 10 mg of drug A (or 40 mg of drug B) should produce both qualitatively and quantitatively different effects than 20 mg of drug A (or 80 mg of drug B).

The basic principles have been illustrated by the two-dimensional case of 5-HT_{2A} vs. 5-HT_7, but they are normally played out in higher dimensions. Most of the drugs in this study perceptibly activate at least several receptors.

Layering

Discerning the mental effects of individual receptors, in drugs that perceptibly activate multiple receptors, involves a layering process. The process begins with the most selective drugs, acting at a single receptor (or group of closely related receptors), then proceeds to drugs that add one additional receptor (or group of closely related receptors) at a time. Table 2 ranks the top six receptors in descending order of their strength of interaction with the thirty-five drugs studied by (Ray 2010).

Receptor	Bsq
serotonin-2B	19.48
serotonin-1A	16.63
serotonin-7	14.93
serotonin-1D	14.57
serotonin-2A	13.81
serotonin-2C	13.35

Table 2. Top Six Receptors. Table ranking the top six receptors in descending order of their strength of interaction with the thirty-five drugs studied by (Ray 2010), based on the breadth statistic B_{sq}. B_{sq} is the square root of the sum of squares of the npK_i values of each of the thirty-five drugs at a given receptor (Ray 2010). Serotonin-2B is overwhelmingly the receptor with the strongest interaction.

5-HT_{2B} is overwhelmingly the receptor with the strongest interaction. Fortuitously, we have a drug, MEM, that is 61-fold selective for the 5-HT_{2B} receptor. It's only other perceptible interaction is with 5-HT_{2A}. Thus the human pharmacology of MEM gives us good insight into the mental effects mediated by 5-HT_{2B} (they are subtle).

MEM: 4.00 5ht2b, 2.21 5ht2a, 2.10 Sigma1, 1.95 5ht7

The only perceptible interactions of the drug DOB are with the three 5-HT_2 receptors, and the qualitative effects of DOB appear to be very similar to those of MEM. This suggests that the

effects of the three 5-HT_2 receptors are qualitatively very similar, and subtle. These three receptors account for the first, fifth, and sixth most prominent receptors in Table 2.

DOB: 4.00 5ht2b, 3.23 5ht2a, 2.97 5ht2c, 2.11 Beta2

The second most prominent receptor in this study is 5-HT_{1A}. Fortuitously, we have a drug, DOET, for which 5-HT_{1A} is the best hit, and the only other strong interactions are with the three 5-HT_2 receptors which were characterized in the first steps of layering. DOET has a weak interaction (npKi = 2.40) with alpha-2B. By the principle of qualitative dose response (previous section), we can exclude the mental effects of alpha-2B by avoiding high doses. Having already determined the effects of the three 5-HT_2 receptors with MEM and DOB, we can now layer on the effects of 5-HT_{1A} (the effects are subtle and transparent, see section on "the flavor of a drug" below).

DOET: 4.00 5ht1a, 3.72 5ht2a, 3.70 5ht2b, 3.13 5ht2c, 2.40 Alpha2B, 2.07 5ht7, 2.05 Alpha2A, 2.00 Alpha2C

The fourth most prominent receptor in Table 2 is 5-HT_{1D}. Fortuitously, we have a drug, 2C-B-fly, for which 5-HT_{1D} is the second-best hit, and the only other perceptible interactions are with the three 5-HT_2 receptors. As with DOET for 5-HT_{1A}, we can use 2C-B-fly to layer on the effects of 5-HT_{1D} (the effects are subtle and transparent, see section on "the flavor of a drug" below). While we do not have drugs that allow us to cleanly layer the remaining 5-HT_1 receptors, we will treat them as if they are also subtle and transparent.

2C-B-fly: 4.00 5ht2b, 3.81 5ht1d, 2.93 5ht2c, 2.89 5ht2a

The third most prominent receptor in Table 2 is 5-HT_7, which is the second-best hit for 5-MeO-MIPT and 5-MeO-DMT (after the best-hit 5-HT_{1A}). The perceptible interactions for these two drugs are shown below with 5-HT_7 highlighted in green, 5-HT_2 in red, and 5-HT_1 in blue:

5-MeO-MIPT: 4.00 5ht1a, 3.79 5ht7, 3.74 5ht1d, 3.32 5ht2b, 2.98 5ht6, 2.85 Alpha2A, 2.61 5ht1b, 2.44 5ht2a, 2.29 Alpha2C
5-MeO-DMT: 4.00 5ht1a, 3.69 5ht7, 3.48 5ht1d, 2.73 5ht6, 2.41 5ht1b, 2.38 D1

We are now in a position to layer the effects of 5-HT_7 on top of 5-HT_1 for 5-MeO-DMT, and on top of 5-HT_1 and 5-HT_2 for 5-MeO-MIPT. To avoid the potentially confounding effects of 5-HT_6, alpha-2, and dopamine-1, we should look at the effects of low to moderate doses. What we find is that the effects of 5-HT_7 (unlike 5-HT_1 and 5-HT_2) are very dramatic.

