One Molecule, Many Stories: How Dopamine Became Psychiatry's Greatest Semantic Artifact

A structural analysis across literature, chemistry, and biology

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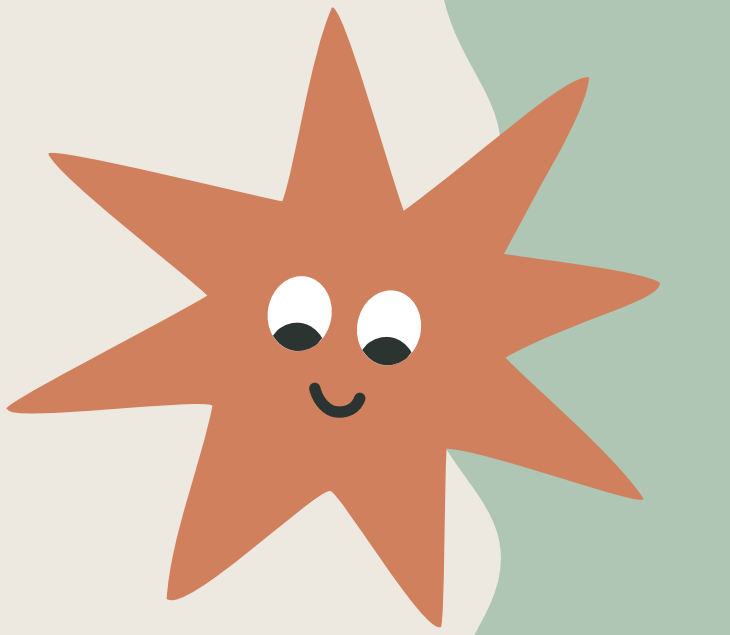
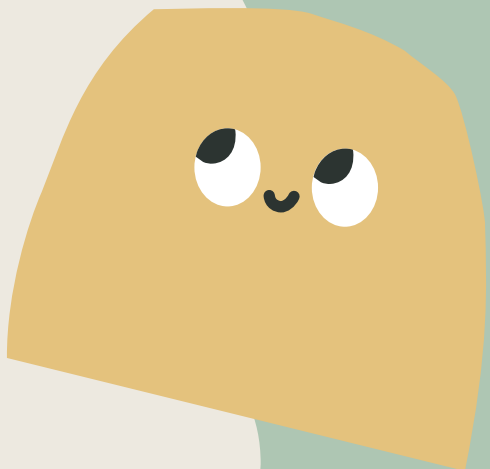




Methods Limitation Statement

- The data and findings summarized in this audit are derived primarily from the titles and abstracts of the referenced publications. In accordance with established reporting standards, such as CONSORT for randomized trials and STROBE for observational studies, full research articles are expected to include comprehensive methodological and reporting details. These typically encompass participant demographics (e.g., age, sex/gender, ethnicity, socioeconomic factors), inclusion and exclusion criteria, study flow, prespecified primary and secondary outcomes, statistical analysis plans, handling of missing data, limitations, and, where appropriate, raw or unadjusted results.
- Abstracts are not required to include this level of detail and often provide only a condensed summary of methods and findings. As a result, analyses based on abstract-level data are inherently limited by incomplete reporting. Any conclusions or critiques presented in this audit should be interpreted within this constraint.
- The responsibility for complete, transparent, and reproducible reporting lies with study authors, journals, and the peer-review process. Where full-text articles were not accessed, this limitation is explicitly acknowledged.
- Transparency helps science improve!

Agenda Highlights

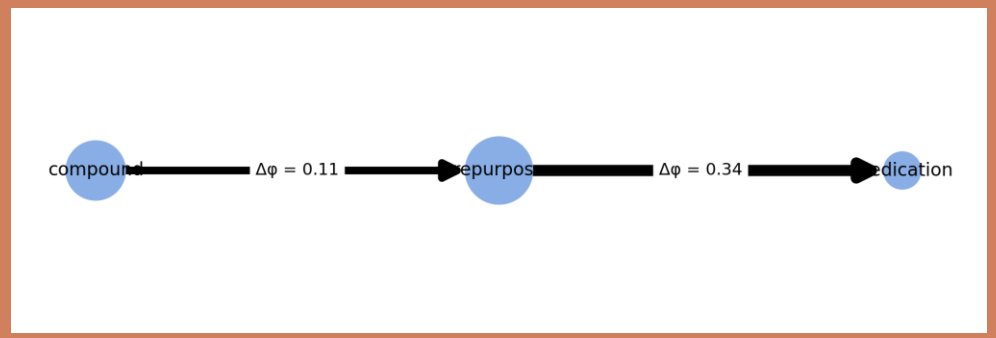
- The Problem: One molecule, too many meanings
- Corpus Audits: Letting the literature speak
- Literature Results: What dopamine actually clusters with
- Chemical Space: Structure without interpretation
- Integration: Putting the system back together

An introduction: These molecules came from food, plants, and coal tar, not from neuroscience.

(Pre-psychiatric chemistry corpus (~840,000 corpus)

We didn't discover these through neuroscience; we noticed what they did to people and then studied.

Chemical - - - - - Modification - - - - - Drug



❑ INDUSTRIAL ROOTS

- Benzene — coal tar
- Aniline — dye chemistry
- Phenol — antiseptic chemistry
- Hydrazine — industrial / fuel

❑ BIOLOGICAL ROOTS

- Phenylalanine — dietary amino acid
- Tyrosine — catecholamine precursor
- Tryptophan — serotonin precursor

❑ BRIDGE MOLECULES

- Phenethylamine — stimulant backbone
- Tyramine — dietary amine
- Tryptamine — psychedelic backbone
- Catechol — dopamine motif
- Indole — serotonin scaffold

A Different Lens

This is a structural problem—not just a chemistry problem.

- • Background in neuroscience and network science
  - I am not anti-medication, anti-psychiatry, or anti-brain-chemistry.
- Focus shifts from molecules → **structure across systems**
- • Data sources:
  - ~2 million scientific papers
  - 1000+ molecules in chemical space
- • Goal:
  - Understand how dopamine is **organized**, not just described
  - Move from function to structure
  - Instead of asking *what dopamine does*
  - We ask: **how is the system around it structured?**

What is an embedding?

