Gradient Review

We will examine how the tendency to produce VER varies with relative affinities for 5-HT_2 and 5-HT_7. The hypothesis is that the presence of VER will be positively correlated with the relative affinity for 5-HT_7 but not 5-HT_2. We will examine more than two-hundred-fifty subjective reports distributed across the twenty-two drugs, in order of decreasing relative 5-HT_7 affinity (npK_i value), to show that VER decreases along this gradient, while there is not a corresponding correlation between VER and relative 5-HT_2 affinity.

In order to evaluate the relationship between VER and relative affinity at 5-HT_7 and 5-$HT_{2A/C}$, the relevant relative affinity data is shown in Table 1, and Figures 1 and 2. The current paradigm points to a key role for 5-HT_{2A} (Nichols 2004), whereas 5-HT_{2B} is considered not to be relevant (Nelson *et al.* 1999). A possible role for 5-HT_{2C} remains uncertain due to a lack of ligands that clearly differentiate 5-HT_{2A} and 5-HT_{2C} (Nichols 2004). Thus the paradigm could be stated in this way: 5-HT_{2A} activation (agonism or partial agonism) is necessary and may be sufficient for psychedelic drug effects. Thus in order to consider the roles of 5-HT_{2A} and 5-HT_{2C}, we will examine them both individually and together.

In the second and third pairs of columns of Table 1, each of the two paradigmatic 5-HT_2 receptors is shown in order of decreasing relative affinity (npK_i). The fourth pair of columns shows the maximum npK_i of the two, and the fifth pair of columns shows the square root of the sum of the squares of the npK_i values of the two. We will see that no matter how you look at it, these values do not correlate with VER. DOET and DOI (which do not typically produce VER) appear near the top of columns two through five, while the wildly psychedelic 5-MeO-DMT appears near the bottom of columns two through five.

Drug	5-HT7		Drug	5-HT2A		Drug	5-HT2C		Drug	5-HT2A/Cmax		Drug	5-HT2A/C
DMT	4.0000		2C-E	3.7572		DOI	4.0000		DOI	4.0000		DOI	5.2773
TMA	3.8036		DOET	3.7222		DMT	3.4175		2C-E	3.7572		2C-E	5.0553
5-MeO-MIPT	3.7932		2C-B	3.6894		2C-E	3.3822		DOET	3.7222		2C-B	4.8698
LSD	3.7715		LSD	3.5380		2C-B	3.1785		2C-B	3.6894		DOET	4.8621
5-MeO-DMT	3.6877		DOI	3.4423		DOET	3.1282		LSD	3.5380		LSD	4.7075
DPT	3.0493		TMA-2	3.4221		LSD	3.1053		TMA-2	3.4221		2C-T-2	4.4018
5-MeO-DIPT	3.0316		DOB	3.2275		2C-T-2	3.0466		DMT	3.4175		DOB	4.3881
Psilocin	2.8172		2C-T-2	3.1772		TMA	3.0154		DOB	3.2275		TMA-2	4.2856
2C-B	2.8091		2C-B-fly	2.8898		DOB	2.9730		2C-T-2	3.1772		DMT	4.2796
2C-E	2.7707		DMT	2.5760		2C-B-fly	2.9289		TMA	3.0154		2C-B-fly	4.1146
DIPT	2.5466		5-MeO-MIPT	2.4383		TMA-2	2.5799		2C-B-fly	2.9289		Aleph-2	3.4834
MDA	2.4091		Aleph-2	2.4231		Psilocin	2.5223		Psilocin	2.5223		Psilocin	3.3085
DOET	2.0702		DOM	2.3628		Aleph-2	2.5026		Aleph-2	2.5026		DPT	3.1139
MEM	1.9549		MEM	2.2132		DPT	2.3074		5-MeO-MIPT	2.4383		TMA	3.0154
DOI	1.8998		Psilocin	2.1411		MDA	2.1516		DOM	2.3628		5-MeO-MIPT	3.0015
DOB	1.8867		DPT	2.0910		5-MeO-MIPT	1.7503		DPT	2.3074		DOM	2.7819
DOM	1.8665		5-MeO-DMT	0.9753		5-MeO-DMT	1.5480		MEM	2.2132		MEM	2.2132
2C-T-2	1.7920		TMA	0.0000		DOM	1.4683		MDA	2.1516		MDA	2.1516
2C-B-fly	1.1715		5-MeO-DIPT	0.0000		MEM	0.0000		5-MeO-DMT	1.5480		5-MeO-DMT	1.8296
Aleph-2	1.0829		DIPT	0.0000		5-MeO-DIPT	0.0000		5-MeO-DIPT	0.0000		5-MeO-DIPT	0.0000
MDMA	0.0000		MDA	0.0000		DIPT	0.0000		DIPT	0.0000		DIPT	0.0000
TMA-2	0.0000		MDMA	0.0000		MDMA	0.0000		MDMA	0.0000		MDMA	0.0000

Table 1: Shows npK_i values for 5-HT_7, 5-HT_{2A}, 5-HT_{2C}, 5-$HT_{2A/C}$max, and 5-$HT_{2A/C}$ for twenty-two drugs. 5-$HT_{2A/C}$max is the maximum of the npK_i values of 5-HT_{2A} and 5-HT_{2C}. 5-$HT_{2A/C}$ is the square root of the sum of squares of the npK_i values of 5-HT_{2A} and 5-HT_{2C}.

