Prospective VER Receptors

Common Denominators

Is it possible that receptors other than 5-HT_2 or 5-HT_7 might be responsible for the production of creative open-eyed Visuals, Ego-loss, or loss of contact with Reality (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 (strong or moderate) 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

Let's construct a frequency distribution of the occurrence of high relative affinity among the ten drugs (Table 1):

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

This frequency distribution shows that there are two absolute common denominators: 5-HT_7 and 5-HT_{1D}; two additional candidates found in nine of the ten drugs: 5-HT_{1A}, and 5-HT_{2B}; as well as a distant fifth which qualifies with a bare majority of six out of ten: $Alpha_{2A}$.

Prospective VER Mediating Receptors

As we consider the possible role of each prospective receptor in mediating VER, we will examine plots of relative affinity values at the prospective receptor against the frequency of VER based on blind ratings of subjective reports (Figures 1-11). 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 receptor and VER values.

This analysis has been made for relative affinity at: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_7, Alpha-2A, and Alpha-2C. In addition the analysis was made for a number of composite statistics grouping closely related receptors that may have similar functions:

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

- Alpha2max – maximum relative affinity at any of the three $Alpha_2$ receptors assayed ($Alpha_{2A}$, $Alpha_{2B}$, $Alpha_{2C}$)

The 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, in Figures 1-11). Alternatively, we can attempt to rule out receptors by looking for compounds with high VER and low relative affinity at the prospective receptor (lower right, VER on the horizontal axis), to illustrate that VER can occur without the participation of the prospective receptor; and to look for compounds with high relative affinity at the prospective receptor and low VER (upper left), to illustrate that high relative affinity at the prospective receptor is not associated with VER (activity data is not available for most of the receptors).

All of the receptors we will consider except for 5-HT_7 and 5-HT_{1D} are less than absolute common denominators. Thus we expect that there are some drugs that produce high VER without high relative affinity at most of the prospective receptors we will consider (lower right region of graphs). For every single prospective receptor other than 5-HT_7, we will find contrary data: upper left or lower right, though perhaps not both (there are receptors for which we lack the data to directly rule out the possibility that they are capable of mediating high VER (upper left), or for which we lack the data to be able to say high VER can be produced without their participation (lower right), but if we don't have one kind contrary data, we have the other).

5-HT_7 – One of the two absolute common denominators is 5-HT_7. Figure 1 presents the blind rating data for 5-HT_7 to illustrate what a good candidate should look like, for a receptor responsible for mediating high VER. The pattern appears as a clean separation between high and low VER drugs along the 5-HT_7 relative affinity axis (at an npK_i value of about 2.67, which coincidentally coincides with the arbitrary boundary between weak and moderate, and low and high relative affinity). We will not find this clean pattern for any other single receptor.

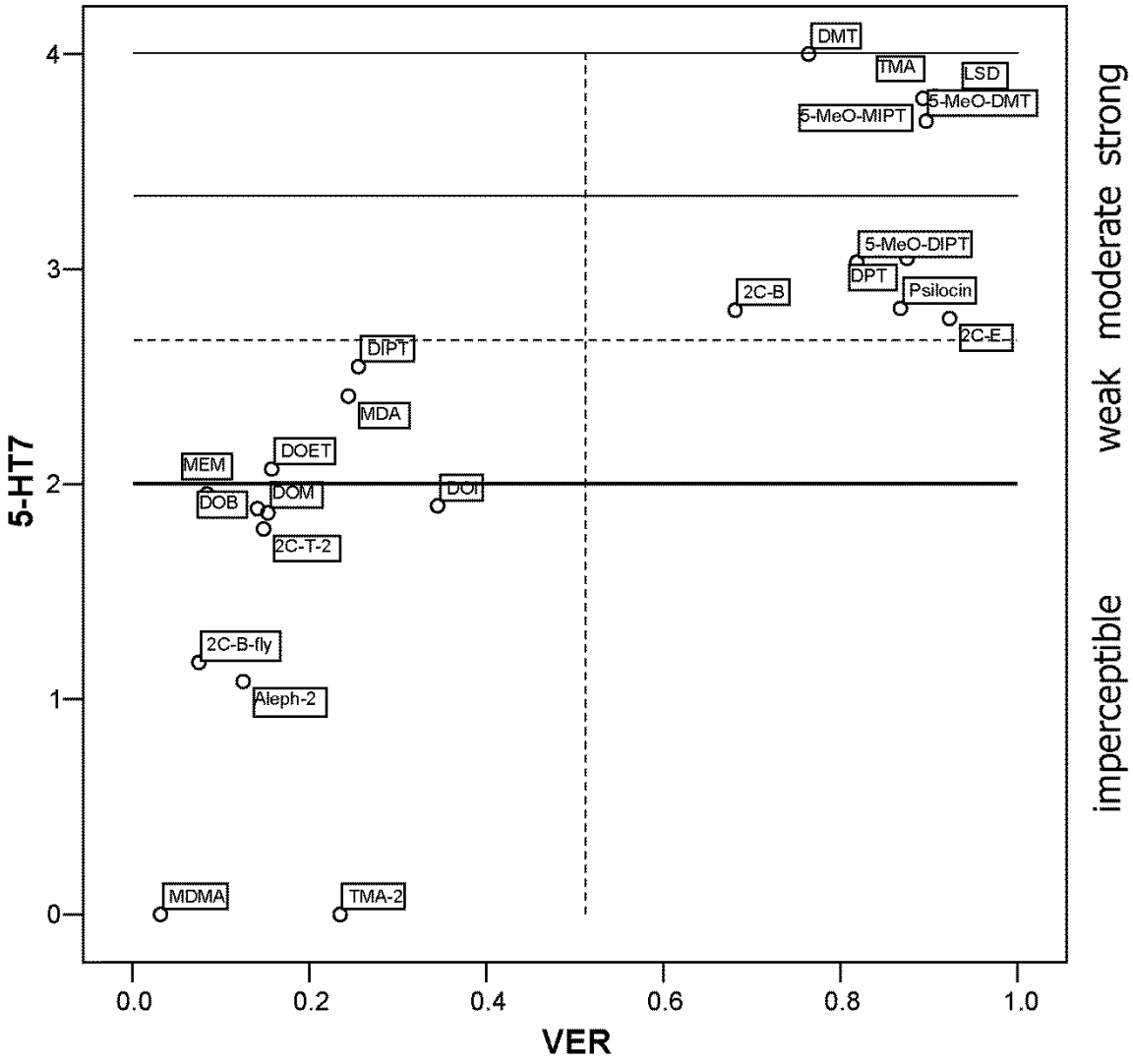
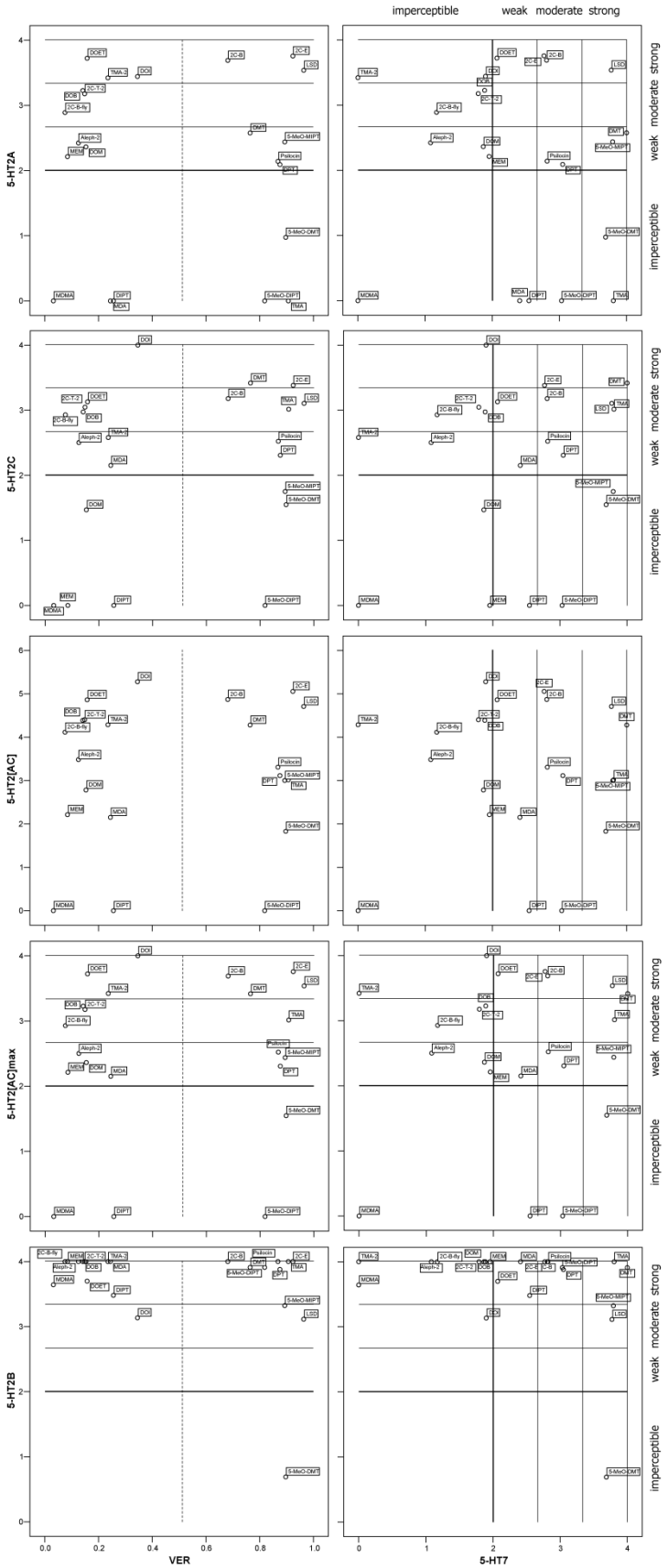