At this stage of the layering process we have learned that the effects of 5-HT_1 and 5-HT_2 are subtle and transparent, and we can look past them in the layering process, as we examine the effects of other receptors. However, the effects of 5-HT_7 are dramatic, and as we examine more receptor interactions, we find that the effects of 5-HT_7 dramatically alter the effects of other receptors. Thus, in using the layering method to discern the effects of individual receptors, we must try to avoid the influence of 5-HT_7, while we can tolerate and look past the influence of 5-HT_1 and 5-HT_2.

With these principles in mind, we can cleanly layer in the effects of a variety of other receptors:

MDA: 4.00 5ht2b, 3.60 Alpha2C, 3.12 Alpha2B, 2.74 Alpha2A, 2.41 5ht7, 2.38 5ht1a
DOM: 4.00 5ht2b, 3.38 Beta2, 2.75 5ht1d, 2.36 5ht2a, 2.30 Alpha2A
Aleph-2: 4.00 5ht2b, 2.79 Beta2, 2.50 5ht2c, 2.42 5ht2a
TMA-2: 4.00 5ht2b, 3.42 5ht2a, 3.04 H1, 2.58 5ht2c

MDA allows us to layer in the effects of the three alpha-2 receptors, DOM and Aleph-2 layer the effects of beta-2, and TMA-2 layers the effects of histamine-1.

While we have learned to avoid layering receptors in the presence of 5-HT_7, there is no drug that allows us to layer dopamine in the absence of 5-HT_7. Psilocin is the only drug of the study whose relative affinity at any dopamine receptor is greater than its relative affinity at 5-HT_7. Thus psilocin is our best hope for characterizing dopamine:

Psilocin: 4.00 5ht2b, 3.40 5ht1d, 3.37 D1, 3.03 5ht1e, 2.88 5ht1a, 2.83 5ht5a, 2.82 5ht7, 2.82 5ht6, 2.67 D3, 2.52 5ht2c, 2.19 5ht1b, 2.14 5ht2a

Having layered 5-HT_1, 5-HT_2, 5-HT_7, alpha-2, beta-2, histamine-1, and dopamine-1, we are in a position to layer more complex drugs:

MDMA: 4.00 Imidazoline1, 3.64 5ht2b, 3.26 Ca+Channel, 3.21 Alpha2C, 3.09 Alpha2B, 3.07 M3, 2.94 Alpha2A, 2.54 M5, 2.43 M4
Mescaline: 4.00 Alpha2C, 3.97 5ht2b, 3.61 5ht1a, 3.44 Imidazoline1, 3.16 5ht1e, 2.92 Alpha2A

For MDMA and mescaline, we have already layered most of the receptor interactions other than imidazoline-1 (except Ca+Channel and muscarinic). Thus by examining the pharmacology of both drugs, we can discern the mental effects mediated by imidazoline.

DMT and DPT are the two drugs of this study that have the broadest interaction with receptors, thus they would be the least appropriate drugs to use in the process of layering. However, these are the only two drugs of this study that present fully perceptible relative affinities of the two alpha-1 receptors:

DMT: 4.00 5ht7, 3.97 5ht1d, 3.91 5ht2b, 3.53 Alpha2B, 3.53 Alpha2C, 3.51 D1, 3.42 5ht2c, 3.28 5ht1e, 3.25 5ht6, 3.16 5ht5a, 3.13 Imidazoline1, 2.95 Alpha1B, 2.75 Alpha2A, 2.70 Alpha1A, 2.58 5ht2a, 2.37 SERT, 2.23 Sigma1
DPT: 4.00 5ht1a, 3.88 5ht2b, 3.41 H1, 3.31 SERT, 3.05 5ht7, 2.97 Imidazoline1, 2.97 Alpha2B, 2.90 Sigma1, 2.86 Alpha1B, 2.84 Alpha2A, 2.79 Alpha2C, 2.71 5ht1d, 2.57 5ht1b, 2.56 Alpha1A, 2.37 D3, 2.33 DAT, 2.31 5ht2c, 2.20 D4, 2.13 5ht1e, 2.09 5ht2a, 2.04 Sigma2

Thus a hypothesis for alpha-1 has been put forward based on DMT and DPT, however it should be acknowledged that it is not clear if receptors can be layered from such complex drugs. The primer/probe method (Ray 2016) has resulted in the creation of new psychedelic drugs, including primed clonidine which should be much more suitable for layering alpha-1.