The data of Table 1 is presented graphically in Figure 1, which shows the drugs of this study arranged in decreasing order of relative affinity at 5-HT_7, 5-HT_{2A}, 5-HT_{2C}, $HT_{2A/C}$max, and $HT_{2A/C}$. The data of Table 1 is also presented graphically in Figure 2, which shows the drugs of this study displayed in two-dimensional plots of relative affinity at 5-HT_7 vs. the four measures of 5-HT_2 relative affinity: 5-HT_{2A}, 5-HT_{2C}, $HT_{2A/C}$max, and $HT_{2A/C}$, allowing us to see at a glance the relative affinities at 5-HT_7 and 5-HT_2 together.

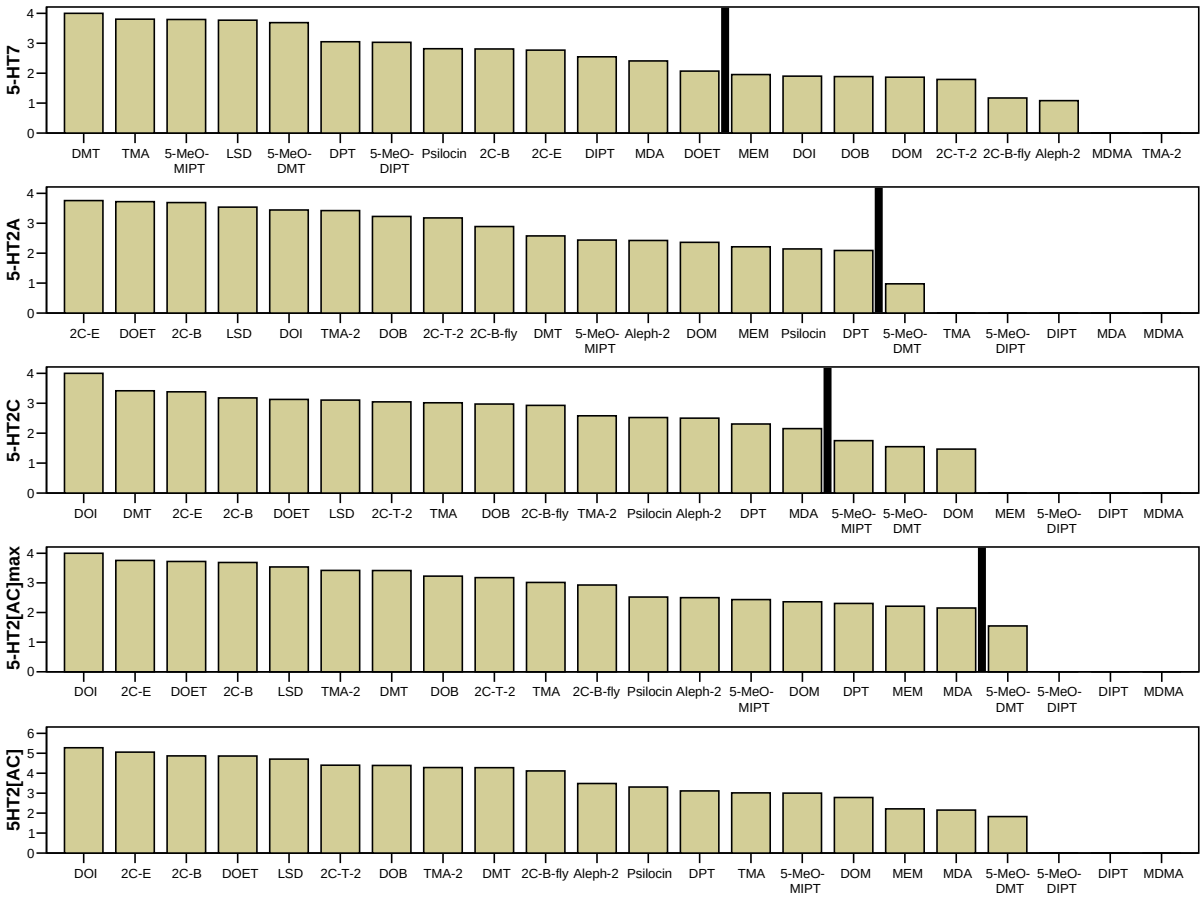

Figure 1: A bar graph representation of twenty-two drugs in order of decreasing relative affinity for 5-$HT_{2A/C}$