Representing Meaning as Structure

•Each paper is converted into a 384-dimensional vector

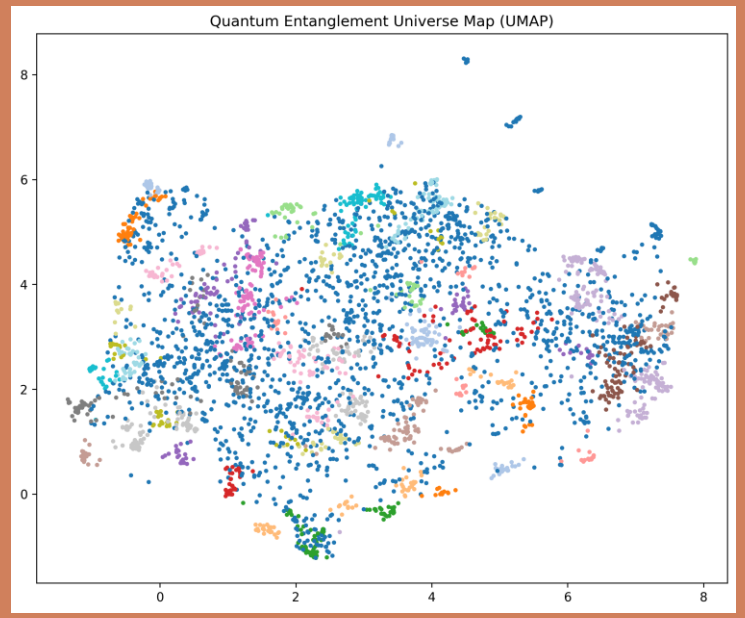
    •This vector captures its meaning in context

Similar papers → close together
Different ideas → far apart

•This allows us to compare papers mathematically
•Instead of descriptions, we get structure
•In simple terms: we turn language into coordinates

What is a UMAP?

Mapping Structure in Two Dimensions



Each point = one paper (384D semantic embedding → 2D projection)

Uniform Manifold Approximation and Projection (UMAP).

- Starts with high-dimensional embeddings (384D)
- Projects them into 2D space
- Nearby points = similar ideas
- Far apart = different ideas

•Preserves relative relationships

•Not exact distances, but meaningful structure

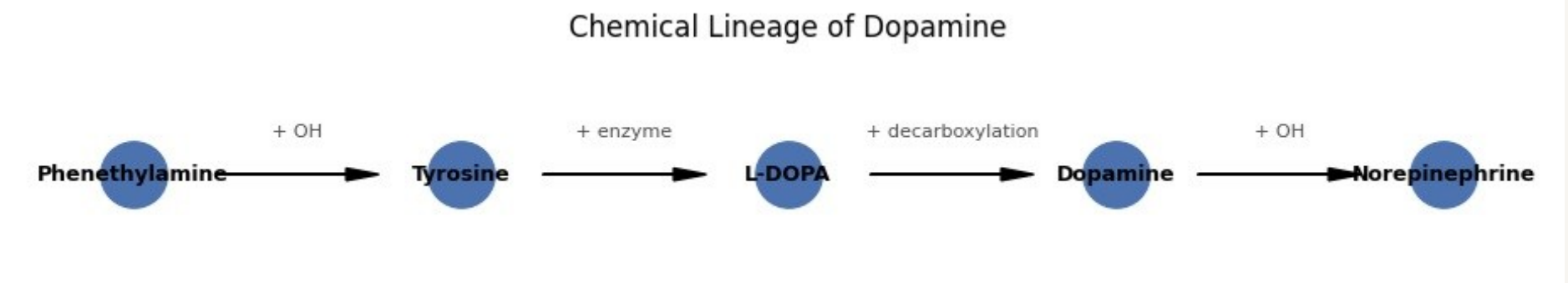
•Each point = one paper

•Together, they form a map of the field

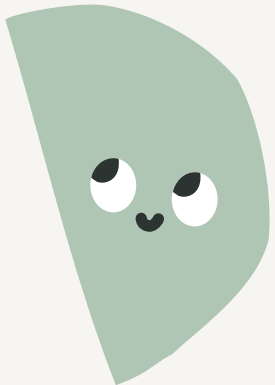
• or more simply, the shape of the literature without interpretation.