The Flavor of a Drug

One would expect that the flavor of a drug would be dominated by the best hit receptor(s). But this is not always the case because there are some receptors (5-HT_1 and 5-HT_2) whose mental effects are "subtle" and "transparent." By subtle is meant that it is difficult to note the effect. By transparent is meant that the mental effects resulting from strong affinity at a transparent receptor do not mask the mental effects of a receptor with less (yet perceptible) affinity for the drug. The rule becomes that the flavor of a drug is dominated by the best hit perceptible receptor other than 5-HT_1 or 5-HT_2.

A caveat to this rule is that if the best hit receptor other than 5-HT_1 or 5-HT_2 has a relative affinity value (npK_i) in the lower third of the perceptible range (thus, below 2.67) then the action of that receptor will be weak and it might not play the role of the dominant receptor (e.g., alpha-2B in DOET or alpha-2C in 2C-T-2). If there is no viable candidate for dominant receptor other than 5-HT_1 or 5-HT_2, then the dominant receptor is just the best hit (DOET, DOB, MEM, 2C-B-fly, 2C-T-2). We should acknowledge that there is a grey area. For a drug like DOET or 2C-T-2, it is not completely clear if its weak but perceptible affinity at alpha-2 would constitute the dominant flavor. This may depend on the particular sensitivities of the subject.

Based on these rules the dominant flavor of MDMA is its best hit, imidazoline-1, while the dominant flavor of psilocin is dopamine-1 the third best hit, after 5-HT_{2B} and 5-HT_{1D}. The thirty-five drugs of the study by (Ray 2010) feature seventeen dominant receptors (Table 3 of dominant flavors).

Drug	Dominant Flavor	Best Hit	2nd Best Hit	3rd Best Hit	4th Best Hit	5th Best Hit
DOET	**5ht1a**	***4.00 5ht1a***	3.72 5ht2a	3.70 5ht2b	3.13 5ht2c	2.40 Alpha2B
DOB	**5ht2b**	***4.00 5ht2b***	3.23 5ht2a	2.97 5ht2c	2.11 Beta2	
MEM	**5ht2b**	***4.00 5ht2b***	2.21 5ht2a	2.10 Sigma1		
2C-B-fly	**5ht2b**	***4.00 5ht2b***	3.81 5ht1d	2.93 5ht2c	2.89 5ht2a	
2C-T-2	**5ht2b**	***4.00 5ht2b***	3.18 5ht2a	3.05 5ht2c	2.84 5ht1d	2.56 Alpha2C
RR-2b	**5ht5a**	4.00 5ht1b	3.59 5ht1a	***3.20 5ht5a***	3.05 5ht1d	2.81 5ht7
EMDT	**5ht6**	***4.00 5ht6***	2.97 5ht1a	2.74 5ht1d	2.73 5ht7	2.49 5ht1e
5-MeO-TMT	**5ht6**	***4.00 5ht6***	3.62 5ht7	3.48 5ht1a	3.38 5ht1d	2.52 5ht1e
6-F-DMT	**5ht6**	***4.00 5ht6***	3.93 5ht2b	3.80 5ht7	3.74 H1	3.66 5ht1d
DMT	**5ht7**	***4.00 5ht7***	3.97 5ht1d	3.91 5ht2b	3.53 Alpha2B	3.53 Alpha2C
5-MeO-MIPT	**5ht7**	4.00 5ht1a	***3.79 5ht7***	3.74 5ht1d	3.32 5ht2b	2.98 5ht6
LSD	**5ht7**	4.00 5ht1b	***3.77 5ht7***	3.75 5ht6	3.73 5ht1a	3.70 5ht1d
5-MeO-DMT	**5ht7**	4.00 5ht1a	***3.69 5ht7***	3.48 5ht1d	2.73 5ht6	2.41 5ht1b
Psilocin	**D1**	4.00 5ht2b	3.40 5ht1d	***3.37 D1***	3.03 5ht1e	2.88 5ht1a
cis-2a	**D3**	4.00 5ht1a	3.79 5ht1b	***3.46 D3***	3.30 5ht7	3.25 5ht6
SS-2c	**D3**	4.00 5ht1a	3.22 5ht1b	***2.82 D3***	2.45 5ht7	2.44 5ht6
DOI	**Alpha2A**	4.00 5ht2c	***3.79 Alpha2A***	3.52 Beta2	3.44 5ht2a	3.13 Alpha2B
2C-B	**Alpha2C**	4.00 5ht2b	3.71 5ht1d	3.69 5ht2a	3.18 5ht2c	***3.12 Alpha2C***
Mescaline	**Alpha2C**	***4.00 Alpha2C***	3.97 5ht2b	3.61 5ht1a	3.44 Imidazoline1	3.16 5ht1e
lisuride	**Alpha2C**	4.00 5ht1a	***3.88 Alpha2C***	3.78 Alpha2B	3.22 Alpha2A	3.01 5ht2b
MDA	**Alpha2C**	4.00 5ht2b	***3.60 Alpha2C***	3.12 Alpha2B	2.74 Alpha2A	2.41 5ht7
2C-E	**Alpha2C**	4.00 5ht2b	3.76 5ht2a	3.54 5ht1d	***3.44 Alpha2C***	3.38 5ht2c
4C-T-2	**Beta2**	4.00 5ht2b	***3.67 Beta2***	3.33 5ht2a	3.09 5ht2c	3.05 Sigma1
DOM	**Beta2**	4.00 5ht2b	***3.38 Beta2***	2.75 5ht1d	2.36 5ht2a	2.30 Alpha2A
Aleph-2	**Beta2**	4.00 5ht2b	***2.79 Beta2***	2.50 5ht2c	2.42 5ht2a	
DPT	**H1**	4.00 5ht1a	3.88 5ht2b	***3.41 H1***	3.31 SERT	3.05 5ht7
TMA-2	**H1**	4.00 5ht2b	3.42 5ht2a	***3.04 H1***	2.58 5ht2c	
MDMA	**Imidazoline1**	***4.00 Imidazoline1***	3.64 5ht2b	3.26 Ca+Channel	3.21 Alpha2C	3.09 Alpha2B
5-MeO-DIPT	**Imidazoline1**	4.00 5ht1a	3.91 5ht2b	***3.24 Imidazoline1***	3.03 5ht7	2.89 5ht1d
DIPT	**Imidazoline1**	4.00 5ht1a	***3.53 Imidazoline1***	3.48 5ht2b	2.98 SERT	2.83 Sigma1
Ibogaine	**Sigma2**	***4.00 Sigma2***	3.57 SERT	3.02 DAT	3.01 NMDA	2.88 KOR
TMA	**Sigma1 & Sigma2**	4.00 5ht2b	***3.95 Sigma2***	***3.95 Sigma1***	3.80 5ht7	3.45 5ht1a
Salvinorin_A	**KOR**	***4.00 KOR***				
Morphine	**MOR**	***4.00 MOR***	2.21 KOR	0.72 DOR		
THC	**CB1**	***4.00 CB1***	3.78 CB2			