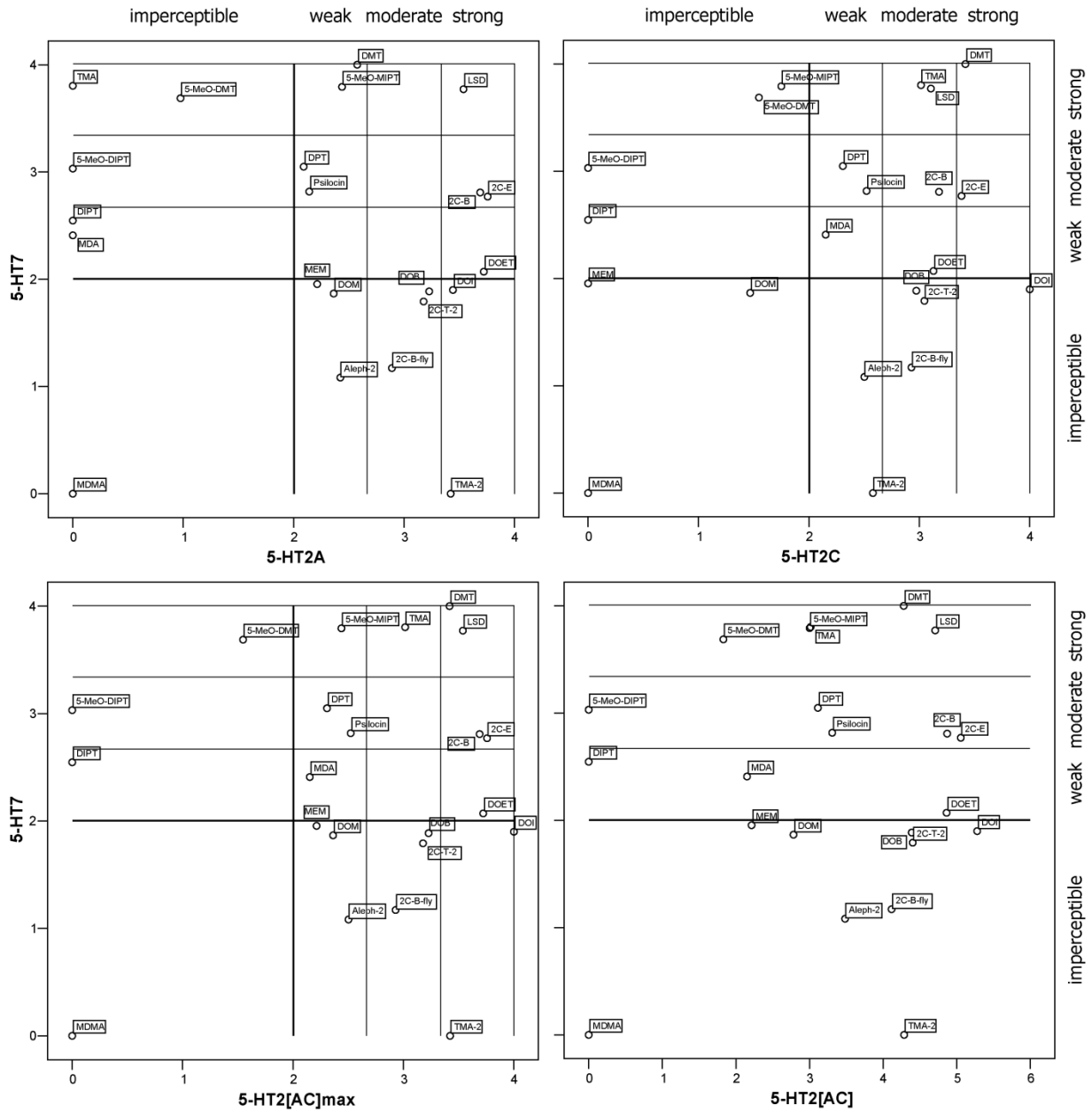

Figure 2: Twenty-two drugs arranged by relative affinity for 5-HT_7 vs. 5-$HT_{2A/C}$

Strong, moderate, weak, or imperceptible 5-HT_7 relative affinity – While we will examine the drugs in order of decreasing relative 5-HT_7 affinity, we will also group them into four relative 5-HT_7 affinity categories. We first divide the npK_i range into perceptible (greater than 2.0) and imperceptible (2.0 or less), then we divide the perceptible range into three equal parts: strong (4.00-3.34), moderate (3.33-2.67), weak (2.66-2.01). The bullet list below shows the four categories, the npK_i range for each category, and the drugs in each category together with their measured npK_i values for 5-HT_7, listed in decreasing order:

- **Strong** (4.00-3.34) – DMT 4.00, TMA 3.80, 5-MeO-MIPT 3.79, LSD 3.77, and 5-MeO-DMT 3.69

- **Moderate** (3.33-2.67) – DPT 3.05, 5-MeO-DIPT 3.03, Psilocin 2.82, 2C-B 2.81, and 2C-E 2.77
- **Weak** (2.66-2.01) – DIPT 2.55, MDA 2.41, and DOET 2.07
- **Imperceptible** (2.00-0.00) – MEM 1.95, DOI 1.90, DOB 1.89, DOM 1.87, 2C-T-2 1.79, 2C-B-fly 1.17, Aleph-2 1.08, MDMA 0.00, TMA-2 0.00

It will be argued here that none of the compounds in the imperceptible range or the weak range typically produce VER. Clear signs of VER occur only in compounds in the moderate and strong categories.

The demonstration that the tendency to produce VER correlates cleanly and without exception with the gradient in relative 5-HT$_7$ affinity among the twenty-two drugs of this study lies at the heart of the argument presented in this manuscript. However, the review of the literature on the relevant subjective effects of the twenty-two drugs presents more than two-hundred-fifty reports and runs more than a hundred pages in length. For this reason, and with great reluctance, the gradient review has been moved to the supporting information in the document S07GradientReports.pdf. I encourage interested readers to treat that document as an integral part of this manuscript. Here I will summarize the results of the gradient review. Raters who were blind to the dose, identity of the drugs, or literature source of the subjective reports, rated the presence or absence of VER in each report, and this rating provides a convenient way of visualizing and summarizing the verbose subjective reports. Figure 3 presents the blind rating data for 5-HT$_7$ and 5-HT$_{2A}$, showing that while 5-HT$_7$ cleanly separates high from low VER drugs, 5-HT$_{2A}$ provides no separation.