Figure 1: Blind rating results (VER) against relative affinity at 5-HT$_7$. The dashed lines provide a clean separation between high and low VER drugs.

5-HT$_2$ – The paradigmatic receptors are 5-HT$_{2A}$ and 5-HT$_{2C}$, while 5-HT$_{2B}$ is a top (9/10) common denominator. Figure 2 shows that whether we examine these receptors individually or in combination, there is no association between relative affinity and VER; relative affinity does not separate high from low VER. We have high VER without high relative affinity, and we have high relative affinity without high VER. There is nothing in the data to support any 5-HT$_2$ receptor or index as being associated with VER. Not surprisingly, 5-HT$_2$ relative affinities also do not correlate with 5-HT$_7$ relative affinities.

Figure 2: 5-HT_2 relative affinities against 5-HT_7 relative affinities (right) and VER (left). The dashed lines provide a clean separation between high and low VER drugs. 5-HT_2 relative affinities do not discriminate between high and low VER drugs, and do not correlate with 5-HT_7 relative affinities. 5-$HT_{2[AC]}$ – square root of the sum of squares of the two relative affinities: 5-HT_{2A}, 5-HT_{2C}. 5-$HT_{2[AC]max}$ – maximum of the two relative affinities: 5-HT_{2A}, 5-HT_{2C}.



5-HT$_1$ – Before examining the individual 5-HT$_1$ receptors, we should consider the possibility that 5-HT$_1$ receptors in general might share some common properties, such as mediating high VER. Figure 3 shows for each drug, the square root of the sum of squares of the relative affinities of the four 5-HT$_1$ receptors assayed (5-HT1), plotted against 5-HT$_7$ relative affinities (right) and VER (left). The drugs were assayed against 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{1E}$. The 5-HT1 index represents a hypothesis whose biological meaning is that when a drug acts at multiple 5-HT$_1$ receptors, each individual 5-HT$_1$ receptor contributes to the behavioral effect (e.g., VER), and that the contributions of the individual receptors add, in proportion to their relative affinity (squared). Figure 3 shows that this index provides a clean separation between high and low VER drugs, as does relative affinity at 5-HT$_7$. This might be taken to indicate that 5-HT1 is as likely a causative mechanism for VER as is 5-HT$_7$. However, the right side of Figure 3 shows that (unlike 5-HT$_2$) there is also a strong correlation between the 5-HT1 index and relative affinity for 5-HT$_7$. The value of the 5-HT1 index that cleanly separates high from low VER (about 5.0), also cleanly separates high from low relative affinity at 5-HT$_7$. This opens the possibility that one of the two indices (5-HT1 or 5-HT$_7$) is a spurious correlation.