Table 3 Dominant Flavor - Table listing the dominant flavor of each drug, and illustrating how it is determined by the rule: the best hit receptor other than 5-HT_1 and 5-HT_2 (unless the candidate non-5-$HT_{1/2}$ receptors have npK_i values below 2.67). The receptor corresponding to the dominant flavor is listed in the column labeled "Dominant Flavor". The table lists the five receptors at which each drug has the highest affinities. The "Best Hit" column displays the receptor at which the drug has the highest affinity, together with its npK_i value (4.0 by definition). The "2nd Best Hit" column displays the receptor at which each drug has its second highest affinity, together with the npK_i value at that receptor. This continues for the 3rd, 4th, and 5th highest affinities. The dominant flavor is highlighted with bold, italics, and blue. There is ambiguity for DOET and 2C-T-2.

In summary, we can interpret the flavor of a drug as being dominated by the mental effect of its best-hit receptor (ignoring 5-HT_1 and 5-HT_2), with the dominant flavor being successively blended with the mental effects of the successively less strongly activated receptors, to produce a perceptual whole, much like the way odorants and tasteants produce the perceptual whole of flavor out of their pattern of interaction with multiple odor and taste receptors ("full-flavor psychopharmacology").

Sources of Subjective Human Data

The mental effects of the compounds in this study are interpreted from the existing literature on the subjective effects in humans of the twenty-two drugs. For each drug of the study, as much

subjective human data as possible has been collected. Subjective data is rejected if there is doubt about the identity of the drug used. Polydrug data is also rejected.

The analysis draws on a wide array of heterogeneous sources, published over a period of many decades. It includes for example, the classic "Doors of Perception" (Huxley 1954), and clinical studies conducted both before the prohibition (Pahnke 1963; Masters & Houston 1966; Snyder *et al.* 1968; Soskin *et al.* 1973; Grof 1975; Soskin 1975) and after relaxing of the prohibition (Griffiths *et al.* 2006; Strassman 2001).

In addition, after the prohibition, human studies continued with unscheduled compounds, outside of the institutional context. The best of this work is that conducted by Alexander Shulgin and associates (Shulgin & Shulgin 1991; Shulgin & Shulgin 1997). The protocol for these studies is described in (Shulgin *et al.* 1986). In addition to the published human data, Shulgin accumulated a large number of reports of human experience with a wide variety of drugs which have not yet been published. The Shulgin archive consists of over twenty-four books of human data, totaling over 3,000 pages. These reports are in the process of being photographed, de-identified, and uploaded to the Internet Archive (Shulgin 2009a; Shulgin 2009b; Internet Archive 2010) and the Erowid archive (Shulgin 2017). The unpublished data from the Shulgin archive will be cited as (Shulgin 2016). In order for me to access the unpublished Shulgin data which contains identifiers, it was necessary to have the project reviewed and approved by the University of Oklahoma Institutional Review Board.