The Scientific Discovery of Dopamine

Dopamine Before Biology/Psychiatry

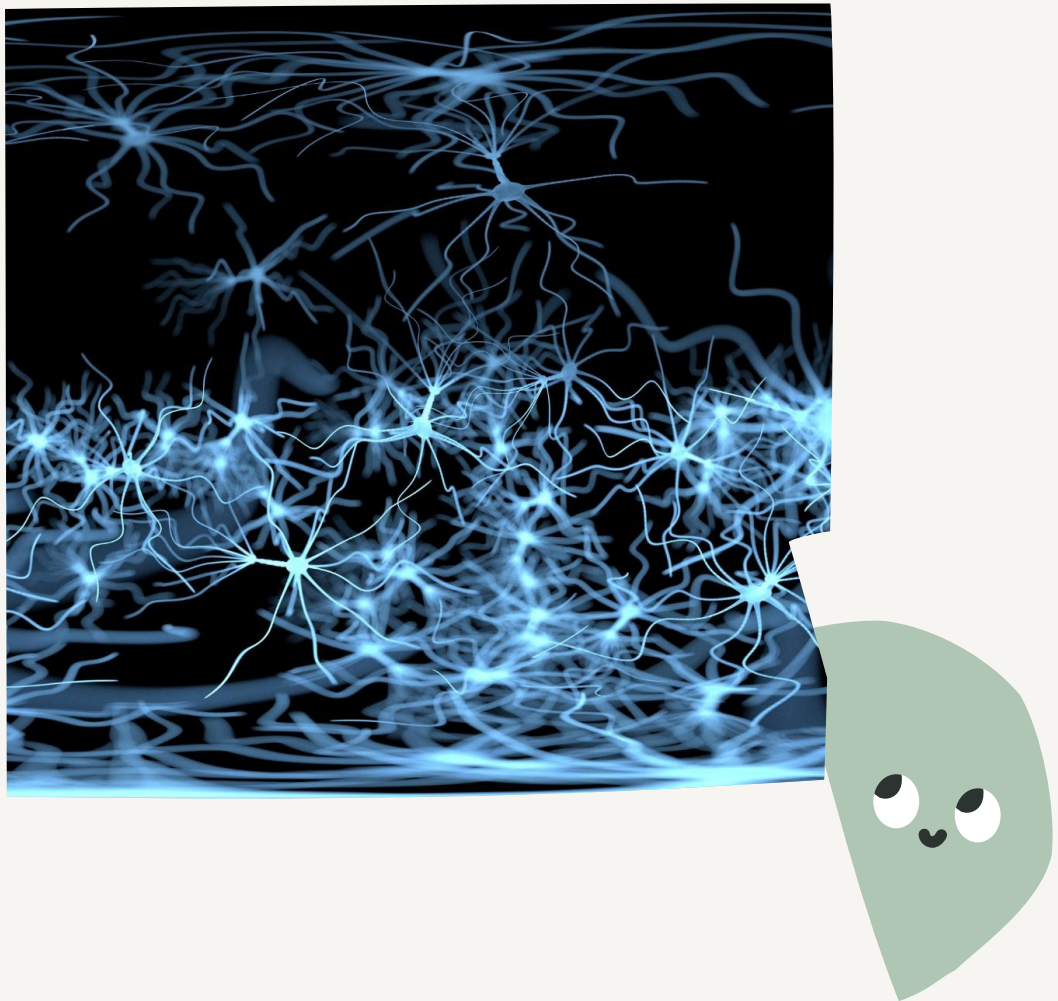


- ❑ **Dopamine isn't a starting point. It's the result of a sequence. 1910**: Synthesized (Barger & Ewens)
  - Known as *3,4-dihydroxyphenethylamine*
  - It was treated as a synthetic intermediate in catecholamine chemistry, not a biological signal. At the time, the focus was on related compounds like epinephrine (adrenaline), already known for strong physiological effects.



- ➢ 1910 ⟶ synthesized (Barger & Ewens)
- ➢ 1910–1950 ⟶ chemically known, function unclear
- ➢ 1957–1959 ⟶ detected in brain
- ➢ 1960s ⟶ linked to motor control

When Dopamine Became Meaningful

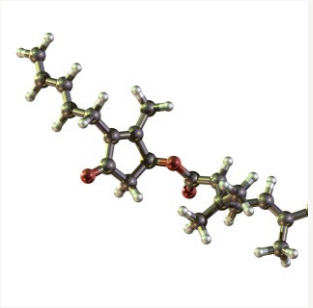


- **1952** → dopamine identified in brain
- **Carlsson (1957–59)**
  - established dopamine as a neurotransmitter linked to motor function

Dopamine in Motor Control

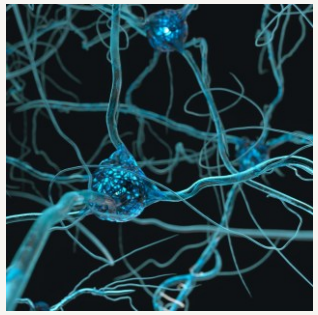
- **L-DOPA findings**
  - reversed motor deficits
  - reinforced dopamine's role in movement
- **1960s–70s**
  - expanded into neurology & psychiatry
  - reward concepts emerge later

The Accepted View of Dopamine



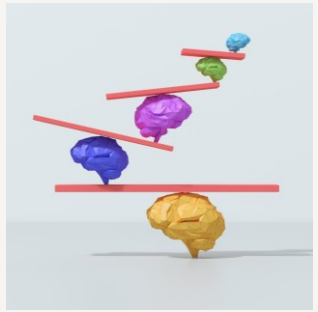
Dopamine Synthesis

Motor control (basal ganglia, movement) Reward and reinforcement Motivation and goal-directed behavior Learning and prediction



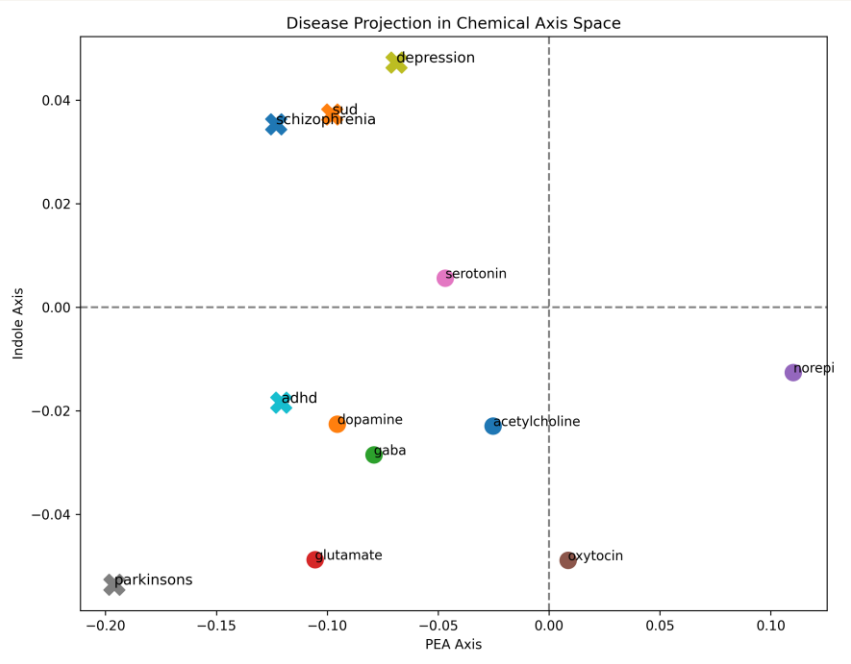
Receptor Binding

Biology has given us incredible detail—receptors, pathways, regional specificity, but that detail is often studied in isolation.