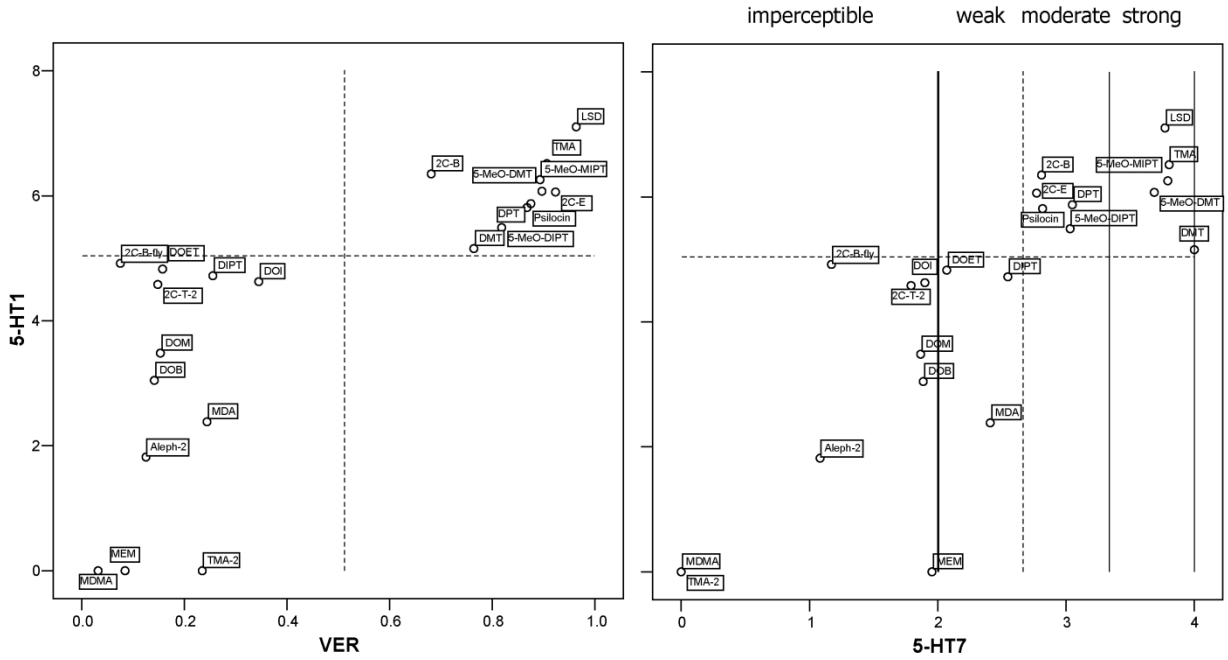


Figure 3: An index (5-HT1) combining the relative affinities at the four 5-HT$_1$ receptors assayed (square root of the sum of squares of the four relative affinities: 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{1E}$) plotted against 5-HT$_7$ relative affinities (right) and VER (left). On the left, the dashed lines provide a clean separation between high and low VER drugs. On the right, the dashed lines cleanly separate high from low relative affinity at 5-HT$_7$. The 5-HT1 index appears to be a good candidate for discriminating high and low VER drugs, although this is likely a spurious correlation.

A closer examination of the 5-HT$_1$ receptors appears to discredit the possibility that they could be the causative mechanism for high VER. Figure 4 shows the relationship of the maximum relative affinity of any of the four 5-HT$_1$ receptors assayed (5-HT$_{1max}$) with 5-HT$_7$ relative affinities (right) and VER (left). On the left side, the horizontal dashed line would provide a

clean separation between high and low VER, but for three drugs: 2C-B-fly, DOET, and DIPT. These three drugs have high relative affinity at 5-HT_1 receptors, but do not produce high VER. The right side of the Figure 4 shows that there is a high correlation between 5-HT_{1max} and 5-HT_7, but that the same three drugs deviate from this correlation in the same pattern (2C-B-fly deviates the most, DIPT the least) that they deviate from the correlation with VER. Although high in 5-HT_1max, these three drugs fall in the low relative affinity range of 5-HT_7. The gradient analysis suggested that drugs with low relative affinity at 5-HT_7 do not produce high VER.

Figure 4 shows that we have no drug with high VER and low 5-HT_{1max}. Thus we cannot demonstrate that these drugs can produce VER without 5-HT_1 affinity. Yet, there are three drugs with high 5-HT_{1max} and low VER, showing that 5-HT_1 affinity alone does not mediate high VER. DOET and DIPT both have their best hit (npK_i = 4.0) at 5-HT_{1A}, and 2C-B-fly has a relative affinity of 3.81 at 5-HT_{1D}. None of the three drugs typically produces VER. If DOET or DIPT are agonists at 5-HT_{1A} and if 2C-B-fly is an agonist at 5-HT_{1D}, we can conclude it is likely that these two receptors do not mediate high VER.

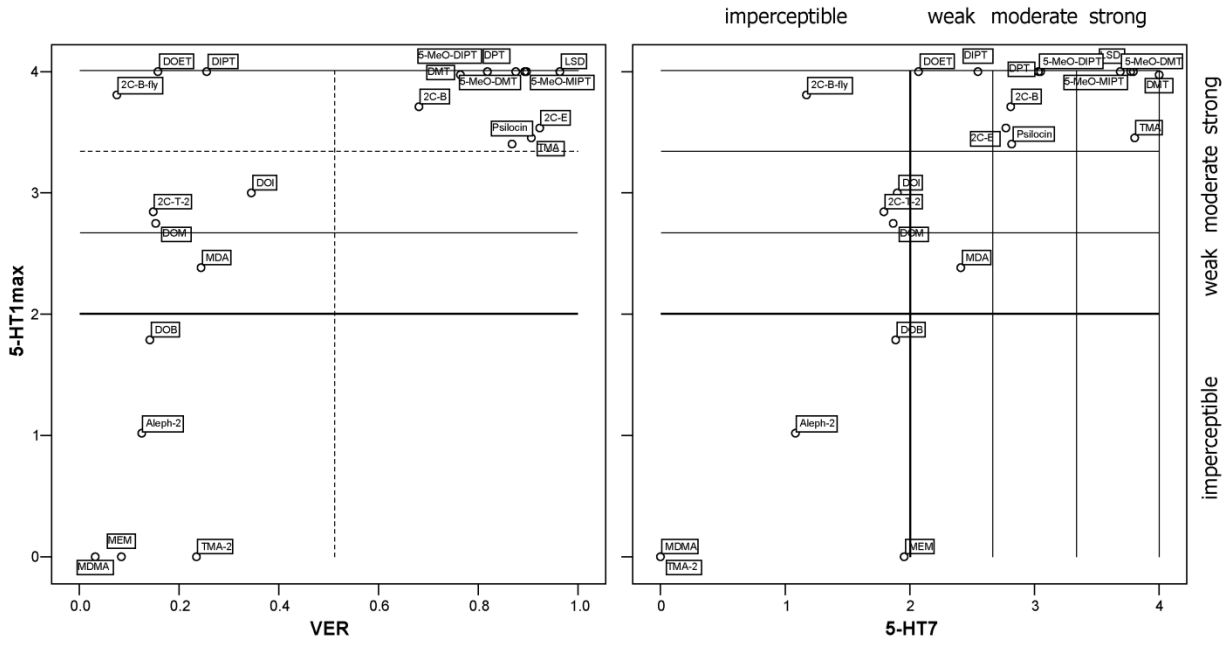


Figure 4: Twenty-two drugs arranged by relative affinity for 5-HT_{1max} vs. VER (left) and 5-HT_7 (right). 5-HT_{1max} is the maximum relative affinity (npK_i) of the four assayed 5-HT_1 receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1E}). The vertical dashed line divides high from low VER. The horizontal dashed line would divide high from low VER drugs but for three outliers (DIPT, DOET, 2C-B-fly).

5-HT_{1D} – 5-HT_{1D} is one of two absolute common denominators of the ten high VER drugs. Figure 5 shows that 5-HT_{1D} relative affinity would cleanly divide high from low VER but for four outliers (2C-B-fly, 2C-T-2, DOM, DOI). We find that these four drugs deviate from the correlation of 5-HT_{1D} relative affinities with 5-HT_7 relative affinities and VER in corresponding patterns. Again, this points to 5-HT_7 as the causative factor in mediating VER.