In addition, human experiments took place not only outside of the institutional context, but outside of the academic or scientific context as well. These unauthorized experiments are reported in a variety of locations, from "The Entheogen Review, The Journal of Unauthorized Research on Visionary Plants and Drugs", to drug archives (Erowid 2010; lycaeum.org 2010), forums (Drugs Forum 2010; Bluelight 2010; Hip Forums 2010), podcasts (Ball 2010; Dopefiend 2010; Lorenzo 2010), YouTube (YouTube 2011), and Tumblr (Tumblr 2012).

Because this study is based primarily on descriptions of the subjective experience, it is not necessary to limit the study to data from proper controlled clinical studies. The primary exclusion criterion is the case that there might be doubt about the identity of the drug used by the subject. For this reason, trip reports uploaded to web sites such as Erowid have been used with caution. Additionally, polydrug use generally obscures the relationship between receptors and mental effects.

There was a period of about five years, 1999-2004, in which a number of companies in the United States sold "research chemicals" to the general public (Figure 4). These companies provided a wide variety of exotic psychedelic drugs, and the compounds were genuine. The era of easy availability of "designer drugs" in the USA came to an end in July 2004, when the DEA conducted "Operation Web Tryp," arresting the operators of five web sites selling "research chemicals" (Editor 2004; justice.gov 2004). Even so, foreign suppliers continue to operate, as well as anonymous internet markets such as Silk Road (which was shut down in October 2013). During the era of research chemicals over the internet, a large number of people have experimented with a wide variety of reliably identified psychedelics, and many of these experiments have appeared as reports on archive web sites such as Erowid.

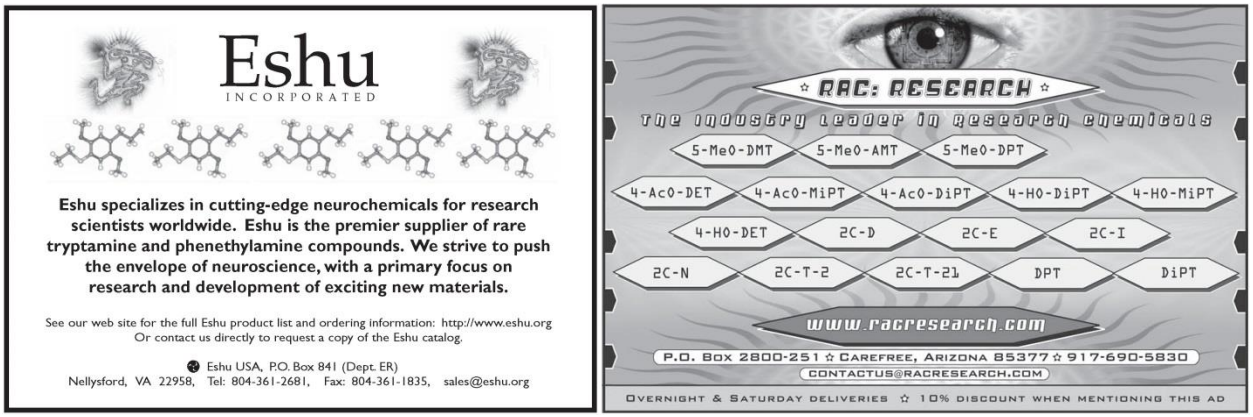

Figure 4: Advertisement for Eshu, "neurochemicals for research scientists" which was placed on page 9 of the Spring/Summer 2000 issue of The Entheogen Review. Advertisement for RAC, "research chemicals" which was placed on page 26 of the Vernal Equinox 2004 issue of The Entheogen Review.

Reports from Erowid and similar sites can be used for some drugs whose natural sources or distinctive qualitative properties allow them to be clearly identified from the report (e.g., DIPT, 5-MeO-DMT, salvia (Salvinorin A), psilocybin mushrooms (psilocybin), peyote cactus (mescaline), cannabis (THC)), or where other data is limited (2C-B-fly, 5-MeO-MIPT, 5-MeO-DIPT). Erowid reports are especially unreliable for rare scheduled drugs such as DOM or DOB. For common scheduled drugs such as LSD or MDMA, Erowid reports can be useful, yet it may be preferable to seek sources where the drugs are reliably identified, which are abundant.

