



Moving beyond 5-HT_{2A}: language models map neurotransmitter receptors to experiential semantics

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Abstract

Rationale Psychedelics exhibit rapid, durable therapeutic effects across diverse psychiatric conditions, yet their broad-spectrum psychoactivity poses challenges for clinical translation.

Objectives As a proof-of-concept, we aimed to quantify associations between 19 neurotransmitter receptors and the subjective effects of 21 psychedelic drugs with broadly assayed binding profiles.

Methods We used a custom Global Vectors for Word Representation (GloVe)-based semantic embedding model trained on 4,496 firsthand experience reports and integrated it with receptor affinities to identify candidate receptor-linked semantic patterns related to distinct psychoactive effects without imposing predefined categorization systems.

Results While 5-HT_{2A} predictably associates with classic facets of psychedelic experience, our analysis reveals novel associations, including 5-HT_{1A} and 5-HT_{1B} with ‘*Cognitive Disruption*’, H₁ with ‘*Interdimensional Communication*’, and 5-HT_{7a} and 5-HT_{1E} with ‘*Visual Complexity*’.

Keywords Psychedelics · Natural language processing · Receptor binding profiles · Subjective effects · Partial least squares regression · Hypothesis generation

Introduction

Psychedelic compounds show promise in treating conditions such as depression, PTSD, and anxiety (Goodwin et al. 2022; Mitchell et al. 2023; Holze et al. 2023). However, limited mechanistic insight hinders efforts to develop psychopharmacological agents that separate the enduring therapeutic benefits of psychedelics, such as those that have been associated with states of ‘*oceanic boundlessness*’, from safety and logistical challenges such as experiences of ‘*vigilance reduction*’ and ‘*dread of ego dissolution*’ (Roseman et al. 2017). Here, we present a data-driven framework combining natural language processing (NLP) and computational biology to link specific receptor targets to discrete experiential outcomes.

Although prior research has highlighted substantial variation in subjective effects of different psychedelics (Lawrence et al. 2022; Mallaroni et al. 2023; Holze et al. 2020), high resolution quantification remains elusive (Tagliazucchi 2022)—party due to the non-pharmacological influences such as “set and setting”, which can modulate efficacy, variability and adverse outcomes (Vizeli et al. 2024; Angyus

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et al. 2024). The pharmacological mechanisms shaping distinct experiential profiles remain similarly undercharacterized (Elk and Yaden 2022).

An exhaustive, controlled clinical investigation of associations between biological sites and subjective effects would require prohibitively large trials across large numbers of human subjects and numerous psychedelic compounds. Fortunately, large-scale datasets of unstructured ‘trip report’ testimonials or from naturalistic psychedelic use offer a rich, cost-effective resource for studying these linkages. As a complement to clinical research, unstructured “trip reports” from naturalistic use represent a scalable and cost-effective source of insight. When integrated with biochemical drug profiles, these narratives enable computational exploration of receptor-level contributions to specific psychoactive effects (Tagliazucchi 2022; Zamberlan et al. 2018; Ballentine et al. 2022).

Despite the encouraging results from an expanding body of clinical trials (Carhart-Harris and Goodwin 2017; Lowe et al. 2022; Mitchell and Anderson 2024; Dahan et al. 2024), psychedelics pose risks, including negative experiences marked by sensory overload, cognitive disruption, and emotional turbulence (Hinkle et al. 2024). Although negative psychedelic experiences can, in some cases, retain the potential to ultimately lead some users to therapeutic breakthroughs (Carbonaro et al. 2016), ‘bad trips’ can be severe and worsen mental health in vulnerable individuals (Evans et al. 2023; Marrocu et al. 2024). Addressing this tension is central to the development of next-generation compounds designed to maximize efficacy while minimizing harm (Simonsson et al. 2024). Achieving reliable therapeutic outcomes with minimal adverse effects remains a major challenge in psychedelic drug development, one with potential to meet a range of diverse and often complex unmet clinical needs. Ideally, therapeutic psychedelic interventions should selectively precipitate effects that may confer clinical benefit such as emotional release, capacity for intimacy and affection, social interaction, optimism, free exploration of consciousness, self-reflection, and even spiritual insight.

Another major challenge in psychedelic research is the difficulty of systematically characterizing subjective effect profiles of different compounds (Tagliazucchi 2022). Some studies have measured contrast between the effects of specific drugs (e.g. psilocybin versus 2C-B (Mallaroni et al. 2023), LSD (Holze et al. 2022), or MDMA (Roseman et al. 2014), LSD versus MDMA [in comparison to d-amphetamine] (Holze et al. 2020), and MDMA versus MDA (Baggott et al. 2019), but these comparisons are coarse in resolution and limited in scope.

Decomposing psychedelic experiences into constituent subjective effects remains challenging (Tagliazucchi 2022).

Psychometric instruments – including the 11-Dimensional Altered States of Consciousness Scale (ASC) (Studerus et al. 2010; Carhart-Harris et al. 2018), the Phenomenology of Consciousness Inventory (Kumar 1986), the Hallucinogen Rating Scale (Strassman et al. 1994; Bouso et al. 2016; Riba et al. 2001), the Mystical Experience Questionnaire (Barrett et al. 2015; Revised Mystical Experience, 2012), the Ego Dissolution Inventory (Dworatzky et al. 2017; Nour et al. 2016), and the Emotional Breakthrough Inventory (Roseman et al. 2019) – aim to quantify the various facets of these states. Though validated (Studerus et al. 2010; Barrett et al. 2015; Nour et al. 2016), and widely used (Carhart-Harris et al. 2018; Barrett et al. 2015), they face two central limitations: (1) incomplete coverage of the full range of distinct effects, particularly those varying across substances or intensity levels; and (2) low specificity, with vague descriptors (e.g. ‘*elementary imagery*’ in the ASC) failing to capture nuanced phenomenology. Addressing these gaps requires a new framework for characterizing psychedelic subjective effects (Yaden et al. 2024).

NLP-based approaches, such as those employed here, offer a complementary strategy to existing psychometric instruments by identifying patterns directly from natural language reports. Such approaches are unconstrained by predefined ontologies composed of distinct subjective effect categories, and therefore are poised to detect signals that are orthogonal to those detected by existing psychometrics. Rather than replacing validated scales, this framework captures distributed word-level structure in large corpora of firsthand accounts, enabling data-driven hypothesis generation about experiential themes that may not be fully represented in structured questionnaires.

Psychedelics exert their varied effects via interactions with numerous CNS receptor sites (Cameron et al. 2023). Among these, serotonin 2A (5-HT_{2A}) has been most extensively studied, with agonism at this site considered central to psychedelic action (Kwan et al. 2022; Husain et al. 2022; López-Giménez and González-Maeso 2018). However, differential outcomes may reflect biased signaling cascades triggered by ligand-specific 5-HT_{2A} activation (Wallach et al. 2023; Jaster and González-Maeso 2023), and are modulated further by factors such as the external context (set and setting) of experiences (Carhart-Harris et al. 2018), and temporal dynamics of drug action (Brouwer et al. 2025). psychedelics engage diverse targets, including other serotonergic receptors, adrenergic, dopaminergic, and histaminergic systems (Inserra et al. 2021; Ray 2010; Klein et al. 2018; Glatfelter et al. 2023; Jain et al. 2025), as well as neurotrophic receptors like TrkB implicated in psychedelic-induced neuroplasticity (Moliner et al. 2023).

How do the individual roles of distinct neurotransmitter receptors work in concert, alongside extra-pharmacological factors, to realize complex psychedelic-induced changes in conscious awareness? Some may drive therapeutic effects; others may contribute to adverse reactions such as anxiety, confusion, or fear. For instance, 5-HT_{2A} activation has been linked to ‘oceanic boundlessness’ and ‘mystical experience’, two states measured by psychometrically validated instruments that correlate with positive clinical outcomes (Roseman et al. 2017; Weiss et al. 2024; Barrett and Griffiths 2018). As emerging insights from this study, however, interactions of serotonergic systems with adrenergic, dopaminergic and histaminergic receptors may modulate the cognitive and emotional depth and breadth of psychedelic experiences. Tailoring machine learning protocols to a corpus of thousands of natural language trip reports, we identify axes of covariation between receptor profiles and semantic themes, generating new hypotheses about the distinct and complementary roles of non-5-HT_{2A} receptors in shaping psychedelic effects.

Methods

Rationale

This analysis was designed to test whether naturalistic experience reports contain reproducible semantic patterns that can be related to known receptor binding profiles. The workflow proceeds from report text to semantic models, drug classification-based validation of these models, receptor-affinity association, and finally to human-interpretable labeling of the resulting latent dimensions. These latent components span the largest patterns of covariance between semantic and biochemical data leveraged herein.