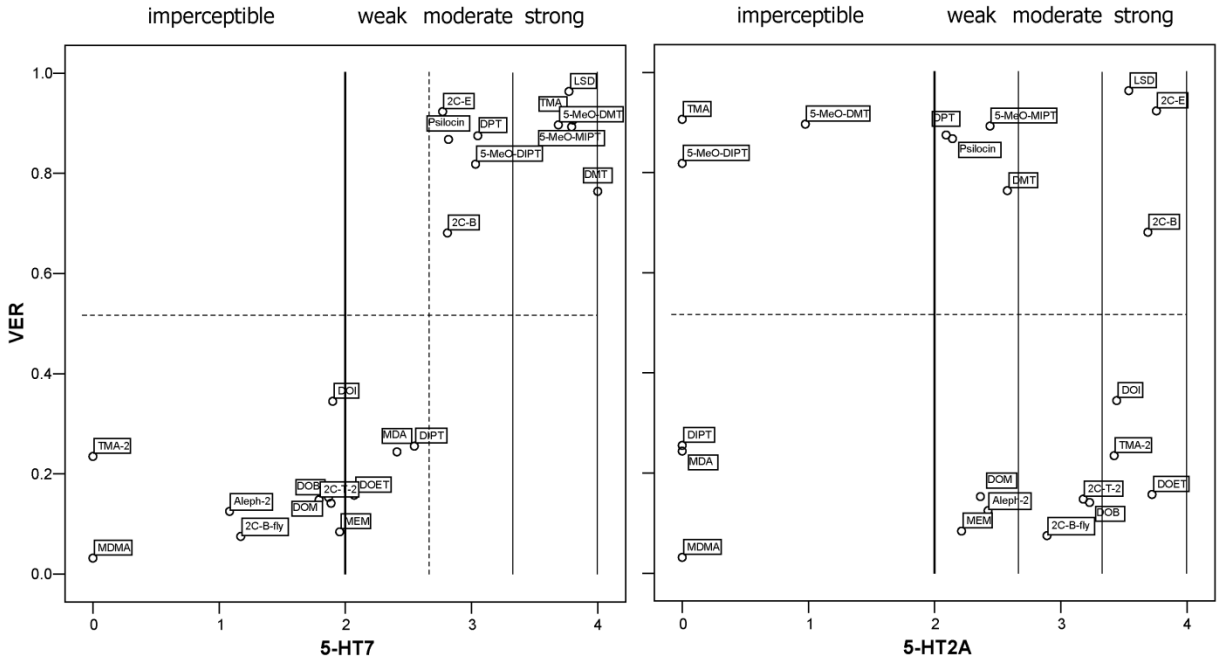

Figure 3. VER plotted against relative affinity of 5-HT$_7$ and 5-HT$_{2A}$. Blind rating results (VER) plotted against relative affinity at 5-HT$_7$ and 5-HT$_{2A}$. Dashed lines cleanly separate high from low VER drugs.

The blind rating was repeated in February 2014 as a graded assignment in my psychopharmacology class. All nineteen students rated at least 30 of 64 pages of reports (one student rated all reports, and one student rated about 45 pages, the rest rated 30 pages), producing much more even participation than in 2013 when participation was voluntary. The results were identical in 2013 and 2014 in two critical senses: 1) The summary VER ratings of individual drugs were strongly bimodal. 2) The twenty-two drugs divided into identical lists of ten high VER and twelve low VER drugs. This suggests that the blind rating results are very robust.

Strong 5-HT_7 relative affinity (npK$_i$ 4.00-3.34) – The five compounds whose npK$_i$ values at 5-HT_7 fall in the "strong" range are DMT 4.00, TMA 3.80, 5-MeO-MIPT 3.79, LSD 3.77, and 5-MeO-DMT 3.69.

DMT and LSD are well known to produce creative visuals and loss of contact with reality, and LSD produces ego-loss. Although 5-MeO-DMT is not as prone to produce visual effects, it typically produces ego-loss and loss of contact with reality. TMA and 5-MeO-MIPT are less well known. The literature shows TMA to produce vivid three dimensional creative visuals, with eyes open or closed. 5-MeO-MIPT is similar to 5-MeO-DMT in structure, receptor profile, and effects. Both 5-MeO-MIPT and 5-MeO-DMT easily cause loss of contact with reality relatively free of visuals.

DMT, TMA, 5-MeO-MIPT, LSD, 5-MeO-DMT all unequivocally produce VER.

Of the five drugs with strong 5-HT_7 signals which unequivocally produce VER, 5-MeO-DMT falls in the "imperceptible" range for 5-HT_{2A}, DMT and 5-MeO-MIPT fall in the "weak" range for 5-HT_{2A}, and only LSD falls in the "strong" range for 5-HT_{2A}; yet unlike the other compounds which are full agonists, LSD is an antagonist or weak partial agonist at 5-HT_{2A}. When we consider both 5-HT_{2A} and 5-HT_{2C} together, we find that the maximum npK$_i$ value of the two is weak (2.44) for 5-MeO-MIPT, and imperceptible (1.55) for 5-MeO-DMT. It is not plausible to suggest that 5-$HT_{2A/C}$ is responsible for the VER producing properties of these two drugs.

Moderate 5-HT_7 relative affinity (npK$_i$ 3.33-2.67) – The five compounds whose npK$_i$ values at 5-HT_7 fall in the "moderate" range are DPT 3.05, 5-MeO-DIPT 3.03, Psilocin 2.82, 2C-B 2.81, and 2C-E 2.77.

These five compounds are all reported to have steep dose-response curves. Because they have moderate 5-HT_7 affinity *relative* to their affinity at other receptors, at low doses they are able to provide a full psychedelic experience, apparently through their effects at other receptors with little or no perceptible effect through 5-HT_7. As dose increases, the effects of 5-HT_7 gradually become felt. Thus, the steepness of the dose-response curve for these compounds is likely due to the absence of 5-HT_7 effects at low doses, and the gradually increasing strength of the dramatic 5-HT_7 signal at increasing doses.