There are no drugs in this study that are high in VER but low in 5-HT_{1D}, thus we cannot demonstrate that high VER can be produced without the participation of 5-HT_{1D}. More important, 2C-B-fly has strong relative affinity for 5-HT_{1D}, while 2C-T-2, DOM, and DOI have moderate relative affinity for 5-HT_{1D}, all without high VER. If these drugs, especially 2C-B-fly, are agonists at 5-HT_{1D}, we can conclude that 5-HT_{1D} likely does not mediate high VER.

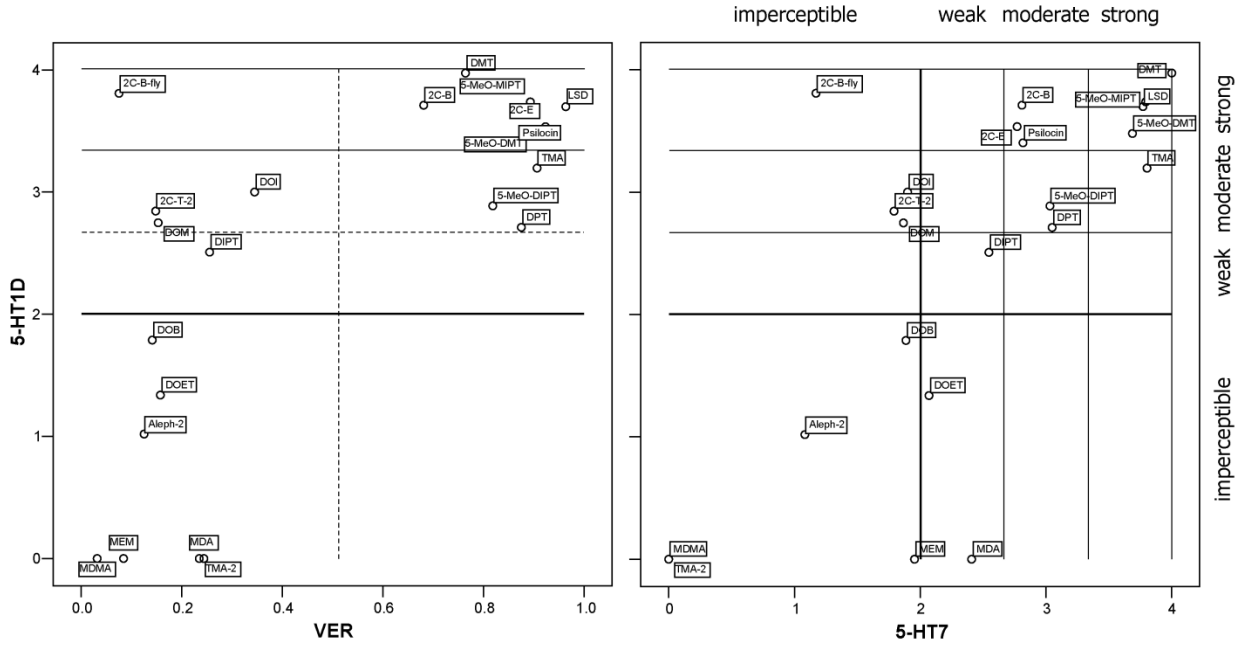


Figure 5: Twenty-two drugs arranged by relative affinity for 5-HT_{1D} vs. VER (left) and 5-HT_7 (right). The vertical dashed line divides high from low VER. The horizontal dashed line would divide high from low VER drugs but for four outliers (2C-B-fly, 2C-T-2, DOM, DOI).

5-HT_{1A} – The left side of Figure 6 shows that if we set aside DOET, DIPT, and DMT, the horizontal dashed line would cleanly separate high from low VER drugs. However the right side of Figure 6 suggests that this pattern is likely an artifact of a strong correlation between relative affinities of 5-HT_{1A} and 5-HT_7. DOET, DIPT, and DMT deviate in corresponding patterns from both correlations. DMT demonstrates that we can have high VER without measurable 5-HT_{1A} affinity (K_i > 10,000nm), showing that 5-HT_{1A} is not necessary for mediating high VER. However, DMT has strong relative affinity at 5-HT_{1D} (3.97) leaving the data consistent with the 5-HT1 hypothesis of Figure 3 (yet as noted above, there is good evidence against 5-HT_{1D}).

Stronger evidence comes from DOET and DIPT which illustrate that we can have 5-HT_{1A} as the best hit without high VER. Thus, if DOET or DIPT is an agonist at 5-HT_{1A}, the properties of DOET, and DIPT can argue against a possible role for 5-HT_{1A} in mediating high VER.

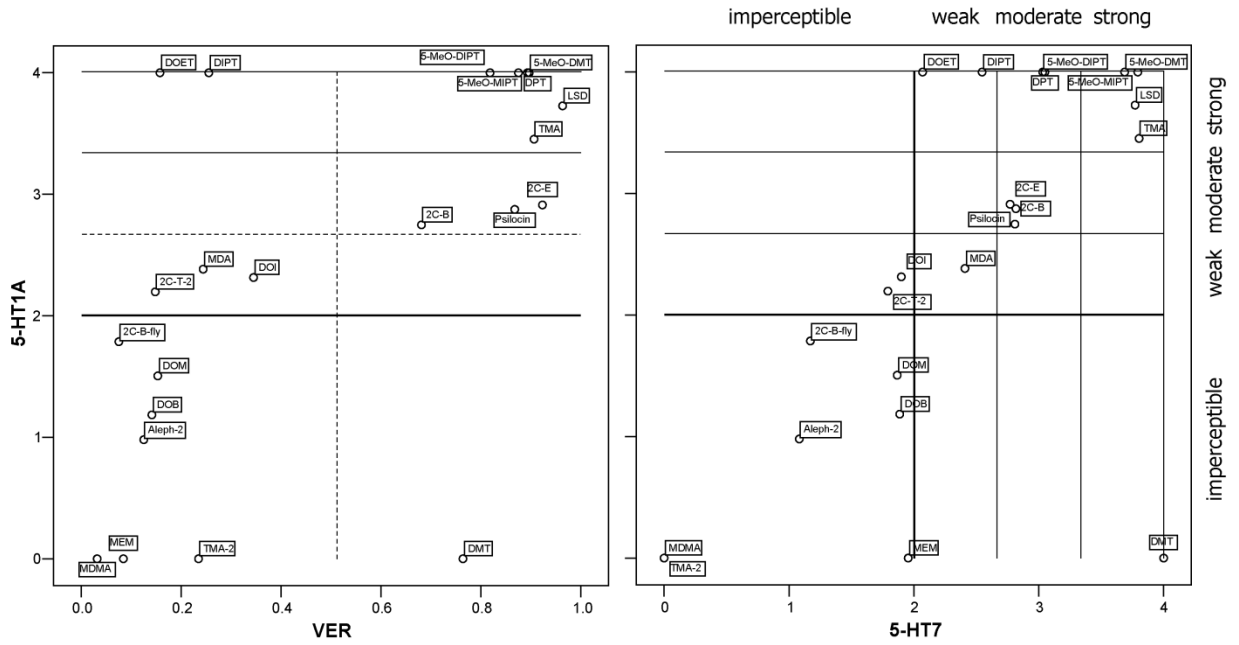


Figure 6: Twenty-two drugs arranged by relative affinity for 5-HT_{1A} vs. VER (left) and 5-HT_7 (right). The vertical dashed line divides high from low VER. The horizontal dashed line would divide high from low VER drugs, but for three outliers (DIPT, DOET, DMT).