We applied an NLP-computational biology framework to 4,496 user experience reports spanning 21 psychedelic drugs (2C-B, 2C-E, 2C-B-fly, 2C-T-2, 5-MeO-DiPT, 5-MeO-DMT, 5-MeO-MiPT, DiPT, DMT, DOB, DOET, DOI, DOM, DPT, LSD, MDA, MDMA, MEM, mescaline, psilocin, TMA-2). A custom word embedding model captured distinctions between reports. Classification models quantified how well qualitative differences captured by semantic embeddings predicted specific compounds. We then analyzed associations between 19 receptor binding affinities and 19 semantic dimensions. To interpret these themes, we used LLM-based summarization (Bzdok et al. 2024). This integrative pipeline suggests receptor-effect relationships that may support hypothesis generation in the development of next-generation psychedelics with optimized effect profiles.

Collection, curation and integration of experiential and biochemical data

Both the experiential corpus and receptor-affinity matrix used in this study were assembled so that each primary compound was represented both by natural-language reports and corresponding biochemical target data. Subsequent curation and integration of these source data led to the creation of a report-level dataset suitable for linking semantic variation in subjective experience descriptions to cross-compound differences in receptor binding profiles.

We sourced reports from <https://www.erowid.org>, the largest public repository of firsthand accounts of psychoactive drug experiences. Additional reports were manually curated over several years from published books, interviews, podcasts, and journal articles when well-described single substance accounts were available, particularly for compounds with available broad receptor affinity profiles, that are underrepresented on Erowid. These supplementary reports were selected based on clarity, descriptive richness, and clear indication of single-substance use. There also was a bias toward authors who were heuristically judged to be more likely to have correctly identified the substance they consumed, based on publicly disclosed aspects of their personal history. The final report dataset (RD) comprised 4,496 reports spanning 21 psychedelic drugs, each with broad receptor affinity profiles, and a minimum of 25 reports to ensure sufficient representation.

Biochemical data for the 21 drugs were derived from in vitro radioligand binding assays (Ray 2010; Rickli et al. 2016), quantifying affinities (K_i values) at up to 42 CNS targets, including receptors, ion channels, and transporters. We used a dataset of 35 psychoactive compounds from NIMH-PDSP (Ray 2010), excluding non-psychedelics like morphine, ibogaine, and THC to focus on 5-HT₂ relevant drugs. MDMA, an entactogen that is often distinguished from classical serotonergic psychedelics, was retained because multiple clinical ketanserin (a 5-HT₂ antagonist) studies have indicated that 5-HT₂ receptors contribute to some of its psychoactive effects (Kuypers et al. 2018; Liechti et al. 2000; Wel et al. 2011, 2012), and because the present study was designed to examine receptor-experience associations across a polypharmacological compound set rather than isolate 5-HT_{2A} selective action alone. Affinities were normalized as npK_i (relative affinity) values (Ray 2010), to compare across compounds. These receptor binding profiles underpinned our analyses linking pharmacology to semantic dimensions of the experience reports in the RD (see Supplemental Table S1).

To isolate language specific to psychedelic effects, we manually filtered reports using the SuperAnnotate platform (Super Annotate, 2024) to remove irrelevant text and exclude polydrug cases, retaining only those involving a

single substance (no combinations). Exceptions were made for alcohol, caffeine, cannabis, nicotine, and prescription psychiatric medications, due to their ubiquity. Curated reports were matched to npK_i profiles for each drug.

The initial corpus of 43,157 words was reduced by removing syntactic filler, metadata, and rare terms, yielding 15,384 words that occurred 4 or more times. Text was lowercased and corrected, producing a semantic space optimized for modeling subjective effect content. This curated report repository provided the basis for exploratory analyses centered around bringing semantic structures in contact with receptor affinity profiles.

Input report dataset overview

The final report database (RD) included 4,496 unique experience reports comprising 186,812 sentences describing subjective effects. Summary metrics are provided in Table 1. To assess verbosity, we calculated the sentence-to-report ratio for each drug. MEM, DOET, and DiPT were described in relatively brief reports, while psilocin, DMT, and MDMA elicited longer, more detailed narratives.

Table 1 summarizes all 21 drugs in the RD, presenting the number of reports per drug, total number of sentences per

Table 1 Summary of report dataset

Drug Name	Drug Class	Experience Report Excerpts	n reports	n sentences	sentences/ report
<i>total</i>	<i>N/A</i>	<i>N/A</i>	<i>4,496</i>	<i>186,812</i>	<i>41.5</i>
MEM	PEA	"Lots of energy, best directed into activity. Clear imaging, thinking. Intense yet serene..."	27	185	6.9
DOET	PEA	"No visual movement. The eyes-closed fantasy images tend to take off on their own... extremely rich..."	41	399	9.7
DiPT	TRYPT	"Remarkable changes in sounds heard... Piano sounds like a bar room disaster..."	59	1,378	23.4
DOM	PEA	"Mood elevation... color enhancement... empathy... closer to mescaline than to amphetamine..."	92	2,176	23.7
2C-B-fly	PEA	"Real time dilation. Past 5 min seemed like at least half an hour... quick waves of effects – really intense to quite manageable"	29	784	27.0
5-MeO-MiPT	TRYPT	"absolutely no visuals... ease of interpretive fantasy... almost dream-like... Food tasted marvelous..."	125	3,427	27.4
DOI	PEA	"a generic sadness came over me, as I reminisced about earlier days... no one else cares"	38	1,065	28.0
TMA-2	PEA	"seeing more life in the woodwork, and the wooden angel hanging on the ceiling was flesh and feathers..."	35	1,022	29.2
MDA	PEA	"euphoric and intense... I saw that every encounter or event is a potential for growth..."	97	2,958	30.5
DOB	PEA	"an incredible Moebius strip representation of reality at the intellectual level"	47	1,590	33.8
5-MeO- DiPT	TRYPT	"marvelous... Everything was shaded with eroticism..."	258	8,786	33.9
5-MeO- DMT	TRYPT	"beheld every thought...in the universe...wracked... ruthless love. It scared the hell out of me..."	320	11,259	35.2
2C-B	PEA	"Energies of nature are so intense! I see a beautiful scene, birds singing, everything is ecstasy oozing out of each sound and image"	255	9,351	36.5
DPT	TRYPT	"outside the hearts there were sparkling jewels or crystals of light of different colors, maybe four rows..."	177	6,619	37.4
2C-T-2	PEA	"'Am I enjoying this?' ... 'No I am experiencing it.' ... Satisfied and contented..."	112	4,193	37.4
mescaline	PEA	"the earth ... a mosaic... beautiful stones...placed in an intricate design... to move in a serpentine manner..."	68	2,696	39.6
DMT	TRYPT	"my speed is so great that everything has come to a stop – here I gaze upon the entire universe..."	619	25,581	41.3
2C-E	PEA	"Strange devil-angel pairing... ecstatic... God-space... brown ooze... funny gargoyles... 4th of July..."	346	16,575	47.9
LSD	ERG	"I felt a psychic storm raging all around me. Clouds of the same hue of purple as the cathedral walls were roiling all around me, but the clouds were thoughts... the storm was pulling my personality like a kite in the wind"	477	22,908	48.0
MDMA	PEA	"cleanliness, clarity, and marvelous feeling of solid inner strength... profundity..."	636	31,273	49.2
psilocin*	TRYPT	"house looked absolutely gorgeous and nature was simply spectacular... almost too exciting..."	638	32,587	51.1

*Psilocin is assumed when apparent ingested compound contained or was identified as psilocin prodrug psilocybin

drug across all reports, and sentence-to-report ratios (sorted in ascending order), which is a measure of average report length per drug. There is an observed variance between the average report length of the drugs in the set, which ranged from ~7 (MEM) to ~51 (psilocin), and had a standard deviation of ~12. Drug class (phenethylamine [PEA], tryptamine [TRYPT], or ergoline [ERG]), and representative excerpts illustrate the linguistic and experiential diversity encountered within the RD. Excerpts are included solely to provide qualitative context for the types of subjective descriptions present in the training corpus.

Non-psychedelic keyword co-occurrence audit

Although we did permit polydrug reports involving alcohol, caffeine, cannabis, nicotine, and prescription psychiatric drugs, these substances can meaningfully influence subjective experiences elicited by our set of 21 primary drugs. This interference has been especially well documented in the case of cannabis, which has been observed to dose-dependently alter subjective reports of psychedelic experience (Kuc et al. 2022). Further, cannabis and its active components have long been recognized both culturally and in scientific literature to have capacity to elicit psychedelic-like effects on their own, especially in high doses (Wolinsky et al. 2024).

We performed a descriptive keyword audit to gain insight as to the degree of potential confounding signal that might be present in the RD due to the presence of permitted polydrug scenarios. Searches were conducted over the report files using five keyword groups: (1) *alcohol, beer, beers, wine, vodka, whiskey, whisky, rum, tequila, champagne, liquor*; (2) *caffeine, coffee, espresso, cappuccino, tea, mate*; (3) *cannabis, marijuana, marihuana, weed, hash, hashish, THC, ganja, bong, spliff, spliffs, joint, joints*; (4) *nicotine, tobacco, cigarette, cigarettes, cigar, cigars, smoke a cig, smoked a cig, smoking a cig, cig*; (5) *antidepressant, antidepressants, SSRI, SSRIs, SNRI, SNRIs, Prozac, fluoxetine, Zoloft, sertraline, Lexapro, escitalopram, Paxil, paroxetine, Celexa, citalopram, Wellbutrin, bupropion, Effexor, venlafaxine, lithium, benzodiazepine, benzodiazepines, benzo, benzos, Xanax, alprazolam, Klonopin, clonazepam, Valium, diazepam, Ativan, lorazepam, Adderall, Ritalin, methylphenidate*.