This means that for this group of compounds, there is a range of low doses that are fully psychedelic, but within which VER may be absent, or mild to moderate. Therefore, unequivocal

evidence of VER might be found only at higher doses. We may be able to detect evidence of VER in the low dose range in the form of visual patterning effects, otherwise we must examine higher doses to detect VER. Loss of contact with reality will only be found in the higher dose ranges for this group of drugs, and ego-loss is only typical of psilocin among this group of five drugs.

Psilocin is well known to produce creative visuals, ego-loss, and loss of contact with reality. DPT was explored in clinical studies before the prohibition, and has been clearly shown to produce creative visuals, and at high doses a visually rendered loss of contact with reality (alternate reality). While 2C-E is not prone to ego-loss or loss of contact with reality, it does produce dramatic creative visuals. 2C-B readily produces patterns laid over the visual field or integrated into the visual field, as well as geometric or organic hallucinations. 5-MeO-DIPT is reported to produce creative visuals at high, but not moderate doses.

Weak 5-HT$_7$ relative affinity (npK$_i$ 2.66-2.01) – The three compounds whose npK$_i$ values at 5-HT$_7$ fall in the "weak" range are DIPT 2.55, MDA 2.41, and DOET 2.07.

Visual effects have not been reported for DIPT, although it causes a dramatic auditory distortion. I do not consider the very distinctive DIPT auditory effect to be an auditory analog of the visual component of VER. Rather, I believe that the auditory effects are a distinct phenomenon with a different mechanism. I am not able to find any evidence of VER in DIPT. Apart from a single atypical report of creative visuals, it is universally agreed that MDA lacks open-eyed creative visual effects, and MDA exhibits no signs of VER through a wide dose range.

A series of excellent controlled clinical studies with DOET by Snyder and associates showed that it produced no open-eyed visual effects over a 5-fold active dose range. DOET was determined to be neither hallucinogenic nor psychotomimetic. This view is supported by the overwhelming majority of the available subjective reports.

Yet there are two DOET reports (one in which 2.0 mg was taken intravenously, the other with 6.0 mg) that claim that Snyder was wrong and that DOET is similar to LSD. One additional report with 6.0 mg describes patterning in the visual field. These three reports come from the Shulgin archive whose experienced subjects are not likely to produce false positives. Shulgin and Shulgin (Shulgin & Shulgin 1991) observed: "It must be noted that there is a considerable variation of individual responses to this material. The effective dose range stated is quite broad [2-6 mg]. Some people are quite sensitive." p. 633. It appears fair to say that VER is *not typical* of DOET, but can be seen rarely in some subjects in very high doses (or when taken intravenously). DOET does *not typically* produce VER, even at very high doses.

Imperceptible 5-HT$_7$ relative affinity (npK$_i$ 2.00-0.00) – The nine compounds whose npK$_i$ values at 5-HT$_7$ fall in the "imperceptible" range are MEM 1.95, DOI 1.90, DOB 1.89, DOM 1.87, 2C-T-2 1.79, 2C-B-fly 1.17, Aleph-2 1.08, MDMA 0.00, TMA-2 0.00.

None of the nine compounds show any evidence of ego-loss or loss of contact with reality, thus in the summary that follows, only open-eyed creative visuals will be discussed.

DOB and MEM are the only drugs in this study which are completely selective for the three 5-HT_2 receptors, as all of their non-5-HT_2 receptors have relative affinity values below the presumed 2.15 limit of perceptibility. DOB and MEM have also been shown to be full agonists at 5-HT_{2A} and 5-HT_{2C} (Ray 2010). As such, DOB and MEM should be the ideal drugs for demonstrating the 5-HT_2 paradigm of psychedelic drug action. Yet the human data shows DOB and MEM to exhibit no signs of VER.

2C-T-2 exhibits primarily introspective effects without any evidence of creative visual effects. The 2C-B-fly literature often describes it as "boring", and there are no reports that suggest creative visuals. While some subjects report a strong sense of movement (simple visuals) with Aleph-2, there are no reports that suggest creative visuals. The pharmacology of MDMA is well known, and it is not known to produce creative visuals. While TMA-2 can produce strong aesthetic visual enhancement (simple visuals), there are no signs of creative visuals.

DOI does not produce creative visuals, but does produce simple visuals (aesthetic enhancement and simple distortion). Of the twenty-two drugs of this study, DOI has the greatest breadth of interaction with the non-serotonin receptors, and also has the third highest breadth of interaction with all receptors (after DMT and DPT). DOI also has the strongest combined interaction with the two paradigmatic receptors (5-HT_{2A} and 5-HT_{2C}), is the only drug in the study to have its best hit at one of the two paradigmatic receptors (5-HT_{2C}), and it has the fifth highest relative affinity value at the 5-HT_{2A} receptor (Ray 2010). Despite this strong interaction with 5-HT_2 receptors, DOI does not produce VER.

I have made a more extensive review of the pharmacology of DOM than of any of the other drugs because DOM is one of the drugs of choice in many animal models of hallucinogens, DOM is widely believed to be "hallucinogenic", and DOM is emphatically considered to be a "classical hallucinogen" comparable to LSD, psilocybin, and mescaline. However there is virtually no evidence of creative visuals for DOM. For DOM there is a single atypical report of creative visual effects (at a low dose of 3.2 mg!). This specific claim of hallucinogenic effects was immediately challenged in the same journal and the original authors later acknowledged that it was an atypical anomaly.