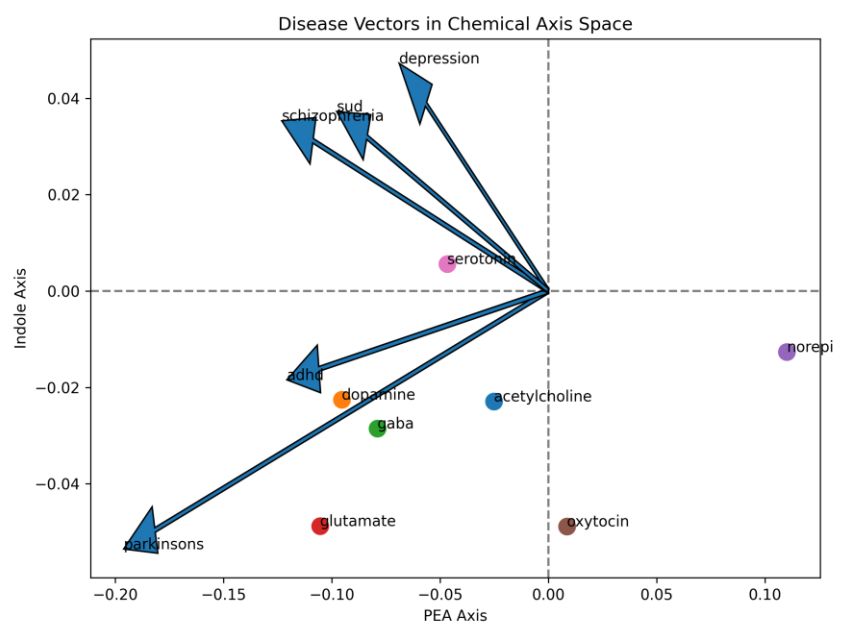


Physiological Roles: One molecule, many assigned functions including psychopathologies (schizophrenia, addiction, depression, and others).

One molecular scaffold is used to explain multiple behavioral and clinical domains



Disorders don't sit on dopamine—they diverge from it.



The Accepted Framework

- **Functional domains**
  - Motor control
  - Cognition
  - Emotion
- **Clinical associations**
  - Parkinson's disease
  - Schizophrenia
  - Addiction
- **Mechanistic explanation**
  - Receptor subtypes
  - Distributed pathways
  - Context-dependent signaling
- One molecule is used to explain multiple domains.

The Evolution of Dopamine's Meaning in Psychiatry

Dopamine Becomes a Biological Signal

Psychiatric Relevance

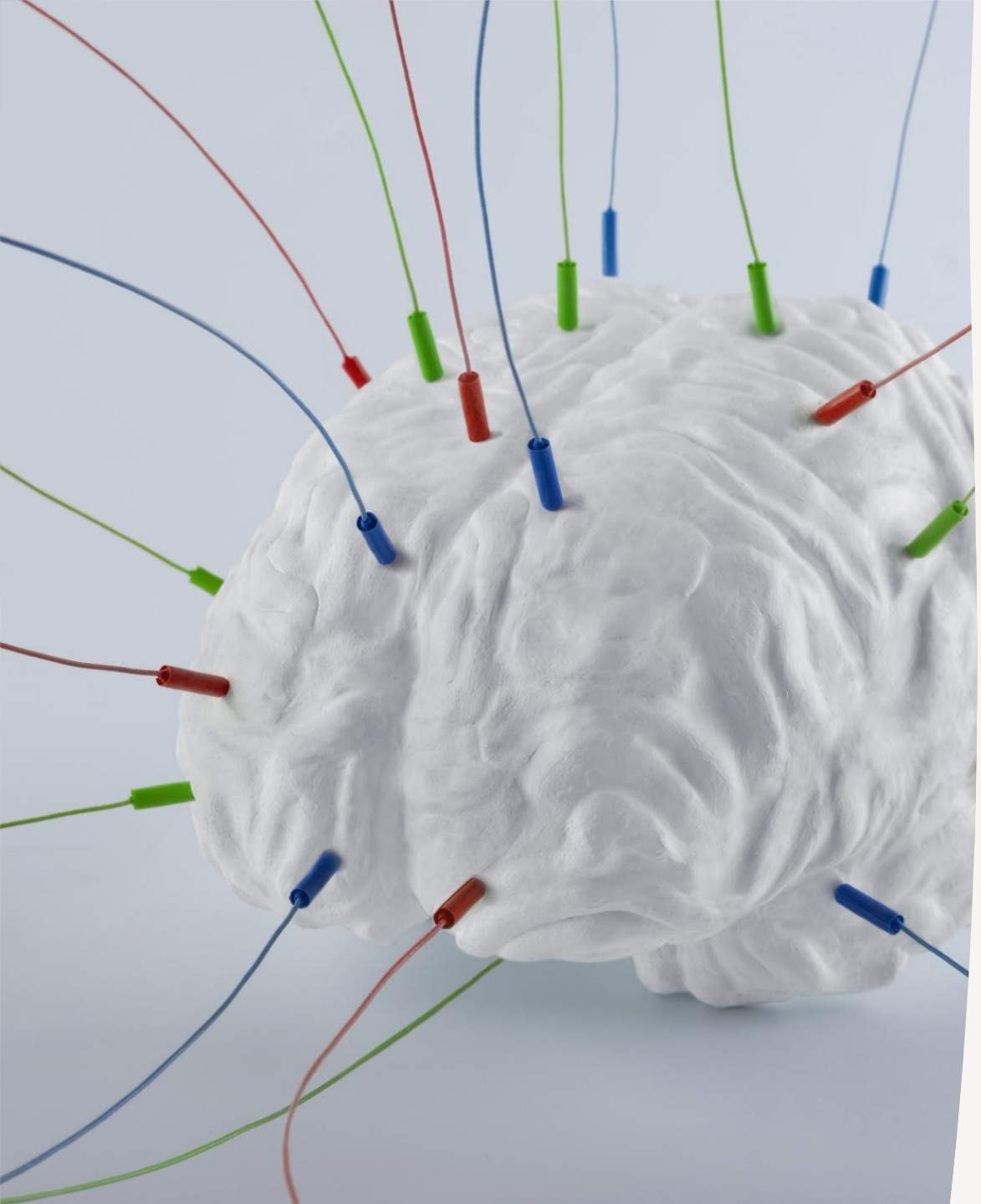
Carlsson's work established dopamine as a neurotransmitter, work that later earned a Nobel Prize. This work was specific to motor function.

Neurotransmitter Functions

- Receptor research (1970s–1990s) expanded how dopamine was interpreted across functions

Reward, Mood, Motivation, Cognition etc...

And with that detail... the interpretation began to expand.