This audit was intended to summarize textual overlap with non-primary substance or medication terms rather than to establish verified co-administration. Because the curated reports were naturalistic and did not contain structured co-use metadata, keyword matches may reflect background history, retrospective comparison, context, or text outside of the acute drug episode. However, we anticipate that this uncertainty has been partially mitigated due to the extensive efforts made to manually remove all irrelevant text that does

not directly describe the subjective effects of each report's primary drug. For visualization, report-level keyword presence was summarized in a heatmap displaying the percentage of files containing at least one keyword in each group.

To evaluate whether cannabis co-mentions materially altered the semantic structure of the report corpus, we performed additional cannabis-negative sensitivity analyses using the modeling procedures described below in the following Methods subsections. First, we repeated the drug classification validation after excluding all reports containing cannabis-related keywords. Second, to distinguish the effect of cannabis-related report removal from the effect of losing reports in general, we performed a matched random-attrition control in which the same number of reports was removed from each drug class at random. Finally, we retrained the GloVe semantic model using only cannabis-negative reports and repeated both the drug-classification and receptor-semantic association analyses.

Semantic model & composing context-aware vectors

To detect and ultimately map semantic patterns contained in the reports, we needed to convert free text into vectors that could be compared across drugs using NLP techniques. In essence, qualitative descriptions of subjective drug experiences were distilled into objective quantitative representations. The purpose of this approach was to capture recurring patterns of experiential language, and then to test whether those patterns were sufficiently drug-specific to support downstream receptor-association.

We used semantic modeling to extract structured representations of experience reports by embedding them in a high-dimensional semantic space. Using GloVe (Pennington et al. 2014), an unsupervised NLP model that captures global word co-occurrence patterns, we generated 100-dimensional vectors for each word, enabling the modeling of both semantic similarity and syntactic relationships. GloVe balances global matrix factorization with local context window methods, allowing for interpretable vector arithmetic and semantic compositionality, as described by Mikolov et al. in 2013 (Mikolov et al. 2013). In other words, GloVe reconciles the advantages of two previously proposed families of semantic modeling techniques (global matrix factorization and context window methods) to enhance the interpretability of relationships seen within the derived semantic space.

To create report-level embeddings, word vectors for all words within each report were summed, producing aggregate vectors that encoded the contextual relationships among subjective effects. These embeddings captured dominant experiential themes and served as the foundation for all downstream analyses linking semantic structure to receptor affinity profiles. Briefly, we selected GloVe rather than

transformer-based contextual models (e.g., BERT) for several practical and methodological reasons. First, the corpus size (4,496 reports) is modest relative to the scale typically required to fine-tune transformer architectures. Second, GloVe produces static, deterministic embeddings that facilitate interpretability and stable projection into downstream linear models such as LDA and PLSR. Finally, our primary aim was to capture global co-occurrence structure across the entire corpus rather than sentence-level contextual nuance. Additional details of model optimization and rationale for GloVe's selection are provided in the Supplementary Materials document.

To validate the semantic embeddings as to their ability to capture drug-specific subjective effects, we trained Linear Discriminant Analysis (LDA) models to classify which drug was described in each pre-processed report (drug names removed from text). LDA projected 100-dimensional embeddings onto axes maximizing between-drug variance while minimizing within-drug variance of the trip reports (Fisher 1936). We used fivefold cross-validation with shuffled splits to assess generalizability of predictive performance to unseen data. Input features were standardized prior to model fitting. Classification accuracy (*i.e.*, correct drug prediction rates) was computed per drug, providing a measure of how distinctly each was represented in the custom GloVe semantic space.

Partial least squares regression

We then linked the derived 100-dimensional semantic space to pharmacology by mapping covariance with the 19-dimensional space defined by the receptor binding affinity profiles of the 21 drugs included in the RD. After estimating these shared biochemical-semantic components, we examined which words aligned most strongly with each component so that the statistical dimensions could be interpreted in experiential terms.

While LDA validated the distinctiveness of drug effects in semantic space, we used Partial Least Squares Regression (PLSR) to link report embeddings to normalized receptor binding profiles (npK_i). As a doubly multivariate method, PLSR is well-suited to relate high-dimensional semantic and biochemical data (Bzdok et al. 2019). Like PCA, GloVe and LDA, PLSR reduces dimensionality (See Supplemental Materials), but it uniquely models shared latent structures between input and response variables.

We optimized receptor selection (See Supplemental Materials) to maximize covariance between semantic themes and receptor affinities. The resulting components contained matched latent variables from both domains, with predictor loadings revealing which words contributed most to each latent pattern. These components captured distinct

covariance structures between subjective report embeddings and drug relative affinity profiles.

To render the components semantically, we projected GloVe word embeddings onto PLSR loadings. This mapped words along key axes of biochemical-experiential variation, creating a receptor-informed semantic structure grounded in natural language and pharmacology.

LLM-supported summarization of semantic components

This section describes how the mathematical PLSR components were converted into readable labels for interpretation. The labels were not treated as discovered clinical categories, but as descriptive summaries of the words most strongly associated with each component end.

To help support interpretation of receptor-effect relationships, a large language model (LLM) was used to summarize word lists sampled from the extremes of semantic PLSR components. Manual interpretation of the full 15,384-word vocabulary was infeasible and prone to subjectivity (Bzdok et al. 2024). Instead, for each of the 19 components, we extracted the top and bottom 1% (153 words each) and submitted them as prompts to GPT-4-32 k.

We took the top and bottom one percent of each ordered list (153 words in each sample) to capture the semantic information at each extreme of all components and used them as 'user' input prompts to the OpenAI LLM GPT-4-32 k, where the 'context' input prompt was as follows:

"Please analyze lists of words taken from large scale analysis of experience/trip reports. Can you please characterize each list using a single word or phrase capturing the meaning of subjective experience themes captured by each list? The themes should be strictly related to mental states and not related to other concepts in reports such as dosage forms and routes of administration. In your response do not simply list back the input words. Do not generalize using the terms 'psychedelic', 'altered perception' or 'hallucination' in your response. The response should be a singular theme/phrase, the one dominant theme of each sample. Avoid responses like X and Y, A or B... etc."

Finally, outputs from these prompts were reviewed by human experts in subjective effect documentation to ensure contextual fit. We did not expect perfect concordance between LLM-generated summaries and human-derived labels, as both represent interpretive abstractions of mathematically defined components. Both human-derived and LLM-generated summaries were not restricted to any pre-existing subjective effect ontology, but they were not free

from ontological presumptions due to prior exposure to extensive bodies of text descriptions of naturalistic and clinical psychedelic use. The underlying latent dimensions are determined by PLSR loadings; and textual summarize serve only as descriptive aids to support interpretation. For comparison purposes, manually derived labels were also generated and are provided in Table S2. The labels describing each semantic dimension can be used to enhance interpretability of study results and support the derivation of new hypotheses about potential linkages between key receptors and particular subjective effects.

Results

Estimated signal contamination from permitted polydrug reports

The results of the non-psychedelic keyword co-occurrence audit are depicted below in Fig. 1. Overall, 40.6% of the reports in the RD included at least one co-mention of keywords from any of the five subsets listed in the Methods section. The most frequent co-mentioned substance across all of the reports was cannabis (25.1%), followed by alcohol (10.6%), nicotine (10.5%), caffeine (6.8%), and psychiatric medications (3.9%).

The reports with higher than average co-mentions of any tracked substance were MDMA (53%), 5-MeO-DiPT (49.6%), psilocin (48.7%), 2C-B (47.1%), 2C-E (46.2%), 2C-T-2 (43.8%), 2C-B-fly (41.4%), and LSD (40.7%).

Within this subset of drugs the rank order of co-mentions generally followed the same pattern seen across the entire RD, with some minor deviations including 2C-B, 2C-E, LSD and psilocin reports exhibiting higher co-mention of nicotine than alcohol keywords. The only two drugs that did not have any reports with cannabis co-mentions were DOET and MEM. We encourage readers to reference Fig. 1 when interpreting the rest of the results of this study, and consider the degree to which findings may be influenced by polydrug signal contamination.

Because cannabis is recognized for both its capacity to induce psychedelic-like effects and modulation of subjective psychedelic experiences (Kuc et al. 2022; Wolinsky et al. 2024), we removed 1,128 reports with cannabis keywords to produce a 3,368 report cannabis-negative version of the RD that enabled several sensitivity analyses. Overall LDA accuracy was 37% compared to the 41% seen with the full corpus, thus, cannabis co-mentions influenced classification performance but did not account for the overall drug-identification structure. Matched random attrition accounted for ~2.3 percentage points of the total accuracy decline, while cannabis-specific removal accounted for an additional ~1.5. In a retrained cannabis-negative PLSR model, R^2 decreased from 0.192 to 0.161 and explained semantic variance from 74 to 62%. Altogether, these results indicate that cannabis co-mentions contributed modestly to the strength of the semantic signal, but their removal did not eliminate either drug-specific language patterns or the broader association between experiential semantics and receptor binding profiles (See Supplementary Figures S1-S3).