Yet the claim that DOM is uniformly hallucinogenic in doses above 5 mg is widely believed even today. This belief emerges in large part because the concept of "hallucinogenic" has been broadly applied to include both simple visuals and creative visuals. A careful examination of all available DOM reports at all doses shows no evidence, other than the one 3.2 mg report, of creative visuals. The specific claim in the clinical literature that DOM is hallucinogenic traces back to a single publication which did not report any subjective data, but did make the claim that DOM produced colored patterns with eyes open. As no subjective data was reported in this paper, it is difficult to evaluate this claim, and it may be an example of either a false positive or researcher bias. DOM obtained a reputation as a heavy psychedelic in the 1960s largely because it was distributed (as STP) in large doses that provoked physical reactions which were confused with the central effects. A careful review of all the literature shows that DOM does not produce VER, if we set aside one anomalous report.

The overwhelming pattern for the nine drugs in the imperceptible range of 5-HT_7 is the absence of VER, with a few exceptions that clearly stand out as atypical. This lack of VER occurs even though several of these drugs have either strong (DOI, TMA-2) or moderate (DOB, 2C-T-2, 2C-B-fly) relative affinity at the paradigmatic 5-HT_{2A} or 5-HT_{2C} receptors. Of the remaining four, three have their best hit at 5-HT_{2B} (MEM, DOM, Aleph-2), while the last (MDMA) has strong relative affinity for 5-HT_{2B}.

Summary of Gradient Review

For all of the ten drugs in the strong and moderate categories (DMT, TMA, 5-MeO-MIPT, LSD, 5-MeO-DMT, DPT, 5-MeO-DIPT, Psilocin, 2C-B, 2C-E), there are abundant and readily available reports providing vivid and detailed descriptions of VER. Vivid and detailed descriptions of these three phenomena are completely lacking for the remaining twelve drugs in the weak and imperceptible categories (DIPT, MDA, DOET, MEM, DOI, DOB, DOM, 2C-T-2, 2C-B-fly, Aleph-2, MDMA, TMA-2), with two exceptions (one report each for MDA and DOM). Both reports are acknowledged in peer-reviewed journals to be anomalous for these drugs.

Recall that I have described open-eyed creative visual effects as falling in the following four categories:

- 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

Both of these anomalous reports (MDA and DOM) fit the category of "seeing objects or scenes that are not there", an exceedingly rare form of visual. Almost all of the creative visuals cited in the gradient review fall in the other three categories. These two reports may have reflected the expectations in drug naïve subjects or researchers of what hallucinations would be like.

Both reports are acknowledged to be anomalous for these drugs. While it is difficult to explain such reports, apart from writing them off as a placebo effect, the more striking pattern is the overwhelming absence of vivid descriptions of VER in this set of twelve psychedelic drugs.

The reports for the twelve drugs in the weak and imperceptible categories also contain occasional atypical references to visual effects that are vaguely suggestive of creative visuals. These occasional atypical vague allusions to creative visual effects must be contrasted with the explicitly vivid descriptions of creative visuals which are the norm for drugs in the strong and moderate categories.

- **Drugs which typically produce VER:** DMT, TMA, 5-MeO-MIPT, LSD, 5-MeO-DMT, DPT, 5-MeO-DIPT, Psilocin, 2C-B, 2C-E
- **Drugs which do not typically produce VER:** DIPT, MDA, DOET, MEM, DOI, DOB, DOM, 2C-T-2, 2C-B-fly, Aleph-2, MDMA, TMA-2

Route of Administration

While most of the 22 drugs are normally taken in a slow-onset oral form, three are often taken in more rapid-onset forms. DMT is often smoked or injected, 5-MeO-DMT is usually smoked, and DPT is often injected or insufflated. Could it be that the VER producing effects of these three drugs is due to the route of administration rather than the receptor profile? If we were to remove these three drugs from the study, the sample of high VER drugs would be reduced from ten to seven, but it would not otherwise change the results or conclusions.

We should also acknowledge that DMT is most commonly used as "ayahuasca" in the slow-onset oral form in combinations with MAO inhibitors which themselves do not produce VER. Yet even in this slow-onset oral form, DMT still produces VER. This observation is more clear in the case of "pharmahuasca" which is a combination of synthetic DMT with synthetic MAO inhibitor, where the drug content is completely known, unlike the case of botanical concoctions of ayahuasca. VER is produced even with oral DMT in combination with moclobemide (Erowid 2014), a prescription antidepressant.

Metzner (Metzner 2013) has recently reported development of a slow-onset method of ingesting 5-MeO-DMT involving insufflation of a 5 mg dose, followed 20 minutes later by a second insufflation of 5-10 mg, producing effects "lasting about 90 minutes or so, with ordinary real-time awareness of one's body and the surrounding space returning gradually and peacefully" (Metzner 2013) p. 69.

With respect to DPT, Soskin (Soskin 1975) noted: "After the drug is injected, its effects are usually noticed within 5 to 15 minutes. In high-dose sessions, deep muscular injection produced such rapid onset of the drug reaction that panic often ensued. We found it best to inject the drug subcutaneously to permit a more gradual transition into the altered state of consciousness." (Soskin 1975) p. 149. Soskin (Soskin 1975) reported VER effects with DPT using his medium-onset method of injection, and Pinchbeck (Pinchbeck 2002) reported VER effects with DPT with medium-onset insufflation. Shulgin and Shulgin (Shulgin & Shulgin 1997) report intense visual effect with DPT taken orally. Thus it appears that the tendency of these drugs to produce VER does not depend on route of administration.

Other Receptors?