Given that the primary criterion for rejecting data is uncertainty about the identity of the drug, I would like to describe a tiered system for classifying the reliability of drug identity:

- Gold standard:
    - Research done by scientists, in which the drugs are obtained from reliable sources such as reputable chemical companies (e.g. Sandoz, Sigma) or in which the drugs were synthesized in the research laboratory and verified by spectroscopy. The work of Shulgin and his associates falls within the gold standard.
    - Drugs obtained from readily available and readily identifiable natural sources are included, such as psilocybin mushrooms, peyote, salvia, and cannabis.
- Tier 1:
    - Unscheduled drugs obtained from disreputable companies selling "research chemicals" (e.g. Figure 4). The drugs provided by these companies have mostly proven to be valid.
    - Readily available scheduled drugs obtainable from natural sources and easily synthesized, with distinctive qualitative properties (e.g. DMT, 5-MeO-DMT)
- Tier 2:
    - Scheduled drugs obtained on the black market. The identities of these drugs are notoriously unreliable.

When interpreting the properties of a drug, an attempt is made to do so exclusively with Gold standard data. If necessary, Tier 1 data is also included. Tier 2 data is not used.

Types of Subjective Human Data

For the most part, the human data used in this study consists of subjective reports written by individuals during or after their drug experience. For example:

> DMT: They were trying to show me as much as possible. They were communicating in words. They were like clowns or jokers or jesters or imps. There were just so many of them doing their funny little thing. I settled into it. I was incredibly still and I felt like I was in an incredibly peaceful place. Then there was a message telling me that I had been given a gift, that this space was mine and I could go there anytime. I should feel blessed to have form, to live. It went on forever. There were blue hands, fluttering things, then thousands of things flew out of these blue hands. I thought "What a show!" It was really healing. (Strassman 2001) p. 192

However, in some cases, the researcher has written a summary of characteristics of the drug, based on the review of, observation of, or participation in, multiple sessions. For example:

> LSD: The drug taker becomes extraordinarily suggestible, reacting with heightened sensitivity to faces, gestures, and small changes in the environment. As everything in the field of consciousness assumes unusual importance, feelings become magnified to a degree of intensity and purity almost never experienced in daily life; love, gratitude, joy, sympathy, lust, anger, pain, terror, despair, or loneliness may become overwhelming. Hidden ambivalent emotion becomes fully conscious, so that two seemingly incompatible feelings may be experienced at the same time. It is possible to achieve either unusual openness and emotional closeness to others or an exaggerated detachment that makes others seem like grotesque puppets or robots (Grinspoon & Bakalar 1997) p. 12-13
>
> DOET, a drug that has been found by several research groups to facilitate the unblocking of imagination and creativity…
> 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…
> 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)

Quantitative data from psychometric tests can be used as well. An excellent example of the use of psychometric tests is the work of Griffiths et al. (Griffiths *et al.* 2006) who showed through psychometric tests that "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". However, we better understand what this means when we also consider the subjective reports and learn that the meaningfulness of the experience was "similar, for example, to the birth of a first child or death of a parent" (Griffiths *et al.* 2006). Psychometric tests do not tell the whole story. In their 14-month follow up, Griffiths et al. (Griffiths *et al.* 2008) explicitly acknowledge this:

> Although the patterns of responses on the various subscales of questionnaires provide an empirical representation of the nature of the psilocybin session experiences, unstructured comments from volunteers are helpful to further understand the sustained high ratings of spiritual significance at the 14-month follow-up. Table 3 presents verbatim written comments about the nature of the spiritual experience for all 24 volunteers, who rated the experience at the 14-month follow-up as being among the top five spiritual experiences of their lives. Although not easily summarized, several themes from these unstructured comments include 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)

All three kinds of data, subjective reports, syntheses of multiple experiences, and quantitative data from psychometric tests were used in this study. The most valuable human data for this work are vivid descriptions of subjective experiences, therefore the references used in this study are strongly biased toward that kind of data.

Sampling of Human Data

One of the core arguments presented here (5-HT_7 mediates depth of consciousness) is based on an analysis of the occurrence of three mental phenomena (open-eyed creative Visuals, Ego-loss, loss of contact with Reality) along a gradient of relative affinity for 5-HT_7. Because frequent reference will be made to these three specific effects, an acronym is introduced as a convenience. "VER" will be used in two slightly different ways. Sometimes VER will refer to "open-eyed creative Visuals *and* Ego-loss *and* loss of contact with Reality", while at other times VER will refer to "open-eyed creative Visuals *or* Ego-loss *or* loss of contact with Reality". The usage should be clear in the context. The three components of VER are not a phenomenological cluster. They may occur alone, and in various combinations. The hypothesis is that when there is strong action at 5-HT_7, at least one of the three elements of VER will appear.