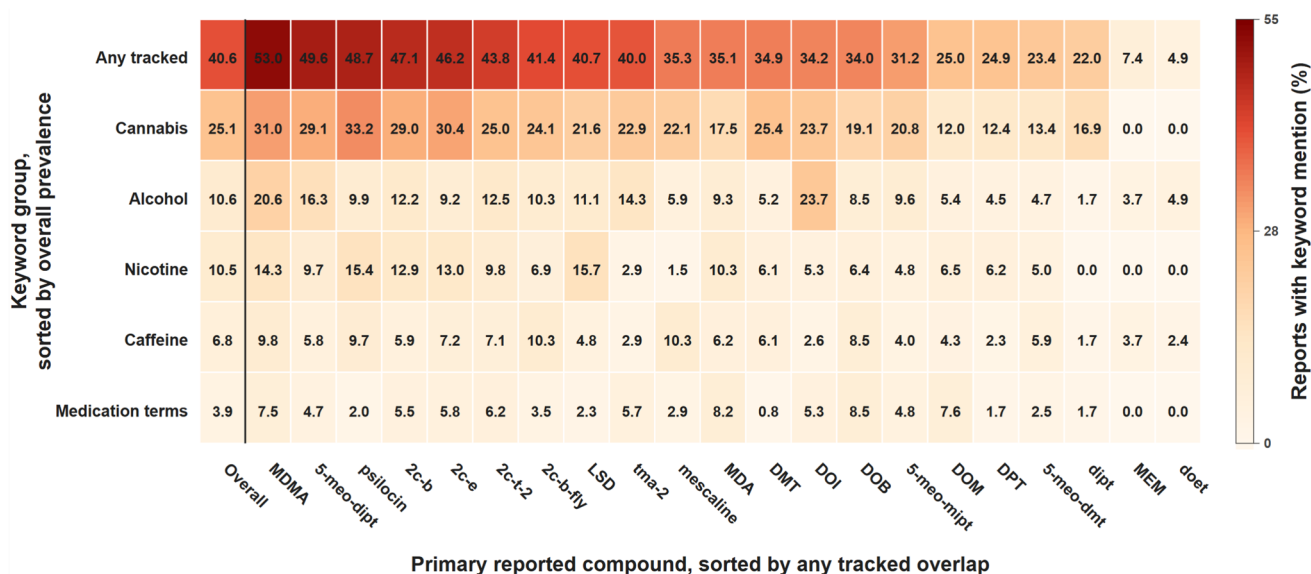


Fig. 1 Keyword overlap with allowed non-psychedelic substance terms. Descriptive keyword overlap with permitted non-psychedelic substance and medication terms in the RD. Each cell shows the percentage of report files for a given primary compound containing at least one keyword from the indicated group (see Methods section for

keyword lists). Rows are sorted by the percentage of reports containing any tracked keyword group across all five subsets; columns are sorted by overall keyword-group prevalence. Values represent keyword/document overlap rather than verified co-administration events

Performance of LDA predictions from report embeddings

We trained a GloVe model on the full RD corpus to generate 15,358 unique word embeddings (occurring ≥ 4 times). By summing word vectors within each report, we derived report-level embeddings representing subjective effect profiles in a high-dimensional semantic space.

To evaluate embedding utility, we trained a Linear Discriminant Analysis (LDA) model to classify which drug was described in each report. Using fivefold cross-validation, we achieved an overall accuracy of 41%—substantially above the 4.8% baseline expected by random assignment. A confusion matrix summarizing performance is shown below (Fig. 2). These results indicate that semantic structures learned from the GloVe model contain discriminative features sufficient to predict drug identity from experiential language alone.

Top-performing report classifications included MDMA (67%), DMT (66%), DiPT (53%), 5-MeO-DMT (53%), psilocin (53%), and LSD (35%). DiPT stands out from the rest of the top-performing drugs in that it has both a relatively lower report count, and sentence-to-report ratio. Notably, LSD was often misclassified as psilocin, and vice versa, reflecting semantic overlaps in their descriptions. Psilocin was the most frequent misclassification target for 16 of the 20 other drugs. MDA was misclassified as MDMA in 34% of cases. Both 2C-B-fly and 5-MeO-MiPT were often mistaken for 5-MeO-DiPT. These patterned deviations suggest that the semantic space captures sufficient nuance to differentiate psychedelic drugs based on experiential language.

PLSR reveals combined contributions of multiple receptor groups to latent variance in experience report semantic space

To identify covariance between subjective report content and receptor binding profiles, we applied PLSR using the optimized set of 19 receptors identified as detailed in the Methods: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{5A}, 5-HT₆, 5-HT_{7a}, Alpha_{2A}, Alpha_{2B}, Alpha_{2C}, D₂, D₃, H₁, Imidazoline₁, M₃, SERT and Sigma₁. For brevity, we refer to all sites assessed in this study as receptors, as the only non-neurotransmitter receptor site is SERT (serotonin re-uptake transporter).

PLSR yielded latent components capturing shared structure between semantic embeddings and npKi profiles. A fivefold external cross-validation produced a mean explained semantic variance of 0.74 ± 0.050 and an R^2 of 0.19 ± 0.028 . The former value reflects how well subjective experience space is summarized; the latter value quantifies how well biochemical profiles can be predicted from report

embeddings—indicating meaningful signal despite the complexity and high dimensionality of the inputs.

Each PLSR component captures a spectrum of experiential meaning (e.g., “*Fear v. Love*”), interpretable through ordered word sequences. Manual interpretation of these extremes would be unscalable, so an LLM was used to generate summary labels (See Fig. 3 above). To ensure robustness, word samples were independently reviewed by a subjective effect expert blinded to LLM outputs. Final LLM-derived labels were retained for Figs. 4 and 5; expert annotations are presented in Table S2.

PLSR components were used to position drugs within a semantic space derived from experience reports (Fig. 4). When interpreting the meaning of the information depicted in Fig. 4, it is important to recognize that the relative positions of drugs within this space do not represent global phenomena and should be considered in the context and bounds of the RD specifically. Latent Component 1 (LC1), the most explanatory axis, spans from ‘*Physical Stimulation and Social Interaction*’ (e.g., MDMA) to ‘*Visual Complexity*’ (e.g., DMT). This pattern suggests that drugs with receptor profiles closer to DMT than MDMA were associated with visually complex language in this dataset, rather than social or somatic stimulation.

LC2 ranges from ‘*Physical Sensation and Emotional Response*’ to ‘*Perceptual Distortion*’. Both MDMA and DMT occupy similar positions along LC2, though their distortions likely differ in origin: MDMA enhances perception of external stimuli (Haggarty et al. 2024; Wit and Bershad 2020; Kolbrich et al. 2008), whereas DMT alters internal imagery and cognition (Strassman et al. 1994; Alamia et al. 2020; Pais et al. 2024; Strassman 1996). Together, LC1 and LC2 differentiate MDMA and DMT along phenomenological and neurobiological axes, consistent with prior research.

Interpretability of drug-specific semantic profiles increased with the addition of successive latent components. The third component (LC3) was summarized as the spectrum between ‘*Spiritual Sensuality*’ and ‘*Escapade/Adventure*’ and was visualized in Fig. 4 via color-coding of drug markers—where red indicated strong association with ‘*Spiritual Sensuality*’, and blue with ‘*Escapade/Adventure*’. Once more, DMT stood at a boundary of the experiential space as the average value of DMT report loadings was the minimum for LC3. 5-MeO-DMT and DPT also occupy the same octant of this compressed, three-dimensional semantic space, as DMT—a region encapsulating a combination of perceptual overload and a sense of transcendence.