5-HT_{1B} – Figure 7 shows that if we set aside DMT, the horizontal dashed line would cleanly separate high from low VER. However, this pattern is likely an artifact of a strong correlation between relative affinities of 5-HT_{1B} and 5-HT_7 which can be seen on the right side of the Figure 7. DMT deviates in the corresponding pattern from both correlations. DMT demonstrates that we can have high VER without high 5-HT_{1B} relative affinity. Therefore 5-HT_{1B} cannot explain the ability of DMT to produce high VER. However, DMT has high relative affinity at 5-HT_{1D} leaving the data consistent with the 5-HT1 hypothesis of Figure 3 (yet as noted above, there is good evidence against 5-HT_{1D}). The highly hallucinogenic DMT has its best hit at 5-HT_7 and has >10,000 nm (immeasurably low) affinity for 5-HT_{1B}. However there is no drug high in 5-HT_{1B} but low in VER, therefore using this data set, we cannot say that 5-HT_{1B} does not mediate high VER.

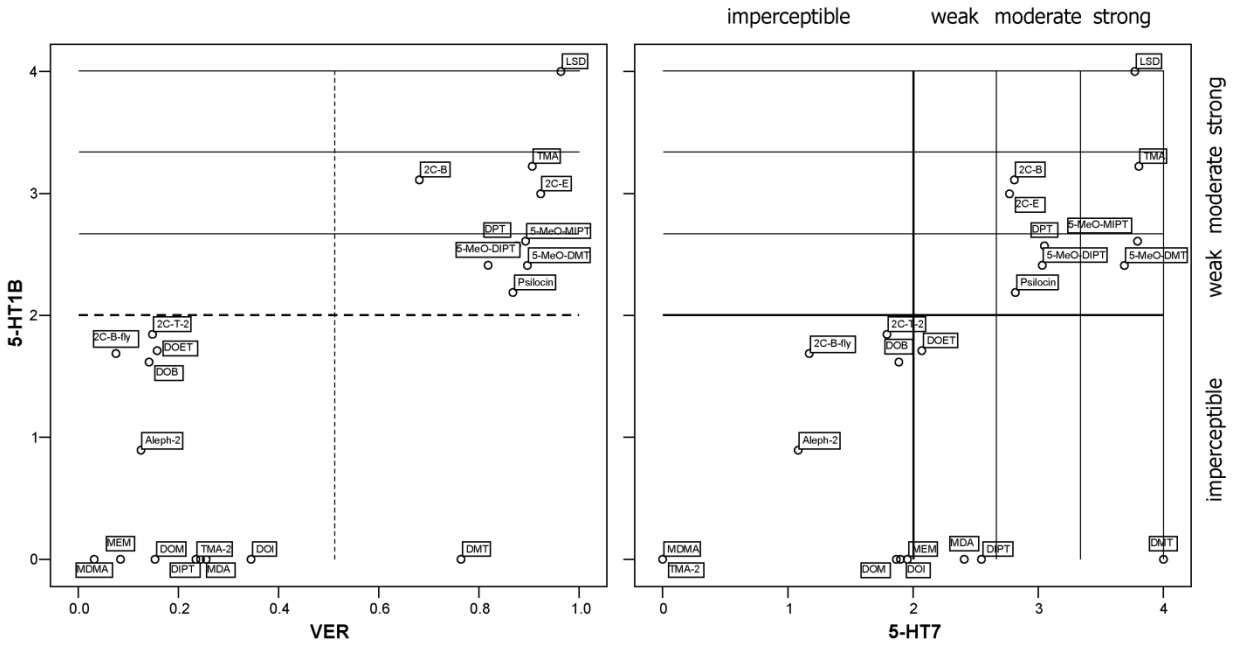


Figure 7: Twenty-two drugs arranged by relative affinity for 5-HT_{1B} vs. VER (left) and 5-HT_7 (right). The vertical dashed line divides high from low VER. The horizontal dashed line would divide high from low VER drugs, but for the outlier DMT.

5-HT_{1E} – Figure 8 illustrates that relative affinity at 5-HT_{1E} is not able to separate high from low VER. None of the drugs of this study have strong relative affinity for 5-HT_{1E}, although there are four with moderate relative affinity (DMT, 2C-B, TMA, psilocin), all of which produce high VER. 5-MeO-DMT, 5-MeO-MIPT, 5-MeO-DIPT, and DPT all have relative affinities below 2.14 for 5-HT_{1E}, therefore 5-HT_{1E} should not explain the ability of these drugs to produce high VER. However the data remain consistent with the 5-HT1 hypothesis of Figure 3 because all four of these drugs have their best hit at 5-HT_{1A} (although as noted above, there is good evidence against 5-HT_{1A}). There is no drug with high 5-HT_{1E} but low VER, therefore using this data set we cannot demonstrate that 5-HT_{1E} does not mediate high VER. However, the inability of 5-HT_{1E} to discriminate high from low VER does not lend support to this receptor as a VER mediating mechanism.