For the purpose of evaluating this hypothesis, a sample of two hundred and fifty reports on the subjective effects of the twenty-two drugs of this study were assembled and each report was evaluated by blind raters for the presence or absence of each of the three components of VER. These reports together with the results of the blind rating are presented in the S07GradientReports.pdf document available with the supporting information. The following procedure was used in sampling the drugs:

- If there is a dose range for which VER is typical
    - Collect a sample of reports that vividly and explicitly describe VER
- If there is no dose range for which VER is typical
    - Collect all reports that vividly and explicitly describe VER
    - Collect all reports that suggest or allude to VER, even though vague

- Collect a sample of typical reports

Among the twelve drugs that have no dose range for which VER is typical, only two reports were found that vividly and explicitly describe VER, although there are several that vaguely suggest or allude to VER. Comparable numbers of reports were gathered for drugs for which VER is typical (average of 8.8 reports/drug) and not typical (average of 9.8 reports/drug), with three exceptions (excluded from averages just reported): A more extensive review of DOM was conducted (34 reports) to counter the widespread belief that it is a heavy hallucinogen; A collection of very short reports on 2C-T-2 were included from (Stolaroff & Wells 1993) for a total of 42 reports; All 19 available reports were included for the rare drug 2C-B-fly. The specific sources of human data can be seen by reviewing the S07GradientReports.pdf document available with the supporting information.

Interpreting Subjective Human Data

At this stage of the research program, a natural scientific instinct would be to quantify the subjective human data, perhaps through some statistical analysis of word usage (Coyle *et al.* 2012; Dye 2012). However, such methods would tend to miss the meaning or feeling contained in the reports. What is called for as a first step in this study is simply to listen carefully to the reports, as many as possible, and catch what they are saying (without the burden of preconceptions about receptor mechanisms or set and setting). This is a fully subjective approach to interpreting fully subjective data.

The initial goal is simply to discover the relationships between receptor affinities and subjective reports, which can be treated as hypotheses. At a later stage of the research program, we can quantify the subjective experience and make an objective analysis of it, in order to test the hypotheses generated by the initial subjective stage. The present manuscript embodies both steps, in that, for example, a subjective reading of the reports led to the observation that VER correlates with relative affinity at 5-HT_7 (together with related observations for a dozen additional receptors or groups of closely related receptors (Ray 2012)), and then the subjective reports were quantified by blind raters as a first step in testing the VER/5-HT_7 hypothesis.

Persons using psychedelic drugs often bring great expectations and even an attitude of reverence to the experience. As a result, the experience can be described with superlatives even if the drug turns out to be an active placebo. Griffiths et al. (Griffiths *et al.* 2006) report that 4 of 36 volunteers had a "complete" mystical experience after the active placebo methylphenidate (also known as Concerta, Methylin, or Ritalin). In measures assessed two months post-sessions, 8% rated the methylphenidate experience to be among the top five most spiritually significant experiences of his or her life, and rated that the methylphenidate experience increased their current sense of personal wellbeing or life satisfaction "moderately" (17%) or "very much" (4%). Therefore, a psychedelic drug cannot be accurately characterized on the basis of a few exceptional reports. Rather, I will try to characterize the drugs on the basis of what is typical for that drug. In some cases it will be necessary to acknowledge a few atypical "false positives", which may correspond to a placebo effect (Griffiths *et al.* 2006).

Recognizing VER

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".

Loss of contact with reality may be just that and no more, leaving the subject in a formless void; or loss of contact with actual reality may be accompanied by the construction of a complete visually rendered alternate reality. The latter is the effect referred to by Nichols (Nichols 2004): "The user may feel transported to an alternate time or place, another dimension, or another plane of existence that may seem completely real."

A wide range of effects appear to be produced by 5-HT_7, 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 I will use them as the primary means of recognizing the effects of 5-HT_7 in subjective reports. Drugs acting through many receptors cause closed-eyed visuals, but here we will only consider open-eyed visuals. The easiest way to detect 5-HT_7 effects from subjective reports is through its distinctive open-eyed creative visual effects. But there are also dramatic open-eyed visual effects that appear to emerge from activation of non-5-HT_7 receptors, and it is essential to be able to distinguish the two.

- Simple Visuals: apparently through non-5-HT_7 receptors
    - 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 receptors
    - 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

The division described above, between creative and simple visual effects apparently mediated by 5-HT_7 or by other receptors, is based on empirical observation of the data, not theoretical considerations. A careful synthesis of the subjective data together with the relative affinity data showed that some visual effects, but not others, are associated with relative affinity at 5-HT_7.

The document S06Training.pdf included in the supporting information explains in pragmatic detail and with abundant examples how to recognize creative visuals, ego-loss, and loss of contact with reality. It provides clear examples of how to distinguish creative visual effects from simple visual effects. This document provides training for blind raters to recognize the presence or absence of VER without any conceptual framework related to receptor systems.