While the LLM-based summaries such as ‘*Escapade/Adventure*’ provide immediate insight as to some of the major themes represented in each component end, we anticipate readers may want to gain a more thorough understanding of exactly which terms these summaries are being

True labels	mdma	67 %	3 %	12 %	0 %	3 %	3 %	3 %	2 %	0 %	2 %	1 %	1 %	0 %	0 %	1 %	0 %	1 %	0 %	0 %	0 %
	dmt	1 %	66 %	15 %	1 %	8 %	1 %	4 %	2 %	0 %	1 %	0 %	1 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %
	psilocin	4 %	10 %	53 %	1 %	5 %	1 %	18 %	3 %	0 %	2 %	0 %	1 %	0 %	0 %	0 %	1 %	0 %	0 %	0 %	0 %
	dpt	0 %	5 %	15 %	53 %	0 %	15 %	7 %	2 %	0 %	2 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %	2 %
	5-meo-dmt	3 %	16 %	15 %	0 %	53 %	3 %	4 %	1 %	0 %	1 %	0 %	1 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %
	5-meo-dpt	7 %	5 %	12 %	3 %	3 %	38 %	10 %	5 %	0 %	6 %	1 %	1 %	3 %	0 %	0 %	0 %	3 %	0 %	1 %	0 %
	lsd	4 %	7 %	38 %	1 %	3 %	1 %	35 %	6 %	0 %	1 %	0 %	1 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %
	2c-e	3 %	5 %	22 %	2 %	3 %	5 %	14 %	27 %	0 %	10 %	1 %	3 %	3 %	1 %	0 %	1 %	1 %	0 %	0 %	1 %
	doet	0 %	2 %	27 %	0 %	7 %	5 %	5 %	2 %	24 %	2 %	17 %	0 %	0 %	0 %	5 %	0 %	0 %	0 %	2 %	0 %
	2c-b	6 %	5 %	20 %	0 %	3 %	9 %	12 %	16 %	0 %	18 %	0 %	4 %	2 %	0 %	0 %	1 %	1 %	0 %	0 %	1 %
	dom	9 %	8 %	21 %	0 %	3 %	7 %	5 %	4 %	12 %	9 %	12 %	2 %	1 %	0 %	2 %	0 %	3 %	1 %	1 %	0 %
	dpt	2 %	18 %	19 %	1 %	10 %	7 %	8 %	7 %	0 %	8 %	2 %	11 %	3 %	1 %	1 %	1 %	0 %	0 %	0 %	1 %
	5-meo-mipt	6 %	6 %	20 %	0 %	3 %	30 %	4 %	6 %	0 %	9 %	2 %	5 %	7 %	0 %	0 %	1 %	1 %	1 %	0 %	0 %
	tma-2	9 %	3 %	23 %	0 %	0 %	20 %	9 %	6 %	0 %	9 %	0 %	11 %	6 %	6 %	0 %	0 %	0 %	0 %	0 %	0 %
	mda	34 %	3 %	15 %	1 %	8 %	3 %	6 %	4 %	3 %	7 %	3 %	3 %	1 %	1 %	3 %	1 %	2 %	0 %	0 %	0 %
	mescaline	4 %	10 %	35 %	1 %	6 %	9 %	9 %	4 %	0 %	12 %	0 %	1 %	0 %	0 %	1 %	3 %	1 %	0 %	1 %	0 %
	2c-t-2	2 %	3 %	21 %	0 %	4 %	21 %	4 %	19 %	0 %	12 %	3 %	6 %	1 %	0 %	0 %	0 %	3 %	0 %	1 %	0 %
	doi	13 %	5 %	24 %	0 %	3 %	13 %	18 %	13 %	0 %	5 %	0 %	0 %	0 %	0 %	0 %	3 %	3 %	0 %	0 %	0 %
	dob	4 %	11 %	30 %	0 %	2 %	13 %	21 %	4 %	0 %	9 %	4 %	0 %	0 %	0 %	0 %	0 %	2 %	0 %	0 %	0 %
	mem	0 %	15 %	30 %	0 %	7 %	19 %	19 %	0 %	4 %	7 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %	0 %
	2c-b-fly	0 %	0 %	21 %	0 %	7 %	31 %	10 %	7 %	3 %	14 %	0 %	3 %	0 %	0 %	0 %	0 %	0 %	0 %	3 %	0 %
		mdma	dmt	psilocin	dpt	5-meo-dmt	5-meo-dpt	lsd	2c-e	doet	2c-b	dom	dpt	5-meo-mipt	tma-2	mda	mescaline	2c-t-2	doi	dob	mem
	Predicted labels																				

Fig. 2 Twenty-one psychedelic drugs show 41% predictive accuracy, 8.5-fold above random. A fivefold external cross-validation assessed LDA model performance, to understand how it responds to the challenge of predicting drug labels from report text hidden during model training. Compared to a naïve chance baseline of 4.8% (uniform random assignment across 21 drugs), performance showed an order of magnitude of improvement. Additionally, performance remained 27% above what would be expected from label imbalance alone (majority-class (psilocin) baseline: 14%). Notably, several compounds with relatively small sample sizes were classified with comparable accuracy to

more frequently represented drugs (e.g. DiPT: 53% accuracy with 59 reports; DOET: 24% with 41 reports), indicating that predictive performance was not driven solely by overrepresentation of the largest class (psilocin: 638 reports; 53% accuracy). Systematic misclassifications appear on lower-left side. Models were trained using 100-dimensional semantic embeddings and corresponding drug classes. Rows sum to 100%, and drugs ordered by true positive rate. These results demonstrate structured semantic content in experience reports is sufficient for algorithmic prediction of drug identity

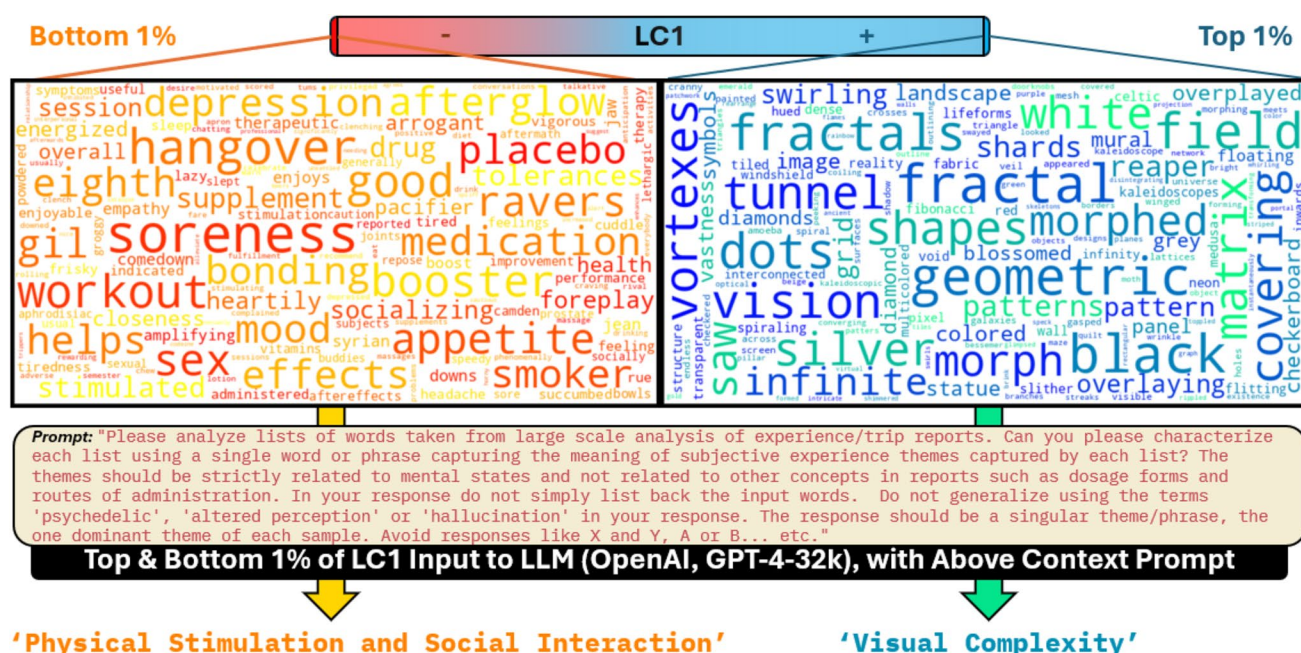


Fig. 3 LLM-based synthesis of experience themes: interpreting latent component meaning. LLM-Based interpretation of latent semantic dimensions. Word lists from the top and bottom 1% of each PLSR-

derived semantic component were visualized as word clouds and summarized by a large language model. Word size reflects proximity to component poles; colors are random and for contrast only