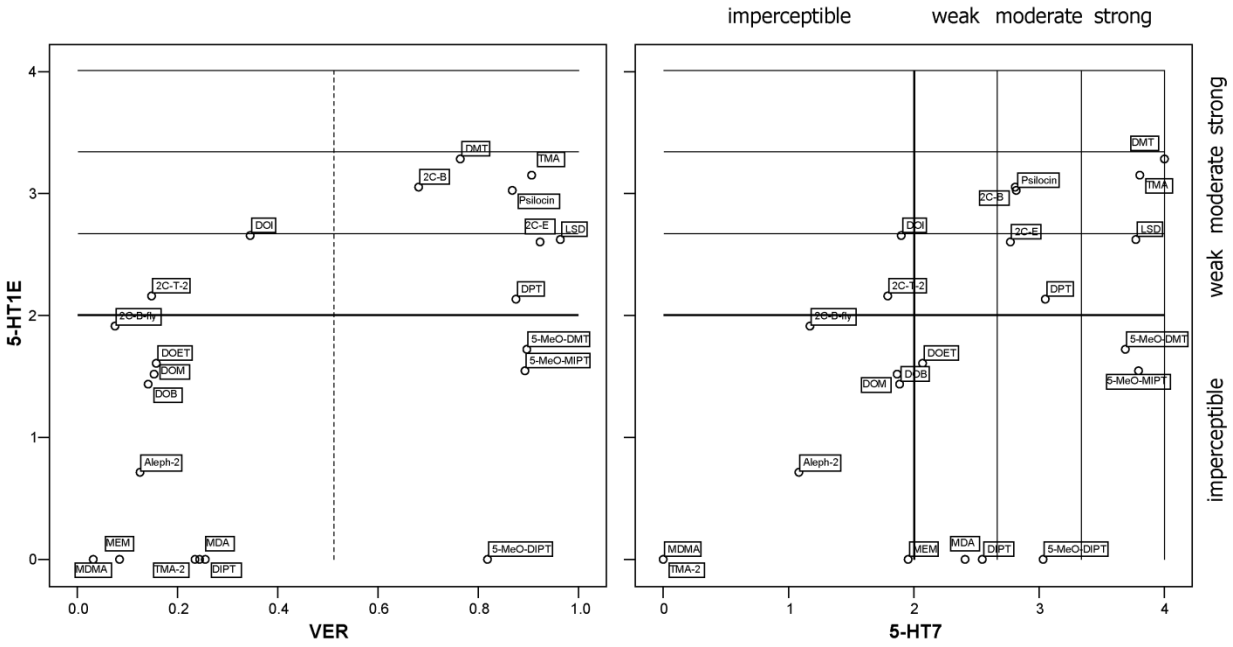


Figure 8: Twenty-two drugs arranged by relative affinity for 5-HT_{1E} vs. VER (left) and 5-HT_7 (right). The dashed line separates high from low VER.

5-HT_1 summary – We note that 5-HT_{1A} and 5-HT_{1B} cannot individually explain the ability of DMT to produce high VER and 5-HT_{1E} cannot individually explain the ability of 5-MeO-DMT, 5-MeO-MIPT, 5-MeO-DIPT, or DPT to produce high VER. If DOET or DIPT is an agonist at 5-HT_{1A} and if 2C-B-fly, 2C-T-2, DOM, or DOI is an agonist at 5-HT_{1D}, we can conclude that 5-HT_{1A} and 5-HT_{1D} do not likely mediate high VER. In short, high VER can be produced without high relative affinity at 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1E}, while the lack of high VER in DOET and DIPT shows that high relative affinity at 5-HT_{1A} does not likely mediate high VER, and the lack of high VER in 2C-B-fly, 2C-T-2, DOM, and DOI shows that high relative affinity at 5-HT_{1D} does not likely mediate high VER. Yet we must acknowledge that within this set of drugs, there is no comparable evidence that high relative affinity at 5-HT_{1B} or 5-HT_{1E} does not mediate high VER.

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. Yet for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D}, 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. Although the 5-HT_1 receptors generally show promising correlations with VER, these are likely spurious correlations arising from corresponding correlations between 5-HT_1 and 5-HT_7 receptors.

We have some evidence against each of the four 5-HT_1 receptors mediating high VER: either high VER can occur without their participation, or their participation can occur without high VER, or both. The hypothesis that 5-HT_1 receptors collectively mediate VER hinges on these drugs sometimes being agonists and at other times being antagonists in this set of receptors, and the pattern of variation in activity fortuitously fitting the hypothesis. It is more parsimonious to accept 5-HT_7 rather than 5-HT_1 as the causative mechanism. 5-HT_1 receptors do not appear to be the causative factors for high VER, however relevant activity data should be obtained to clarify the situation.

Alpha$_2$ – Alpha$_{2A}$ qualifies as a weak fourth common denominator, in that it has high relative affinity in six of the ten high VER drugs. Also, Alpha$_{2C}$ follows close behind with five out of ten. Although they are unlikely candidates, we will examine the Alpha$_2$ receptors.

Before examining the individual Alpha$_2$ receptors, we should consider the possibility that Alpha$_2$ receptors in general might share some common properties, such as mediating VER. Thus Figure 9 shows the relationship of Alpha2 and Alpha2max, with VER and 5-HT_7, for each of twenty-two drugs. Alpha2 is the square root of the sum of the squares of the relative affinity at the three Alpha2 receptors, and Alpha2max is the maximum relative affinity at any of the three Alpha$_2$ receptors assayed (Alpha$_{2A}$, Alpha$_{2B}$, Alpha$_{2C}$). Figure 9 shows that as seen with 5-HT_2, there is nothing in this analysis to suggest a role for Alpha$_2$. Neither Alpha$_2$ nor Alpha$_{2max}$ provides a separation between high and low VER. Not coincidentally, neither index shows a correlation with 5-HT_7 relative affinity.

5-MeO-DMT and psilocin have high VER with very weak participation of any of the three Alpha$_2$ receptors. At the same time DOI, MDA, and MDMA have low VER although they have strong participation of Alpha$_2$. This is a strong argument against a role for Alpha$_2$ in the production of high VER.