Gradient analysis showed that all drugs in both the strong (4.00 – 3.34) and moderate (3.33 – 2.67) range of relative affinity for 5-HT_7 show clear signs of producing VER; and that all drugs in the weak (2.66 – 2.01) and imperceptible (2.00 – 0.00) range of relative affinity for 5-HT_7 do not typically produce VER. I will use the phrase "high relative affinity" as an abbreviation for "strong and moderate relative affinity" (npK_i of 4.00 – 2.67). I will use the phrase "low relative affinity" as an abbreviation for "weak and imperceptible relative affinity" (npK_i of 2.66 – 0.00). Although the imperceptible range has been defined as npK_i of 2.00 – 0.00 in the figures, the value 2.00 is an arbitrary round number. When I speak of "imperceptible" I will usually mean the more realistic npK_i range of 2.15 – 0.00.

High 5-HT$_2$, Low 5-HT$_7$

Having established which drugs do and don't typically produce VER, we can look at some special cases that are particularly informative. First we will examine drugs with high relative affinity ($npK_i > 2.66$) for 5-HT$_{2A}$ or 5-HT$_{2C}$ and imperceptible relative affinity ($npK_i \leq 2.15$) for 5-HT$_7$ (roughly the lower right quadrant of Figure 2, 5-HT$_7$ vs. 5-HT$_{2[AC]max}$). We find six drugs in this quadrant: 2C-B-fly, 2C-T-2, DOB, TMA-2, DOET, DOI. The gradient analysis established that none of these six drugs typically produce VER. Below is a listing of the relative affinity profiles of these drugs, including only high relative affinity values:

2C-B-fly: 4.00 5ht2b, 3.81 5ht1d, 2.93 5ht2c, 2.89 5ht2a
2C-T-2: 4.00 5ht2b, 3.18 5ht2a, 3.05 5ht2c, 2.84 5ht1d, 2.56 Alpha2C
DOB: 4.00 5ht2b, 3.23 5ht2a, 2.97 5ht2c
TMA-2: 4.00 5ht2b, 3.42 5ht2a, 3.04 H1
DOET: 4.00 5ht1a, 3.72 5ht2a, 3.70 5ht2b, 3.13 5ht2c
DOI: 4.00 5ht2c, 3.79 Alpha2A, 3.52 Beta2, 3.44 5ht2a, 3.13 Alpha2B, 3.13 5ht2b, 3.00 5ht1d, 2.90 M4, 2.89 Beta1, 2.88 Alpha2C, 2.83 SERT,

All six of these drugs have been shown to be full agonists at 5-HT$_{2A}$ and 5-HT$_{2C}$ (Ray 2010). TMA-2, DOET, and DOI have strong relative affinity for 5-HT$_{2A}$, while 2C-B-fly, 2C-T-2, and DOB have moderate relative affinity for 5-HT$_{2A}$. DOI has strong relative affinity for 5-HT$_{2C}$, while 2C-B-fly, 2C-T-2, DOB, and DOET have moderate relative affinity for 5-HT$_{2C}$. These observations strongly suggest that neither 5-HT$_{2A}$ nor 5-HT$_{2C}$ produce VER.

Collectively, these six compounds have high relative affinity for the following receptors: 5-HT$_{1A}$, 5-HT$_{1D}$, 5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{2C}$, Alpha$_{2A}$, Alpha$_{2B}$, Alpha$_{2C}$, Beta$_1$, Beta$_2$, H$_1$, M$_4$, SERT. If these drugs are agonists at these receptors, this suggests that none of these receptors are responsible for producing VER.

Low 5-HT$_2$, High 5-HT$_7$

Now we will examine drugs with high relative affinity for 5-HT$_7$ and imperceptible relative affinity for both 5-HT$_{2A}$ and 5-HT$_{2C}$ (roughly the upper left quadrant of Figure 2, 5-HT$_7$ vs. 5-HT$_{2[AC]max}$). Here we find two drugs: 5-MeO-DIPT, and 5-MeO-DMT. Gradient analysis showed both drugs to produce VER. While 5-MeO-DMT does not typically cause creative visuals, it does typically cause ego-loss and loss of contact with reality. 5-MeO-DIPT is reported to produce creative visuals at high, but not moderate doses. Below is a listing of the relative affinity profiles of these drugs, including only perceptible npK_i values (greater than 2.15):

5-MeO-DMT: 4.00 5ht1a, 3.69 5ht7, 3.48 5ht1d, 2.73 5ht6, 2.41 5ht1b, 2.38 D1
5-MeO-DIPT: 4.00 5ht1a, 3.91 5ht2b, 3.24 Imidazoline1, 3.03 5ht7, 2.89 5ht1d, 2.72 SERT, 2.66 Alpha2C, 2.64 Sigma2, 2.41 5ht1b, 2.40 Alpha2B

Note that neither drug has perceptible relative affinity at either of the paradigmatic 5-HT$_{2A}$ or 5-HT$_{2C}$ receptors, thus those two receptors cannot plausibly be responsible for their VER producing effects. Although 5-MeO-DIPT has strong relative affinity for 5-HT$_{2B}$, 5-MeO-DMT

has no perceptible affinity for any of the three 5-HT_2 receptors, thus no 5-HT_2 receptor can explain its effects.

Collectively, these two compounds have high relative affinity for the following receptors: 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2B}, 5-HT_6, 5-HT_7, Imidazoline$_1$, SERT. If these drugs are agonists at these receptors, this suggests that these receptors are candidates for producing VER. Yet recall that in the "High 5-HT_2, Low 5-HT_7" section we suggested that the following four receptors are not responsible for producing VER: 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2B}, SERT, leaving only 5-HT_6, 5-HT_7, and Imidazoline$_1$ as candidates. Is it possible that receptors other than 5-HT_2 or 5-HT_7 might be responsible for the production of VER? We will address this question by using the "common denominator" method, and by close examination of individual receptors and groups of related receptors.