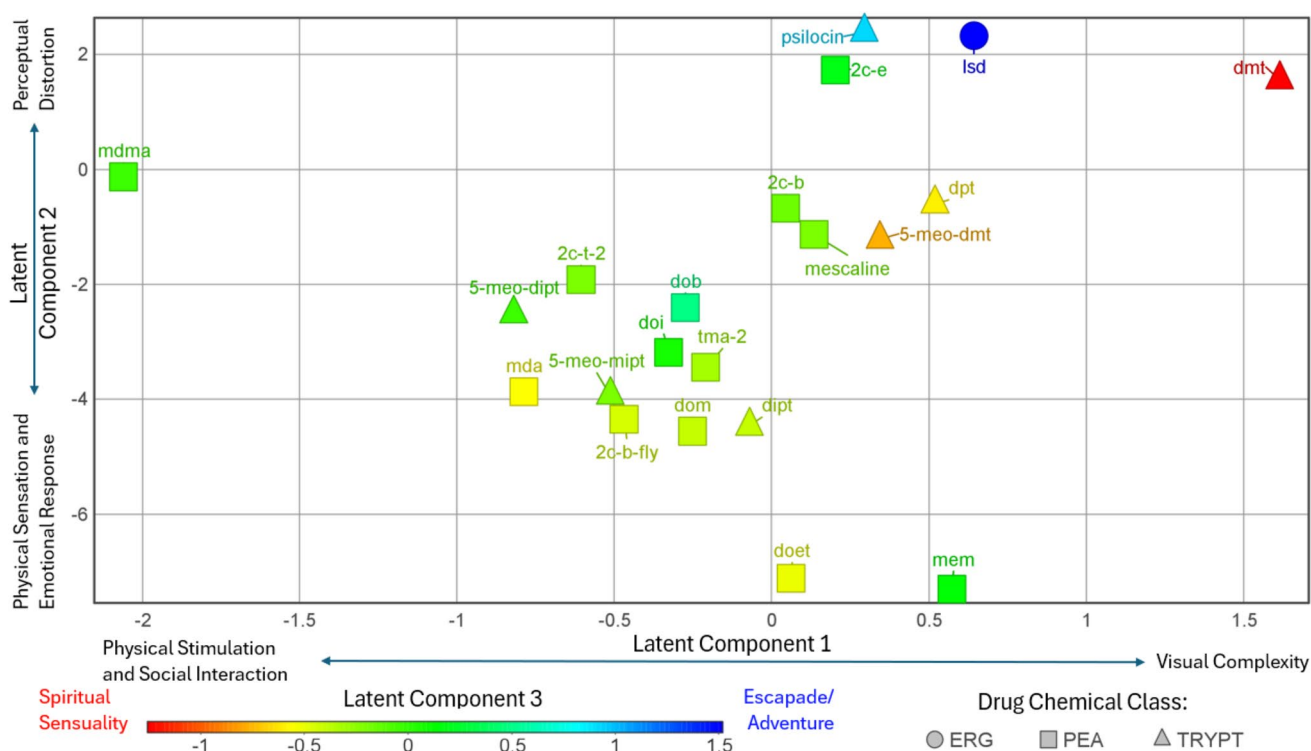


Fig. 4 Distribution of drugs in biochemical-experience space. Drugs positioned in semantic space via PLSR-transformed report embeddings. Drug means along LC1 and LC2 are shown as x/y axes; LC3 is encoded as color. Marker shapes reflect chemical class (ERG=circle,

PEA=square, TRYPT=triangle). Separation across components highlights how subjective effects relate more closely to receptor profiles than to structural similarity



Fig. 5 Relationships between receptor binding affinities and experience space dimensions. Heatmap showing relationships between receptor binding profiles and PLSR-derived semantic dimensions. Each row corresponds to a latent component labeled by themes extracted from the top and bottom 1% of associated words (formatted as “positive v.

negative”). Color intensity reflects strength of receptor contribution, with red and blue denoting positive and negative loading directions, respectively. Receptor columns are clustered by similarity in their semantic associations, offering a systems-level view of how semantic report dimensions covary with biochemical profiles

derived from (See Table S2, which lists all terms in each component end). Manual inspection of the LC3 positive pole revealed words like *freaked*, *police*, *screamed*, *pissed*, *begged*, *hid*, *paranoid*, and *scared*, pointing to themes of interpersonal conflict, distress, and perceived danger—hallmarks of “bad trips”. While they must be interpreted with a fair degree of reservation (as it is possible co-administration of other substances such as alcohol or cannabis, non-pharmacological contextual factors associated with the environments LSD is commonly used in, and potential differences in the LSD user demographic compared to other groups of individuals, may influence such greater opportunities for interpersonal conflict or distress), these results thematically highlight a central aim of this work: to map adverse experiential patterns onto drug associated receptor profiles that may guide pharmacological design of compounds that minimize such outcomes.

To assess how receptors contribute to subjective effects of the drugs plotted in Fig. 4, we analyzed the PLSR y-loading matrix, which quantifies the strength and direction of associations between receptor affinities and latent semantic components. These relationships were visualized as a clustered heatmap (Fig. 5), enabling comparison of receptors based on similarity in association with experiential effects. The 19 components were grouped into four clusters based on their receptor association patterns.

The top cluster: LC9 (*‘Intense Emotional Release’* v. *‘Interdimensional Communication’*), LC1 (*‘Physical Stimulation and Social Interaction’* v. *‘Visual Complexity’*), and LC8 (*‘Emotional Turbulence’* v. *‘Surreal Imagery’*), exhibited strong positive associations with 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{5A}, 5-HT₆, 5-HT_{7a}, SERT, Sigma1 and H₁. Notably, the strongest loading for the positive end of LC9 (*‘Interdimensional Communication’*) was not linked to serotonin, but to histamine. These findings reinforce established associations between serotonergic signaling and visual-perceptual alterations; and could support the generation of new hypotheses involving other receptors such as H₁.

The second cluster included LC4 (*‘Physical Intimacy and Affection’* v. *‘Cognitive Disruption’*), LC16 (*‘Romantic Intimacy’* v. *‘Confinement and Distortion’*), LC7 (*‘Social Interaction and Optimism’* v. *‘Physical Discomfort and Distress’*), and LC18 (*‘Physical Cleansing and Social Interaction’* v. *‘Exploration of Consciousness’*). While 5-HT_{2A} was positively associated with *‘Cognitive Disruption’*, relationships between 5-HT_{2A} and other components were minimal. 5-HT_{1A} and 5-HT_{1B} showed positive associations with LC4 and LC7; and 5-HT_{5A} with LC7 and LC16. Positive emotional and social effects (found at the negative ends of components) were not associated with serotonin receptors

but instead with Alpha₂ adrenergic receptors, imidazoline₁ receptor, and the muscarinic acetylcholine receptor M₃.

The third cluster included LC11 (*‘Auditory and Musical Engagement’* v. *‘Visual Distortions and Interpretations’*), LC3 (*‘Spiritual Sensuality’* v. *‘Escapade/Adventure’*), LC6 (*‘Substance Consumption and Sensory Alteration’* v. *‘Emotional Self-Reflection in Nature’*), LC13 (*‘Sensory Perception and Communication’* v. *‘Sensory Disorientation’*), and LC14 (*‘Auditory Sensations’* v. *‘Emotional Turbulence’*). The negative ends of these components were strongly associated with higher relative affinity at Alpha_{2B}, Alpha_{2C}, Imidazoline₁, H₁, SERT, and Sigma₁ receptors. Themes appearing in the negative end summaries included states of transcendence, multidimensional journeys, auditory distortion, and musical engagement.

In contrast, the positive ends of the third cluster of showed association with 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2C}, M₃, D₂ and D₃. Associations of D₂ and D₃ with *‘Sensory Disorientation’* and *‘Visual Distortions and Interpretations’* may be related to changes in perception of reality; whereas association of D₂, D₃ and 5-HT_{1B} with *‘Emotional Self-Reflection in Nature’* indicated both a connection to external reality in outdoor settings, and introspective, emotional states. There were also some undesirable associations in this group such as 5-HT_{1B} with *‘Escapade/Adventure’* (potentially related to ‘bad trips’, described above) and M₃ with *‘Emotional Turbulence’*.

Two latent components, LC12 and LC17, did not cluster with broader receptor-component groupings and appeared instead as individual (singlet) rows. LC12 had negative and positive ends defined by *‘Auditory Sensations’* v. *‘Emotional Turmoil and Self-Reflection’*, respectively. Its negative end was associated most strongly with 5-HT_{1A} and SERT; its positive end was most strongly associated with Alpha_{2A} and M₃. The negative end of LC17 (*‘Overwhelming Fear and Wonder’*) was associated most strongly with Alpha_{2A}, 5-HT_{1E}, 5-HT_{5A}, and 5-HT₆; whereas its positive end (*‘Social Interaction and Communication’*) was most strongly associated with Sigma₁.

The fourth cluster included LC10 (*‘Recreational Entertainment’* v. *‘Physical Distress and Panic’*), LC19 (*‘Physical Interaction and Sensory Perception’* v. *‘Overwhelming Sensory Overload’*), LC5 (*‘Sensory Amplification’* v. *‘Spiritual Revelation’*), LC2 (*‘Physical Sensation and Emotional Response’* v. *‘Perceptual Distortion’*), and LC15 (*‘Media Interaction and Absorption’* v. *‘Outdoor Refreshment and Relaxation’*). This cluster had the lightest shading (smaller y-loading values), which indicated that while these components do capture a distinguishable aspect of the semantic variance seen within the RD, they do not explain as much biochemical variance as those in the other clusters.

LC2, defined as ‘Physical Sensation and Emotional Response’ v. ‘Perceptual Distortion’ had the lightest row in the heatmap in Fig. 5. The presence of many terms (Table S2) from the positive ‘Perceptual Distortion’ end of the component (‘reality’, ‘room’, ‘color’, ‘door’, ‘space’, ‘things’, ‘sky’, ‘trees’, ‘house’, ‘mirror’, ‘bed’, ‘thoughts’ and ‘clock’) were reminiscent of themes related to set and setting. The same pattern was observed in a review of the negative ‘Physical Sensation and Emotional Response’ end of the component (‘ravers’, ‘peppermint’, ‘salty’, ‘carbonated’, ‘interpersonal’, ‘reggae’, ‘blizzard’, ‘sleeplessness’, ‘manager’, ‘competition’, ‘macdonald’, ‘fries’ and ‘profane’). These findings suggest that LC2, and potentially other components in the final cluster – were areas of subjective experience that may be partially influenced by receptor interactions, but also that may often be better explained by set and setting.