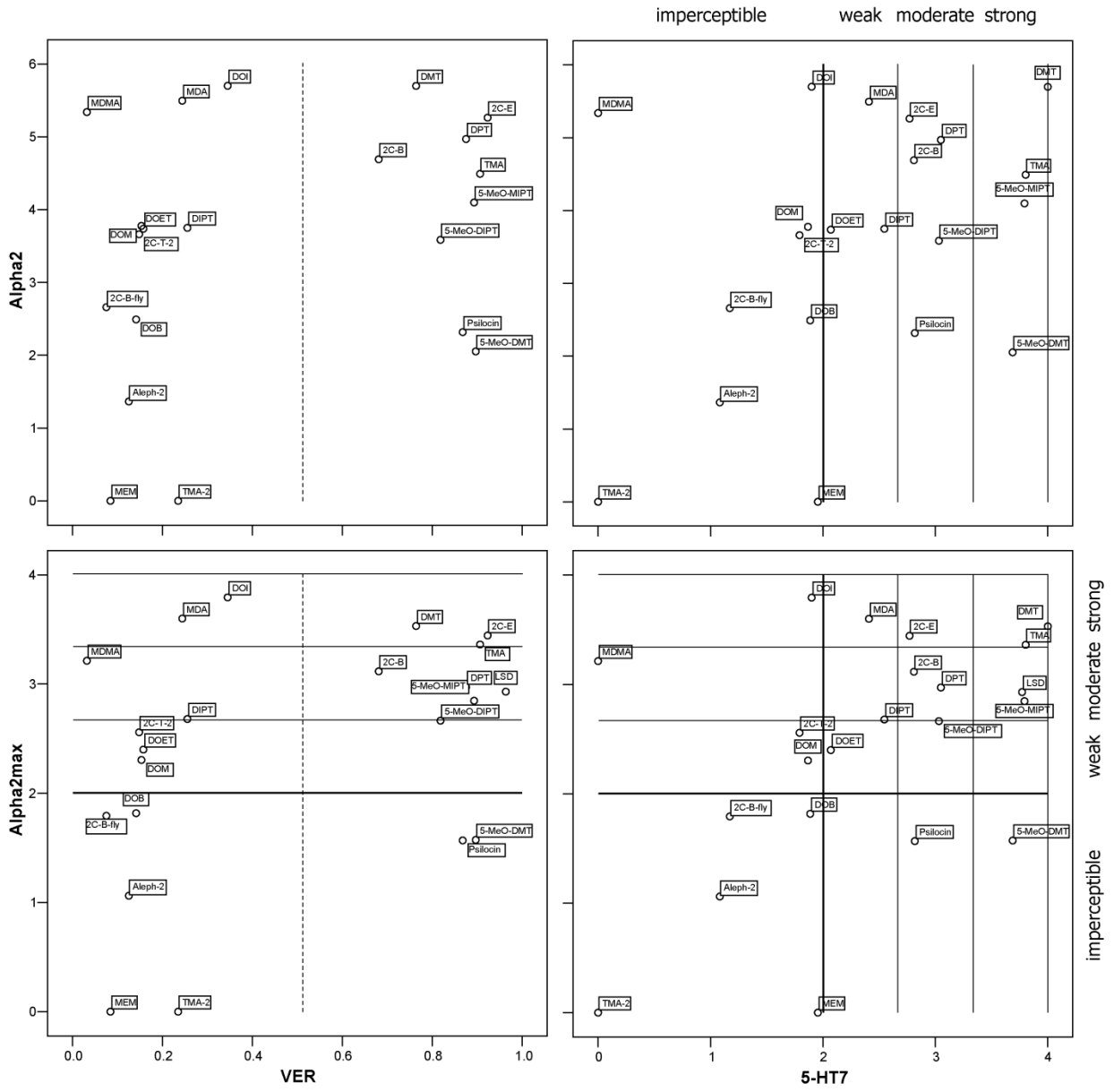


Figure 9: The relationship of Alpha2 (upper row)) and Alpha2max (lower row), to VER (left) and 5-HT_7 (right), for each of twenty-two drugs. Alpha2 is the square root of the sum of the square of the relative affinity at the three $Alpha_2$ receptors, and Alpha2max is the maximum relative affinity at any of the three $Alpha_2$ receptors assayed ($Alpha_{2A}$, $Alpha_{2B}$, $Alpha_{2C}$). The dashed line separates high from low VER drugs. (LSD was not assayed at $Alpha_{2A}$ or $Alpha_{2C}$)

$Alpha_{2A}$ – Figure 10 displays $Alpha_{2A}$ vs. VER and 5-HT_7, and shows that as seen with 5-HT_2, there is nothing in this analysis to suggest a role for $Alpha_{2A}$. $Alpha_{2A}$ does not provide a separation between high and low VER. Not coincidentally, $Alpha_{2A}$ does not show a correlation with 5-HT_7 relative affinity.

5-MeO-DMT, psilocin and 5-MeO-DIPT produce high VER with very weak relative affinity for Alpha$_{2A}$. At the same time, DOI, MDMA, and MDA do not produce high VER although DOI has strong relative affinity for Alpha$_{2A}$, while MDMA and MDA have moderate relative affinity for Alpha$_{2A}$. This is a strong argument against a role for Alpha$_{2A}$ in mediating high VER.

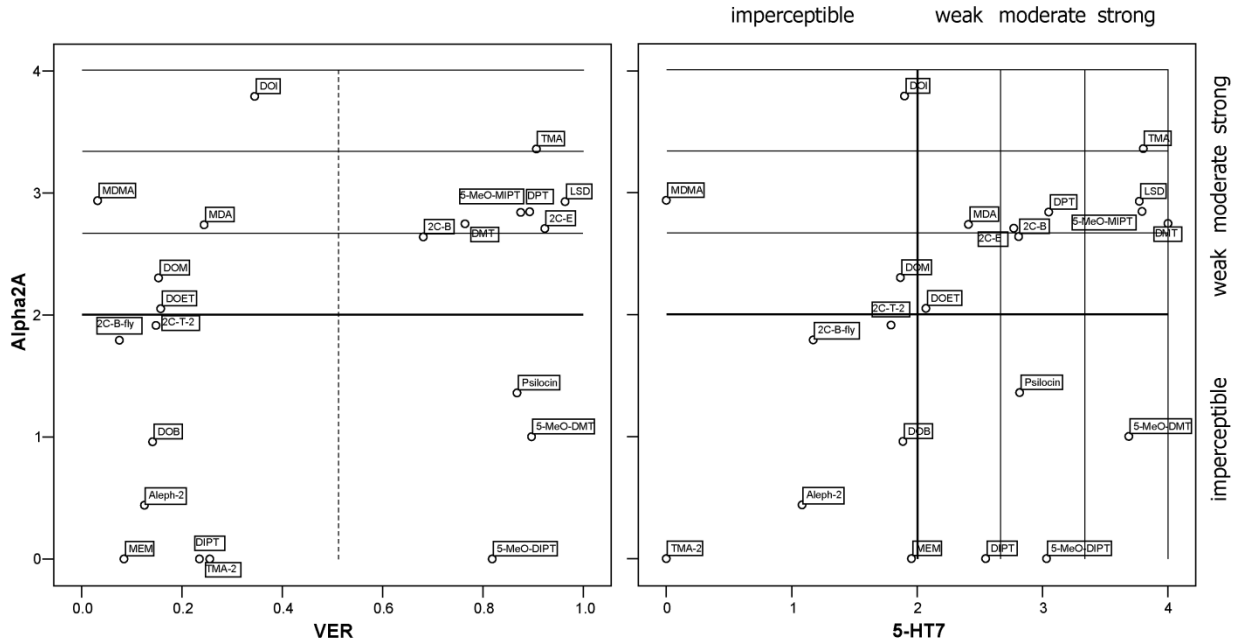


Figure 10: Relative affinity for Alpha$_{2A}$ vs. VER (left) and 5-HT$_7$ (right) for twenty-two drugs. The dashed line separates high from low VER drugs. (LSD was not assayed at Alpha$_{2A}$)

Alpha$_{2C}$ – Figure 11 displays Alpha$_{2C}$ vs. VER and 5-HT$_7$, and shows that as seen with 5-HT$_2$, there is nothing in this analysis to suggest a role for Alpha$_{2C}$. Alpha$_{2C}$ does not provide a separation between high and low VER. Not coincidentally, Alpha$_{2C}$ does not show a correlation with 5-HT$_7$ relative affinity. 5-MeO-DMT and psilocin produce high VER with very weak relative affinity for Alpha$_{2C}$. MDA, MDMA, and DOI do not produce high VER while MDA has strong relative affinity for Alpha$_{2C}$, and MDMA and DOI have moderate relative affinity for Alpha$_{2C}$. Both Alpha$_{2C}$ and Alpha$_{2A}$ are unlikely candidates for mediating high VER.