Common Denominators

Is it possible that receptors other than 5-HT_2 or 5-HT_7 might be responsible for the production of VER? We will address this question by using the "common denominator" method, and by close examination of individual receptors and groups of related receptors. In the early days of research on the mechanisms of action of hallucinogens, a decision was made to "… study a series of agents and to determine what characteristics they have in common… a mechanism common to fewer than the majority of the agents could be eliminated from serious consideration. If these agents produce similar behavioral effects (in animals or in humans), then they must share a related mechanism of action" (Glennon 1990). Here I will reapply the common denominator approach, using modern methods, and recognizing the qualitative heterogeneity of "behavioral effects" of the psychedelic drugs (some produce VER, some do not). Although Glennon spoke of a mechanism common to the majority of drugs, it is my view that within the drugs of this study a fully explanatory mechanism should be an absolute common denominator, found in all ten drugs producing the effects in question (VER). None-the-less, we will take the broad approach and use Glennon's majority rule.

Gradient analysis showed that all drugs with high relative affinity for 5-HT_7 show clear signs of producing VER, therefore we will search for common receptors in the high relative affinity range among the ten drugs that typically produce VER:

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
TMA: 4.00 5ht2b, 3.95 Sigma2, 3.95 Sigma1, 3.80 5ht7, 3.45 5ht1a, 3.36 Alpha2A, 3.22 5ht1b, 3.20 5ht1d, 3.15 5ht1e, 3.02 5ht2c, 2.98 Alpha2C
5-MeO-MIPT: 4.00 5ht1a, 3.79 5ht7, 3.74 5ht1d, 3.32 5ht2b, 2.98 5ht6, 2.85 Alpha2A
LSD: 4.00 5ht1b, 3.77 5ht7, 3.75 5ht6, 3.73 5ht1a, 3.70 5ht1d, 3.64 5ht5a, 3.54 5ht2a, 3.16 D3, 3.11 5ht2b, 3.11 5ht2c, 2.93 Alpha2A
5-MeO-DMT: 4.00 5ht1a, 3.69 5ht7, 3.48 5ht1d, 2.73 5ht6
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
5-MeO-DIPT: 4.00 5ht1a, 3.91 5ht2b, 3.24 Imidazoline1, 3.03 5ht7, 2.89 5ht1d, 2.72 SERT

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
2C-B: 4.00 5ht2b, 3.71 5ht1d, 3.69 5ht2a, 3.18 5ht2c, 3.12 Alpha2C, 3.11 5ht1b, 3.05 5ht1e, 2.81 5ht7, 2.75 5ht1a
2C-E: 4.00 5ht2b, 3.76 5ht2a, 3.54 5ht1d, 3.44 Alpha2C, 3.38 5ht2c, 3.00 5ht1b, 2.91 Alpha2B, 2.91 5ht1a, 2.77 5ht7, 2.71 Alpha2A

There are two absolute common denominators: 5-HT_7 and 5-HT_{1D}. However Glennon did not speak of an absolute common denominator, but rather "the majority of the agents". Let's construct a frequency distribution of the occurrence of high relative affinity among the ten drugs (Table 2):

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

Table 2: Frequency distribution of high relative affinity receptors across the ten drugs that produce high VER

The frequency distribution suggests four strong candidates: 5-HT_7, 5-HT_{1D}, 5-HT_{1A}, and 5-HT_{2B}, as well as a distant fifth: $Alpha_{2A}$ which qualifies with a bare majority of six out of ten. We will now examine these candidates, and a few others, one by one.

Prospective VER Producing Receptors

We will consider the possible role of each prospective receptor in producing VER by examining plots of relative affinity values at the prospective receptor against the frequency of VER based on blind ratings of subjective reports. We will pair each of these plots with a plot of the relative affinities of the prospective receptor against relative affinity at 5-HT_7. This pairing will help to clarify the relationships between the prospective receptors and VER values. A detailed analysis of sixteen receptors or receptor indices which runs fourteen pages in length is presented in the document S04ProspectiveReceptors.pdf in the supporting information. Here I will present a summary of that analysis.

The general approach is to attempt to find support for a receptor as mediating VER by looking for a consistent and unbroken positive correlation between relative affinity and VER. The VER data is bimodal (data ranges from 0 to 1 with no values between .35 and .65), so in practice, this appears in the plot as having the data restricted to the upper right and lower left quadrants (as is found only for 5-HT_7 and 5-HT1).

Having drugs in either the upper left or lower right argues against the receptor playing a role in mediating VER. Drugs in the upper left (VER on the horizontal axis, unlike Figure 3) of the plot indicate high relative affinity with low VER, suggesting that high affinity is not associated with high VER. Drugs in the lower right of the plot indicate low relative affinity with high VER, suggesting that high VER can occur without participation of the receptor.

Neither 5-HT_2 receptors nor Alpha-2 receptors provide any separation of high from low VER drugs. Thus this analysis does not provide any support for a role of any of the three 5-HT_2 receptors or two prospective $Alpha_2$ receptors in mediating VER. It should also be noted that relative affinities at 5-HT_2 and Alpha-2 do not correlate with relative affinities at 5-HT_7.

On the other hand, both 5-HT_7 and the composite statistic 5-HT1 cleanly separate high from low VER drugs (5-HT1 is the square root of the sum of squares of the relative affinities of the four 5-HT_1 receptors assayed). This might be taken to indicate that 5-HT1 is as likely a causative mechanism for VER as is 5-HT_7. However, there is also a strong correlation between the 5-HT1 index and relative affinity for 5-HT_7. This opens the possibility that one of the two indices (5-HT1 or 5-HT_7) is a spurious correlation.

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

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