Several component summaries in Fig. 5, like ‘Emotional Self-Reflection in Nature’, ‘Spiritual Revelation’, and ‘Social Interaction and Communication’, highlighted subjective effects with clear relevance to therapeutic applications. Potential examples of such applications could include, but are not limited to, enhancing social and communicative functioning in specific contexts such as social anxiety, or family therapy. Other themes, including ‘Sensory Perception and Communication’, ‘Visual Distortions and Interpretations’, and ‘Interdimensional Communication’ were not as easily related to established clinical indications. Nonetheless, psychometric tools that measure them could be featured in an “enhanced array” of techniques designed to facilitate connection between objective data such as brainwave signatures, and subjective changes experienced in response to psychedelic drugs (Barksdale et al. 2024). Assessing results like those in Figs. 3, 4 and 5 gives clarity as to which qualities set different psychedelic drugs apart, and which receptors might be involved in manifesting such differences. Key PLSR results are summarized in Tables S3 and S4. Table S3 lists the top positive and negative y-loadings (-0.212 to 0.238) by receptor and component. Table S4 includes all receptor-effect associations within 0.05 of these extremes (i.e., >0.188 or <-0.162).

Discussion

Overall, this study should be interpreted as a demonstration of a hypothesis-generation support framework, linking biochemical sites bound by psychoactive drugs to semantic themes, rather than as causal evidence that any individual receptor determines a discrete subjective effect. The classification model results indicate that report-level representations contain reproducible drug-associated structure, while

the PLSR results identify latent patterns through which this semantic structure covaries with receptor affinity profiles across compounds. The commentary below expands upon the semantic model performance in terms of capturing the qualitative and distinctive aspects of the drugs included in the study, and major receptor associated themes suggested by this framework. These results and discussions thereof should all be considered by readers to be bounded by the limits of the RD, binding profiles, and the interpretive steps required to summarize mathematical components in semantic terms employed in this study.

Our dataset reflects naturalistic self-reports drawn primarily from public online archives. As such, the composition of reports likely reflects differences in user populations across substances (e.g., demographic, cultural, or experiential differences between users of different substances). However, the RD does not include structured demographic variables, clinical histories, setting, verified dosages, routes of administration, or measures of prior psychedelic experience. These user-level factors were not directly modeled and may contribute to some of the observed semantic variation. Because the present corpus cannot disentangle pharmacology from context, expectation, dose, demographic composition or cultural framing, hypotheses generated with support from the results of this work should be pursued with caution. Further, as was mentioned in the Results section regarding the strong association between LSD and the ‘Escapade/Adventure’ theme, user- and context-level differences may be systematically associated with particular compounds rather than randomly distributed across the dataset.

Several limitations related to uncertainty about dosing information are inherent to drug experience report data. Substance identity cannot be independently verified, and some reports may reflect misidentification or variability in compound purity. In addition, while many reports involving polydrug combinations were excluded, concurrent use of alcohol, caffeine, cannabis, nicotine or prescription psychiatric medication was permitted due to their ubiquity (See Fig. 1). These substances are all recognized to modulate subjective experience and likely introduce additional variance not directly attributable to the primary psychedelic compounds. This is especially relevant in the case of cannabis co-administration, as cannabis is known to modulate the qualitative aspects of psychedelic drugs (Kuc et al. 2022), and to induce psychedelic-like effects on its own (Wolinsky et al. 2024). A cannabis-negative sensitivity analysis reduced, but did not eliminate, concerns that cannabis co-administration significantly impacted the major findings of this study. Similarly, unknown antidepressant, anxiolytic, stimulant, antipsychotic, or other prescription medication use could be interfering with the results of the analysis. Still, because our PLSR framework links semantic structure to

drug-specific receptor affinity profiles across many reports per compound, systematic receptor-level covariance is unlikely to be driven solely by incidental co-use. Nonetheless, future work could explicitly model co-administration variables where metadata are available.

Despite the many limitations of our dataset detailed above, the custom GloVe-based embeddings derived from the carefully curated RD enabled nuanced modeling of 4,496 experience reports, achieving 41% accuracy using LDA, well above the 4.8% baseline chance. MDMA, DMT, psilocin, DiPT and 5-MeO-DMT reports were the most accurately predicted, suggesting these compounds elicit distinct and consistent subjective states. MDMA was the best-predicted compound overall, consistent with its entactogenic/empathogenic/connectogenic subjective effect profile (Stocker and Liechti 2024). We acknowledge that MDMA is often distinguished from classical psychedelics as the prototypical entactogen, a class defined by “touching within” and by effects involving emotional openness, empathy, and interpersonal connectedness (Nichols 1986, 2022). However, other scholars have discussed connectogenic compounds like MDMA as a subclass within the broader psychedelic, or psychedelic-like compound space (Cruz et al. 2024; Barber and Aaronson 2022; Holka-Pokorska 2023; Vollenweider 2001). Importantly, our decision was further supported by clinical ketanserin studies indicating that 5-HT_{2A} antagonism attenuates some, but not all, acute subjective effects of MDMA, suggesting that 5-HT_{2A} related signaling contributes to its psychoactive profile. Accordingly, MDMA was retained as an intentionally non-classical, polypharmacological comparator to the rest of the drugs represented in the RD.

Prediction patterns mirrored known pharmacological and experiential similarities. Tryptamines DMT and 5-MeO-DMT, both known to disrupt external reality contact (Tittarelli et al. 2015), were often confused with each other, despite DMT producing elaborate visual scenes and entity encounters (Luan et al. 2024), while 5-MeO-DMT evokes ego dissolution without complex imagery (Davis et al. 2018). Both were also frequently misclassified as psilocin, which shares structural similarity and, at higher dosages, reliably induced mystical-type experiences involving sensations of unity, sacredness, and transcendence of space and time (Nicholas et al. 2018). Confusion between psilocin and LSD further echoed their overlapping phenomenological profiles (Holze et al. 2022). These systemic deviations suggest that semantic embeddings derived from natural language reports recapitulate key features of drug class similarity and may reflect shared underlying neurobiological mechanisms.

This validation exercise underscores the predictive power of our semantic model and highlights the importance of broad receptor affinity profiles. While 5-HT_{2A} is widely

regarded as central to psychedelic action (Kwan et al. 2022; Husain et al. 2022; López-Giménez and González-Maeso 2018), our findings challenge an exclusive 5-HT_{2A} framing. Psychedelics have long been recognized to engage multiple neurotransmitter systems (Zamberlan et al. 2018; Ballentine et al. 2022; Inserra et al. 2021), yet the roles of specific receptors in shaping distinct subjective effects remain poorly resolved.

Recently published data demonstrated through comprehensive functional assay of a set of 41 different compounds that “psychedelics have potent and efficacious actions at nearly every serotonin, dopamine, and adrenergic receptors” (Jain et al. 2025). This study emphasizes one major limitation of the findings in this study, as they are based on binding data, which is quite coarse in comparison to the comprehensive, pathway-specific signaling efficacy data mentioned above. An iteration of the technique described herein applied to these newly available data may provide the scientific community with an enhanced means for machine assisted human intelligence-based hypothesis generation support.

Using PLSR, we identified covariance between semantic report structure and receptor binding profiles. 5-HT_{2A} showed strong associations with specific experiential dimensions: 0.174 ‘*Cognitive Disruption*’ 4+ (All following component ends will be represented according to this presentation style: Y-loading value ‘*Summary*’ Component number and ‘+’ or ‘-’ end), 0.159 ‘*Visual Distortions and Interpretations*’ 11+, 0.156 ‘*Visual Complexity*’ 1+, and 0.156 ‘*Surreal Imagery*’ 8+, which is consistent with its recognized involvement in mediating these particular psychedelic effects (Cameron et al. 2023; López-Giménez and González-Maeso 2018).

Before turning to non-5-HT_{2A} receptors, it is worth emphasizing that all receptor-effect associations identified in this study should be interpreted in the context of concomitant modulation of serotonergic pathways. Also, a further caveat is that both the source reports and LLM summaries of component themes discussed herein are culturally and linguistically situated. The method used does remove dependence on predefined psychometric categories, but it does not remove interpretive priors from the labeling process. While the summarized latent components are directly connected to both the report corpus and the receptor binding profiles of the drugs described in the corpus, and therefore can be viewed as defining a hybrid semantic-biochemical space mapping covariance, they are still mathematical objects, and their reduction to succinct verbal LLM or human expert derived labels still leaves lots of room for varied interpretation.

We also observed substantial contributions from non-5-HT_{2A} receptors, often underappreciated in psychedelic

research. For instance, 5-HT_{2C} and 5-HT_{7A} were linked to visual and transpersonal themes, including 0.193 0.210 'Visual Complexity' 1+, 0.167 0.194 'Surreal Imagery' 8+, 0.161 0.156 'Interdimensional Communication' 9+, and 0.143 0.155 'Cognitive Disruption' 4+. Many words from the positive end of LC8, summarized as 'Surreal Imagery', echoed mystical experience-like therapeutic states (e.g. 'mysterious', 'otherworldly', 'breakthrough', 'heavenly').