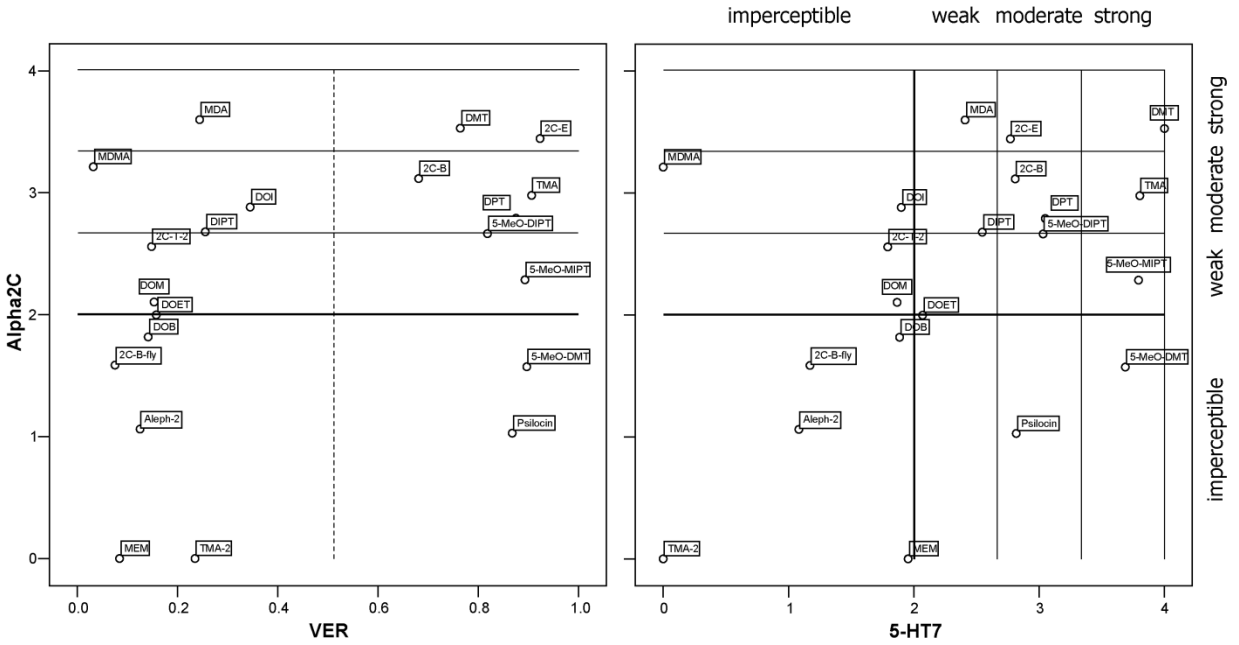


Figure 11: Relative affinity for $Alpha_{2C}$ vs. VER (left) and 5-HT_7 (right) for twenty-one drugs. The dashed line separates high from low VER drugs. (LSD was not assayed at $Alpha_{2C}$)

Summary of prospective receptors

The common denominator method combined with close examination of individual receptors points very strongly to 5-HT_7 as the one receptor most likely to be responsible for mediating high VER.

Table 2 summarizes key features of the review of prospective receptors. For all receptors, there are drugs in the upper right and lower left quadrants of the relative affinity vs. VER plots, with the exception of 5-HT_{2B} which lacks drugs in the lower left quadrant. Table 2 then presents only the presence or absence of drugs in the upper left (UL) or lower right (LR) quadrants (VER on the horizontal axis). The receptors are grouped in the table by these patterns. The ten on the right side of the table (5-HT_{2A}, 5-HT_{2C}, 5-$HT_{2[AC]}$, 5-$HT_{2[AC]max}$, 5-HT_{2B}, 5-HT_{1A}, $Alpha_2$, $Alpha_{2max}$, $Alpha_{2A}$, $Alpha_{2C}$) all have drugs in both the upper left and the lower right quadrants of the plot. The four in the lower left part of the table either have drugs in the upper left of the plot (5-HT_{1max}, 5-HT_{1D}), or in the lower right of the plot (5-HT_{1B}, 5-HT_{1E}), but not both. 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 of the plot (VER on the horizontal axis) indicate high relative affinity with low VER, suggesting that if the drugs are agonists at the receptor (activity data is not available for most receptors), then strong activation of the receptor does not mediate high VER. Because this category of evidence against a role for receptors in mediating VER relies on an assumption about activity, the relevant activity data should be obtained to clarify the issue. When there are no drugs in the upper left (5-HT_7, 5-HT_1, 5-HT_{1B}, 5-HT_{1E}), this data set cannot directly rule out the possibility that high relative affinity for the receptor can mediate high

VER. Drugs in the lower right of the plot indicate low relative affinity with high VER, suggesting that high VER can occur without high relative affinity for the receptor.

Only two entries in the table, 5-HT_7 and 5-HT1, have a pattern that cleanly suggests a causative mechanism for mediating high VER. There is no drug that produces high VER that does not also have high relative affinity for at least one of the four 5-HT_1 receptors assayed; yet each one of the four individual 5-HT_1 receptors assayed includes drugs in either the upper right or lower left quadrants, or both. Most likely the positive pattern found in the 5-HT1 plot arises as a spurious correlation with VER due to the clean correlation between 5-HT1 and relative affinity at 5-HT_7. In every case of a violation of the correlation between relative affinity at 5-HT_7 and any 5-HT_1 receptor or index, the ability to separate high from low VER follows 5-HT_7, not 5-HT_1. The hypothesis that 5-HT_1 receptors collectively mediate VER hinges on these drugs sometimes being agonists and at other times being antagonists at this set of receptors, and the pattern of variation in activity fortuitously fitting the hypothesis. The most parsimonious interpretation of the data is that 5-HT_7 may be the only receptor that mediates high VER. The common denominator method combined with close examination of individual receptors points very strongly to 5-HT_7 as the one receptor most likely to be responsible for mediating high VER.

Receptor	UL	LR
5-HT7	No	No
5-HT1	No	No
5-HT1max	Yes	No
5-HT1D	Yes	No
5-HT1B	No	Yes
5-HT1E	No	Yes

Receptor	UL	LR
5-HT2A	Yes	Yes
5-HT2C	Yes	Yes
5-HT2[AC]	Yes	Yes
5-HT2[AC]max	Yes	Yes
5-HT2B	Yes	Yes
5-HT1A	Yes	Yes
Alpha2	Yes	Yes
Alpha2max	Yes	Yes
Alpha2A	Yes	Yes
Alpha2C	Yes	Yes

Table 2: Distribution of drugs in upper left (UL) and lower right (LR) quadrants of plots of VER vs. relative affinity for sixteen receptors or receptor indices. Presence of drugs in UL or LR quadrants argues against a receptor as responsible for high VER. UL implies high relative affinity at the receptor without high VER, while LR implies high VER without high relative affinity at the receptor. "Quadrant" is not rigidly defined as four equal portions of the plane. Left and right are clearly defined by the bimodal distribution of VER. Upper and lower vary from receptor to receptor, based on two principles. First, an effort is made to draw a horizontal line that separates high from low VER with the fewest outliers. Second, if this is not possible, upper and lower are divided on the boundary between moderate and weak (and high and low) relative affinity (2.67), and this is the boundary in most cases. However, for 5-HT_{1max} the boundary corresponds to that between moderate and strong relative affinity (3.33), and for 5-HT_{1B} the boundary between weak and very weak (2.00) (see horizontal dashed lines in corresponding VER vs. relative affinity plots).

Reference List

Glennon, R. A. (1990). Do classical hallucinogens act as 5-HT2 agonists or antagonists? Neuropsychopharmacology, 3, 509-517.