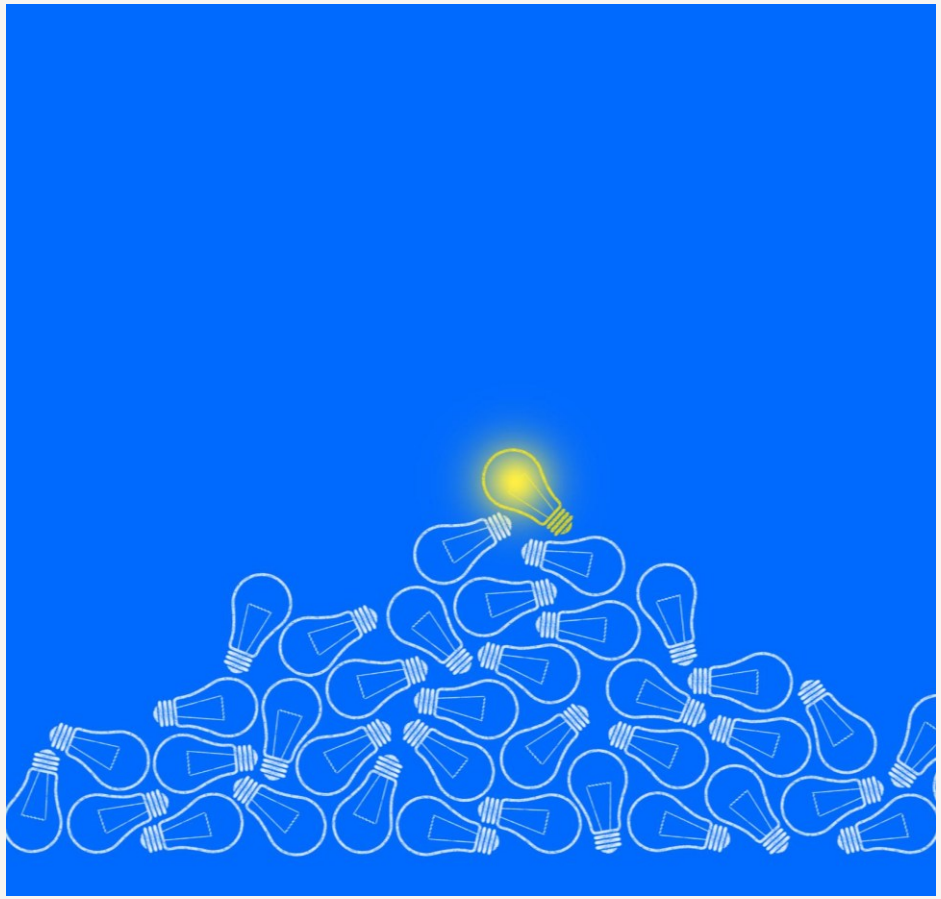
Dopamine Expands into Psychiatry

Schizophrenia
- Dopamine dysregulation

Addiction
- Reward Pathways

Mood
- Broader associations

Dopamine as an Explanatory System



Critiques of Dopamine Hypothesis

•Dopamine hypothesis criticized as too reductive
•Increasing recognition of system complexity

- **Dopamine Interactions**
- Dopamine interacts with other neurotransmitters and environmental factors.

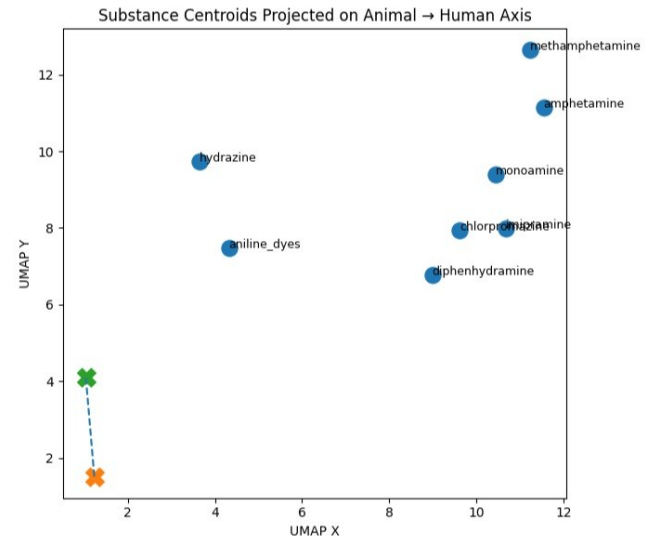
Semantic Artifact Concept

Dopamine's meaning is shaped by how we study and interpret it

At this point, the model starts to strain.

What does the chemical literature tell us about monoamine origins?

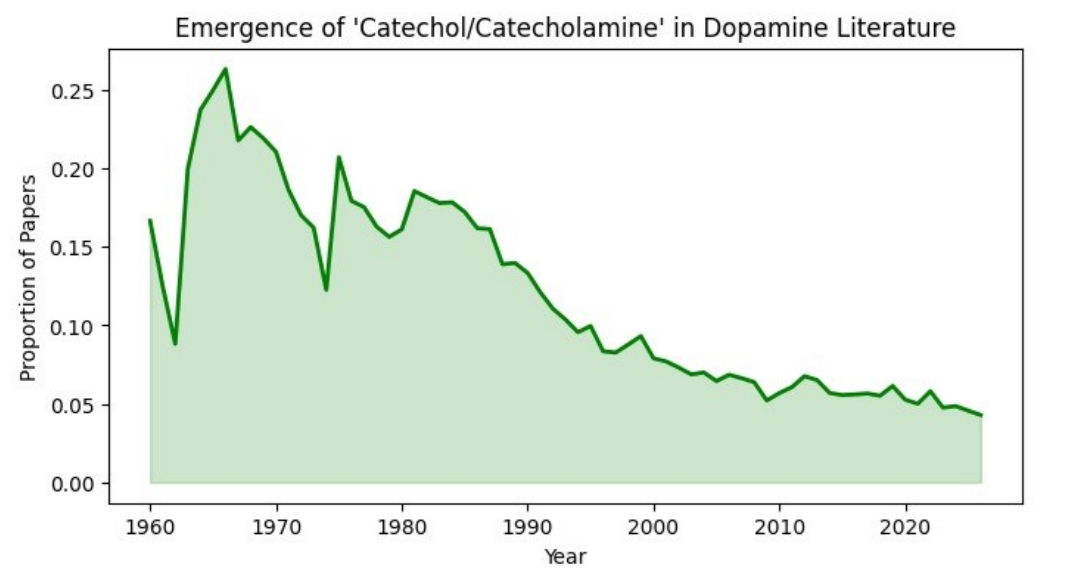
- 1959 → Drug + MAO + animal physiology
- 1960s → Metabolism + neurotransmitter chemistry
- 1967 → Theory emerges
- 1975 → Reviews consolidate
- 1979 → Human translation (late, messy)