Another non-5-HT_{2A} serotonin receptor, 5-HT_{1A}, strongly associated with 0.238 'Cognitive Disruption' 4+ and 0.187 'Physical Discomfort and Distress' 7+, suggesting a role in adverse experiences despite its usual association with anxiolytic effects (Smith et al. 2023). Simultaneously, the strong association we see here between 5-HT_{1A} and -0.155 'Auditory Sensations' 12- could be seen as support for investigation of a new avenue of research: the role of 5-HT_{1A} in auditory perception, a previously existing area with limited data (Gentile Polese et al. 2021; Pillai et al. 2020; Saraf et al. 2024).

5-HT_{1A} and 5-HT_{1B} show highly similar profiles across latent components (Fig. 5), both strongly associated with 0.238 0.216 'Cognitive Disruption' 4+. Absolute differences between the values at the two receptors across the 19 LCs range from 0.005 to 0.091, with a median of 0.025. We generally do not call attention to individual cells with values below 0.1, and it may be that any real differences in subjective effects mediated by 5-HT_{1A} and 5-HT_{1B}, if any, cannot be distinguished by these methods.

D₂, D₃, and 5-HT_{1B} exhibited similar semantic associations, indicating potential serotonergic-dopaminergic interplay in psychedelic experiences (Martin et al. 2024; Sakashita et al. 2015). D₂ and D₃, previously implicated to influence psychedelic effects (Vollenweider and Smallridge 2022), specifically in both creative cognition and the cognitive effects of psychedelics (Sayalı and Barrett 2023), were most strongly linked to 0.191 0.146 'Sensory Disorientation' 13+, and 0.149 0.180 'Cognitive Disruption' 4+. LSD showed the highest relative affinity for both receptors, possibly contributing to their overlap. LSD's biphasic effects (Marona-Lewicka and Nichols 2007), where later phases have been observed to include paranoia and altered self-reference, may involve dopaminergic mechanisms, including those of dopaminergic LSD metabolites (Nichols 2016). These findings align with the central role of D₂ in antipsychotic drug action (Howes et al. 2024), and support ongoing inquiry into the complex relationship between psychedelics and schizophrenia, which have recently been proposed to be revisited as potential treatments for certain symptoms of schizophrenia (Sapienza et al. 2025).

Alpha_{2A}, Alpha_{2B}, Alpha_{2C} were all associated with themes of 0.182 0.101 0.102 'Emotional Turmoil and Self-Reflection' 12+, -0.146 -0.157 -0.170 'Social Interaction

and Optimism' 7-, -0.106 -0.137 -0.113 'Physical Intimacy and Affection' 4-, and -0.106 -0.130 -0.110 'Physical Cleansing and Social Interaction' 18-. Alpha_{2A} specifically aligned with -0.156 'Overwhelming Fear and Wonder' 17-, while Alpha_{2B} and Alpha_{2C} were connected to -0.121 -0.170 'Romantic Intimacy' 16-, and -0.134 -0.132 'Substance Consumption and Sensory Alteration' 6-. Robust induction of self-reflection stands out as a specific effect that could be leveraged to treat anxiety and depression (He and Gan 2025). Specifically, states of self-reflection "may serve as a therapeutic target for depressive symptoms in adults with ADHD traits" (Tamura et al. 2025).

The Imidazoline₁ receptor, pharmacologically grouped Alpha₂ receptors (Khan et al. 1999), was distinctly linked themes of -0.212 'Physical Intimacy and Affection' 4-, -0.159 'Auditory and Musical Engagement' 11-, and -0.150 'Sensory Perception and Communication' 13-. Studies have implicated Imidazoline₁ in mood regulation, anxiolysis, and dysphoria (Valverde et al. 2021; Halaris and Piletz 2003; Lowry and Brown 2014; Zeidan et al. 2007; Holt 2003; Piletz 2003; Piletz et al. 2008). Agmatine, a proposed endogenous ligand (Ernsberger et al. 1995), is thought to modulate the antidepressant like effect of serotonin re-uptake inhibitors via Imidazoline₁ (Jesse et al. 2010; Taksande et al. 2009).

The M₃ receptor, a muscarinic acetylcholine target, resembled Alpha_{2A} in profile, and exhibited highest affinity for MDMA (npK_i: 3.07), DOI (npK_i: 2.51), and 2C-B (npK_i: 2.22). It was linked with themes of -0.186 'Social Interaction and Optimism' 7-, -0.175 'Physical Stimulation and Social Interaction' 1-, 0.150 'Emotional Turbulence' 14+ (also -0.132 'Emotional Turbulence' 8-), 0.146 'Emotional Turmoil and Self-Reflection' 12+, -0.144 'Physical Cleansing and Social Interaction' 18-, -0.137 'Physical Intimacy and Affection' 4-, and -0.133 'Intense Emotional Release' 9-. M₃ is classically associated with delirians and with anticholinergic side effects seen in anti-histamines and antipsychotics (Healy 2023).

H₁, Sigma₁ and SERT clustered together in latent component space, each strongly linked to -0.157 -0.183 -0.168 'Auditory Sensations' 14-, suggesting possible roles in auditory processing, similar to 5-HT_{1A}. Sigma₁ stood out for its positive association with 0.130 'Social Interaction and Communication' 17+. SERT's strongest linked themes were -0.168 'Auditory Sensations' 14-, -0.166 'Sensory Perception and Communication' 13-, 0.153 'Interdimensional Communication' 9+, 0.134 'Surreal Imagery' 8+, -0.133 'Auditory Sensations' 12-, and -0.122 'Substance Consumption and Sensory Alteration' 6-, some of which mirror known SSRI effects (Edinoff et al. 2021; Praharaj 2004; Harmer et al. 2003; Gopal et al. 2005).

H₁ was most associated with 0.218 'Interdimensional Communication' 9+, a theme central to DMT experiences

(entity encounters and richly structured otherworldly experiences (Lawrence et al. 2022)). Although H1 is traditionally linked to sleep–wake regulation (Hough 1999), and allergic responses (Akdis and Blaser 2003), its association here suggests a possible role in transpersonal psychedelic content.

Sigma₁, implicated in DMT's physiological effects and cellular stress modulation (Cheng et al. 2024), also aligned with '*Interdimensional Communication*' and '*Social Interaction and Communication*'. While Sigma₁ also may be implicated in otherworldly DMT experiences, the nature of its potential role in functions relevant to '*Social Interaction and Communication*' could also be of relevance to more mundane, everyday experiences.

Several receptor-effect associations offer experimental opportunities. The convergence of 5-HT_{2C} and 5-HT_{7a} on '*Visual Complexity*' and '*Surreal Imagery*' could be further explored through comparative analyses of their intracellular signaling pathways or anatomical co-expression. The link between 5-HT_{1A} and auditory processing could be probed through psychedelic-evoked changes in auditory cortex activity (Brockett and Francis 2024; Tang and Trussell 2015; Riga et al. 2016; Hurley 2006). The development of novel functionally-biased muscarinic agonists (Nelic et al. 2024), may offer promising new tools for dissecting M₃'s potential role in socially facilitative psychedelic effects. The association between H₁ and '*Interdimensional Communication*' could be explored through co-administration studies using DMT and selective H₁ antagonists. More broadly, future work could also investigate how pharmacology interacts with contextual factors to shape the ultimate structure and content of psychedelic experiences.

Conclusion

This study provides a proof-of-concept framework for mapping the complex receptor-experience relationships that underlie the diverse phenomenology of psychedelics. Moving beyond the prevailing focus on 5-HT_{2A} as the singular mediator of the psychedelic state, we show that a range of other receptors are distinctly associated with specific cognitive, emotional, and perceptual alterations. These associations suggest that many subjective effects attributed to psychedelics may arise from a complex interplay of contextual factors and combinatorial receptor engagement, not a monolithic pharmacological mechanism. Such receptor-level mappings offer immediate hypotheses for causal investigation and provide an empirical scaffold for designing next-generation compounds with narrower, intentionally selected psychoactive profiles.

Beyond therapeutic applications, our findings reframe psychedelics as structured perturbation tools for

consciousness research. By integrating biochemical and linguistic data, we circumvent the limitations of existing ontologies and the combinatorial complexity of traditional deterministic pharmacological research. If specific receptor combinations can reproducibly and selectively evoke distinct states such as awe, insight, or ego dissolution, the path may be open to new classes of psychoactive therapeutics—and, more fundamentally, a shift from treating mental illness to engineering human experience itself.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and competing interests DB is a scientific advisor for MindState Design Labs, LLC (MDL) and has received fees and shares from the company. FSB is a scientific advisor for MDL and Wave-Paths, Ltd, and has provided consultation for Gilgamesh Pharmaceuticals, Inc. and has received fees or shares from these companies. RCH is a scientific advisor to Tryp Therapeutics, Osminid, Entheos Labs, Otsuka, and MDL and has received fees or shares from these companies. TR, JK, LL, PW and AT are all employees of, and have received both payment and shares from MDL. PS has no competing interests. There was no ethics committee approval for this study, as such approval was not applicable, because the study relied on publicly accessible experiential accounts as opposed to recruitment and active participation of consenting individuals.

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