Blind Rating

As an aid in summarizing and visualizing the verbose and voluminous human data, each of two-hundred-fifty reports of subjective experiences with the twenty-two drugs was characterized by human raters who were blind to the drug, dose, subject, place, and literature source of the reports. The blind was achieved by manually editing the 250 reports, removing all specific references to drugs, doses, places, persons, or literature source. For example: "I have taken [this drug] twice. My first dose was [Y] mg." This editing can be seen clearly by examining the two blinded documents in the supporting information (S08RatingUnevaluated.pdf and S09RatingEvaluated.pdf), and comparing them to the unblinded document S07GradientReports.pdf also available in the supporting information.

For each report, raters were asked to evaluate the presence or absence of each of three mental phenomena: open-eyed creative visuals, ego-loss, and loss of contact with reality. These three phenomena were chosen because careful synthesis of the literature and affinity data for the twenty-two drugs showed that these specific phenomena are associated with relative affinity for 5-HT_7. Before rating the reports, the raters were required to read a training document, S06Training.pdf (available in the supporting information). The training document provides specific instructions with examples of how to recognize the three mental phenomena. The two-hundred-fifty reports with drugs, doses, subjects, and literature sources removed were assembled by Perl scripts (available in supporting information as S10PerlScripts.zip) into a different random order for each rater. An example of the report file before and after rating for a rater who evaluated all 250 reports is available as S08RatingUnevaluated.pdf and S09RatingEvaluated.pdf in the supporting information. Here is the first report from the unevaluated file:

```
Report: 51221
Another patient described a visionary scene of being on a mountaintop where
he was embraced by two figures that he identified as Christ and the Holy
Spirit.  Concomitant with this embrace, he claimed to have experienced an
intuitive insight that, in spite of his cancer, life still somehow made sense
and there was no ground for anxiety.
PA - Creative visuals
PA - Ego-loss
PA - Loss of contact with reality
```

After review by the University of Oklahoma Institutional Review Board (see Ethics Statement below) the students in my spring 2013 psychopharmacology course were invited to participate, and informed that the data they generated would be used in the publication of my research. They were given no other assignment for one week, and received full credit for the week's activities whether they participated or not. The Perl script that randomized the subjective reports produced one file for each student, with the student's name in the file name. I then sent the files directly to the students by email, and they returned the results directly to me by email, with their names still

in the file name. Students were encouraged *not* to participate for any of a variety of reasons (S06Training.pdf, p. 10 in supporting information). Ten of thirty-four students did not participate at all, and there was great variation in effort among the twenty-four students who did participate (Table 4). The complete set of ratings by all twenty-four participating students is included in the supporting information as the file S10BlindRating2013.zip.

Rep	Dec		Rep	Dec
9	27		78	234
11	33		84	252
24	69		84	248
27	81		91	272
32	95		94	282
37	111		95	285
40	120		119	357
42	124		133	397
53	159		249	746
68	204		250	750
73	219		250	750
73	219		250	750

Table 4. Numbers of reports evaluated by individual blind raters. Ten of thirty-four students did not participate at all in the blind rating exercise. Of the twenty-four who did participate, the level of participation varied widely. This table shows the distribution of participation of the twenty-four participating students. "Rep" is the number of reports evaluated by each rater. "Dec" is the number of presence/absence decisions made by each rater.

In this context, VER is present if any one or more of the three elements (open-eyed creative Visuals *or* Ego-loss *or* loss of contact with Reality) are reported by the rater as present. When multiple ratings of multiple reports are averaged across an individual drug, this form of VER takes values between zero and one, and is presented in Figure 12 of the main manuscript (and in S04ProspectiveReceptors.pdf available in the supporting information). The results were pooled and calculated by a Perl script, which used all ratings produced by all twenty-four participating students. The blind rating results for each of the two-hundred-fifty reports are presented in the document S07GradientReports.pdf available in the supporting information. Although quantitative, the blind rating results are not suitable for statistical analysis because of the way the data was sampled (described above in the "Sampling of Human Data" section).

Ethics Statement

This manuscript does not describe primary research with human subjects; however, the research required access to the Shulgin archive which contains identifiers. In order for me to access the Shulgin archive it was necessary for me to be trained in research with human subjects, to develop a protocol for the secure storage and proper handling of the data, and to submit a description of the protocol and an application to the University of Oklahoma Institutional Review Board. This protocol described the overall project including the synthesis of NIMH-PDSP assay data with

descriptions of subjective human experience. It was determined that my project meets the criteria in 45 CFR 46, as amended, for exemption from IRB review. I was given permission to proceed with the Shulgin archive research project. The protocol for the use of students as blind raters was reviewed by the University of Oklahoma Institutional Review Board who determined that the research does not meet the criteria for human subject's research because the proposed activity involves no direct participant interaction. I was given permission to proceed with the blind rating project. The only humans used in this study were my students who participated in the blind rating. All the assays performed by the NIMH-PDSP are in transfected immortalized human cells for which IRB approval is not necessary (e.g. HEK-293 cells).

Reference List

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