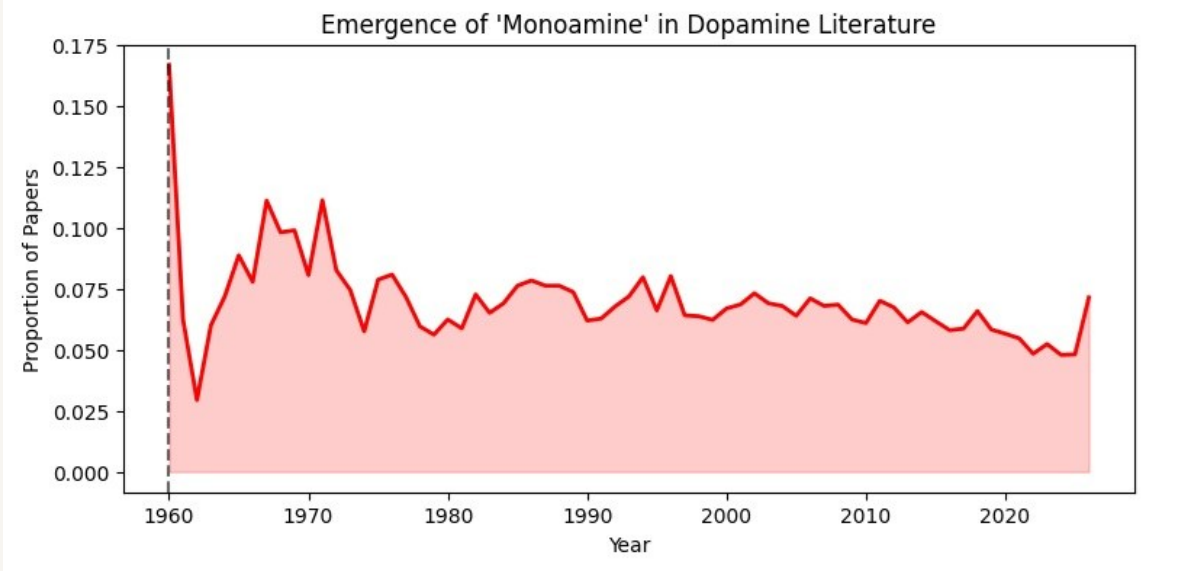


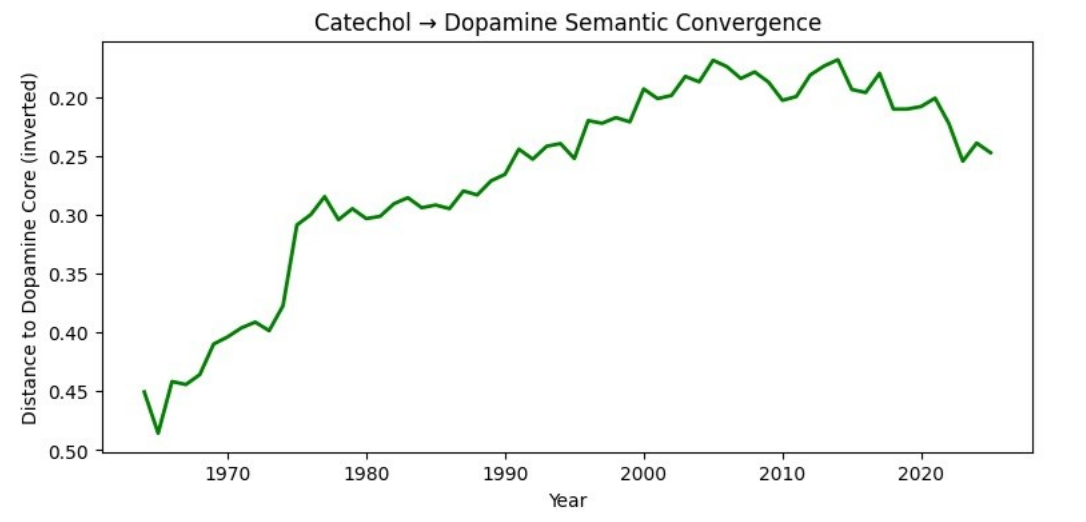
➢ **1959 — first appearance (animal)**

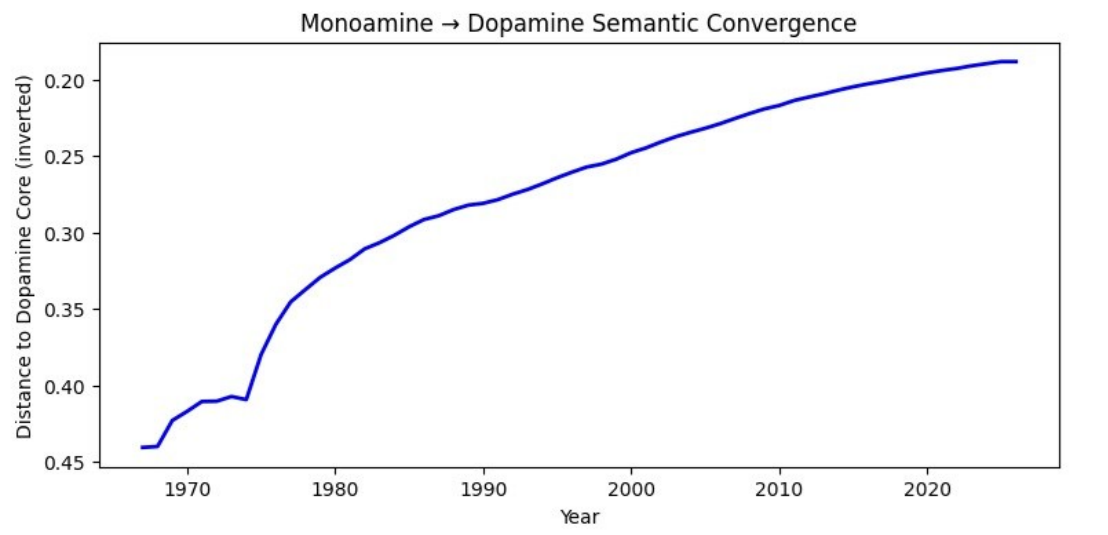
- The very first paper:
- **"Monoamine oxidase, psychoenergizers, and tranquilizers…"**
- This was not structure, synthesis or classification, it was drug effects + enzyme + behavior.
- 1961 – pharmacotherapy of depression; moving toward system level explanation
- Monoamine wasn't discovered, it was assembled, and the rest is history

Dopamine Didn’t Start as a Monoamine







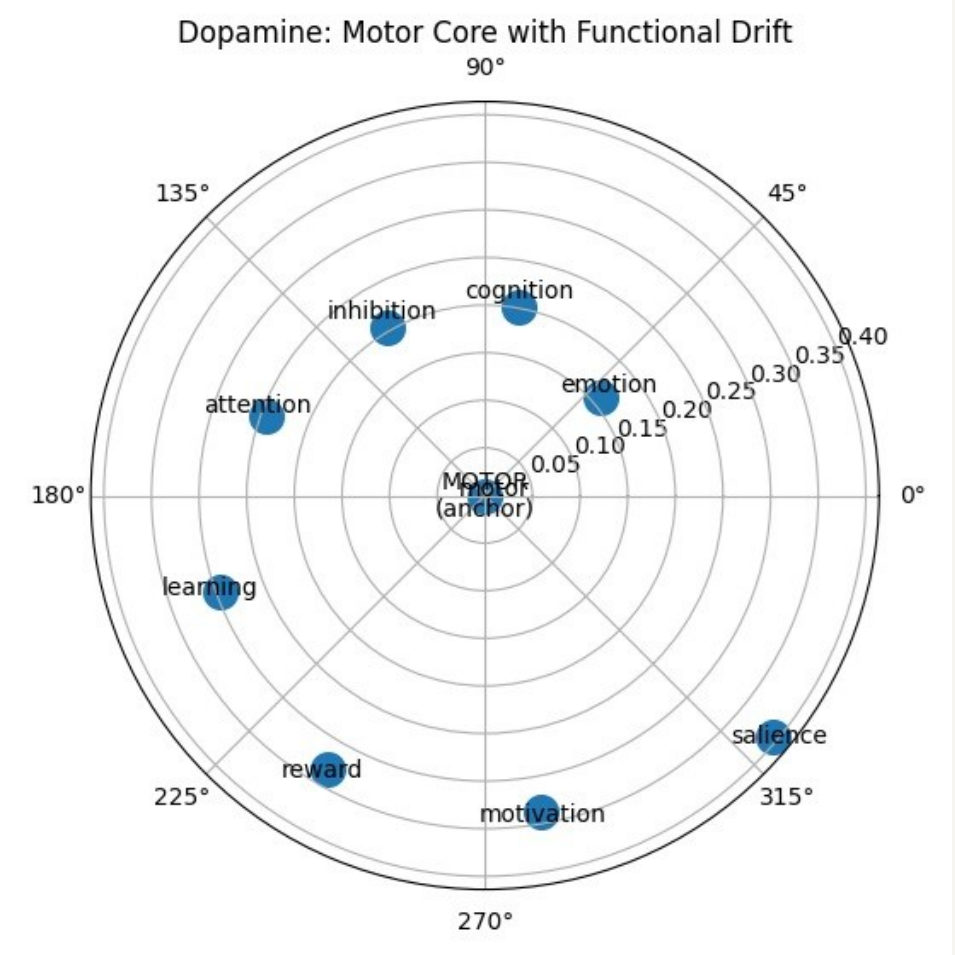


Dopamine: what the scientific literature says – dopamine, chemical literature and molecular spaces.

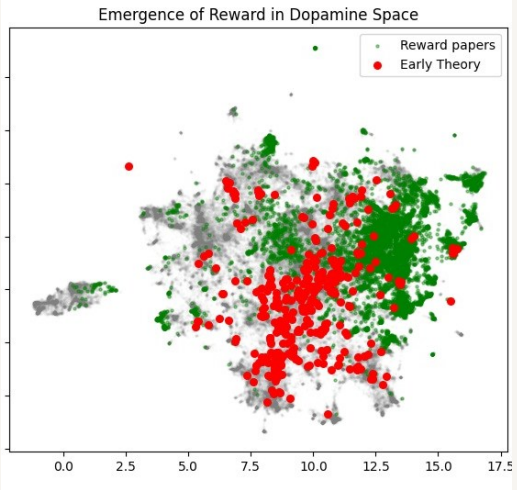
Dopamine Science (~175k references).

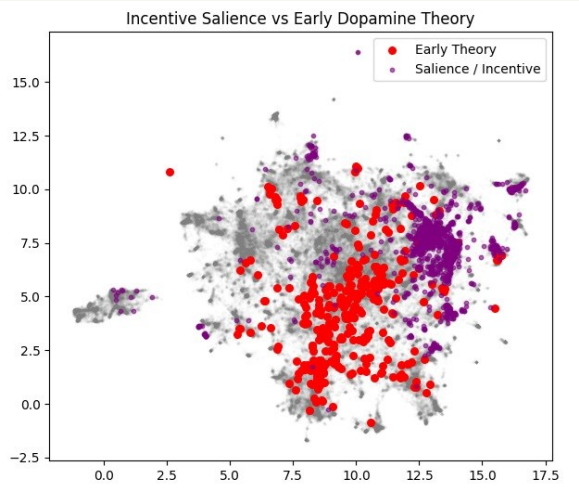
As functions are added, they don't just move away from motor, they rotate into different semantic directions.

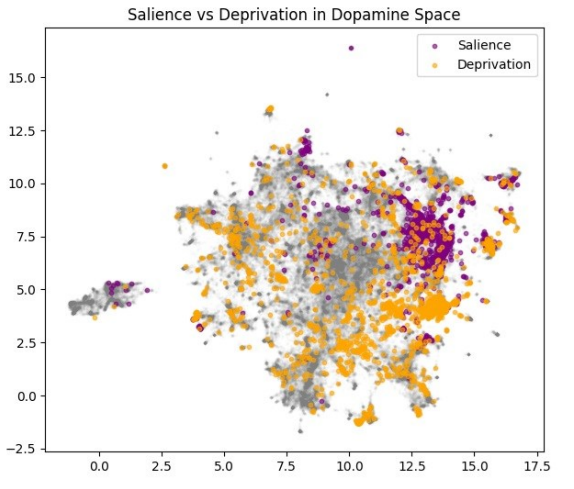
What we call 'dopamine functions' may actually reflect a progression away from its core signal.



Dopamine: From motor signal to 'Pleasure Molecule'







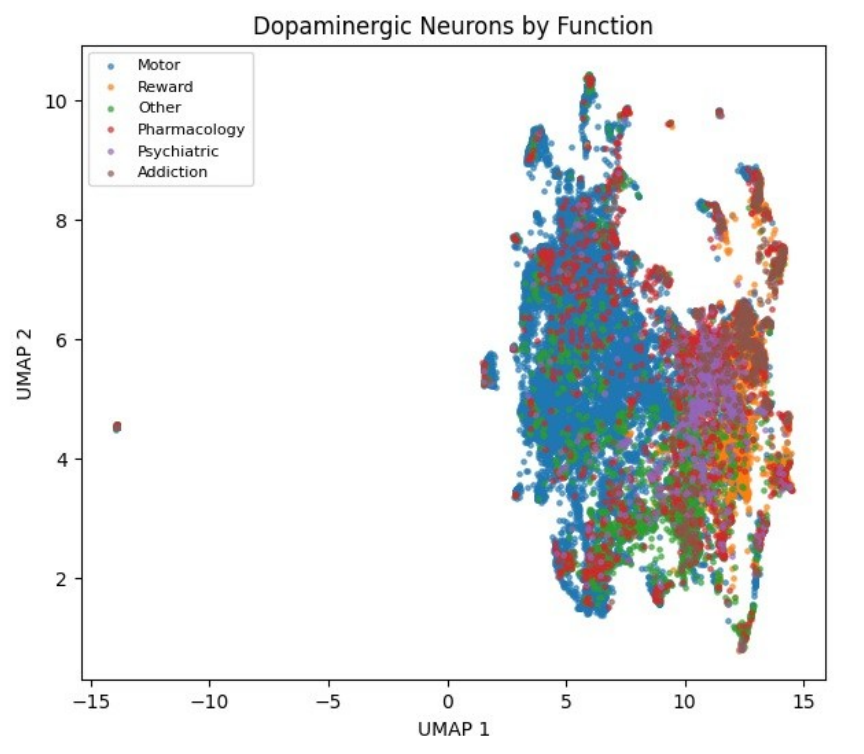
Dopamine's True Role

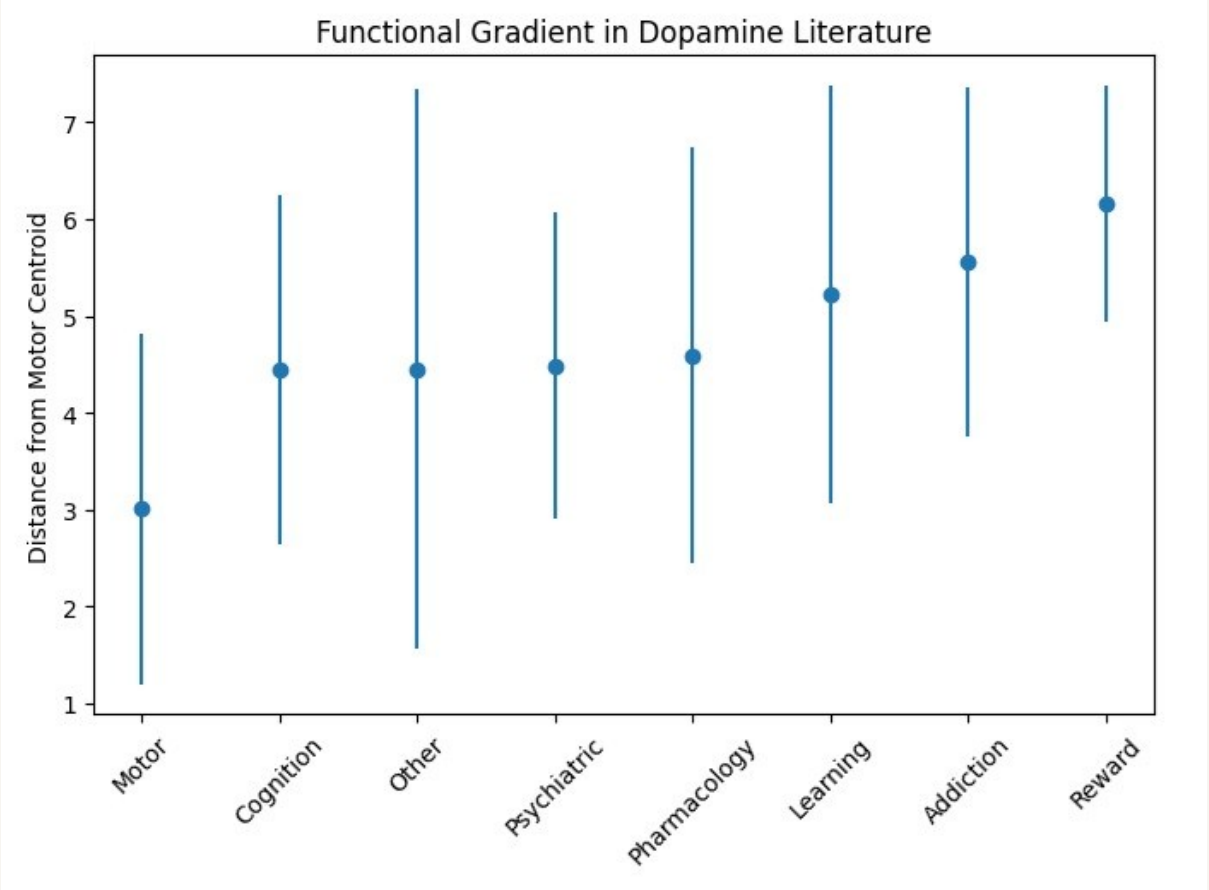
The further a function sits from motor, the more it reflects interpretation rather than direct signal.

```
Distances from Movement:
→ Inhibition: 1.4853643954302769
→ Reward: 3.839021925053974
→ Salience: 3.848707709840465
→ Early: 2.6114689144666516
```

```
Distances:
Move ↔ Inhib: 1.4853643954302769
Move ↔ Reward: 3.839021925053974
Inhib ↔ Reward: 3.1474308440573506
```

The drift isn't just global. It persists even when we isolate dopaminergic neurons

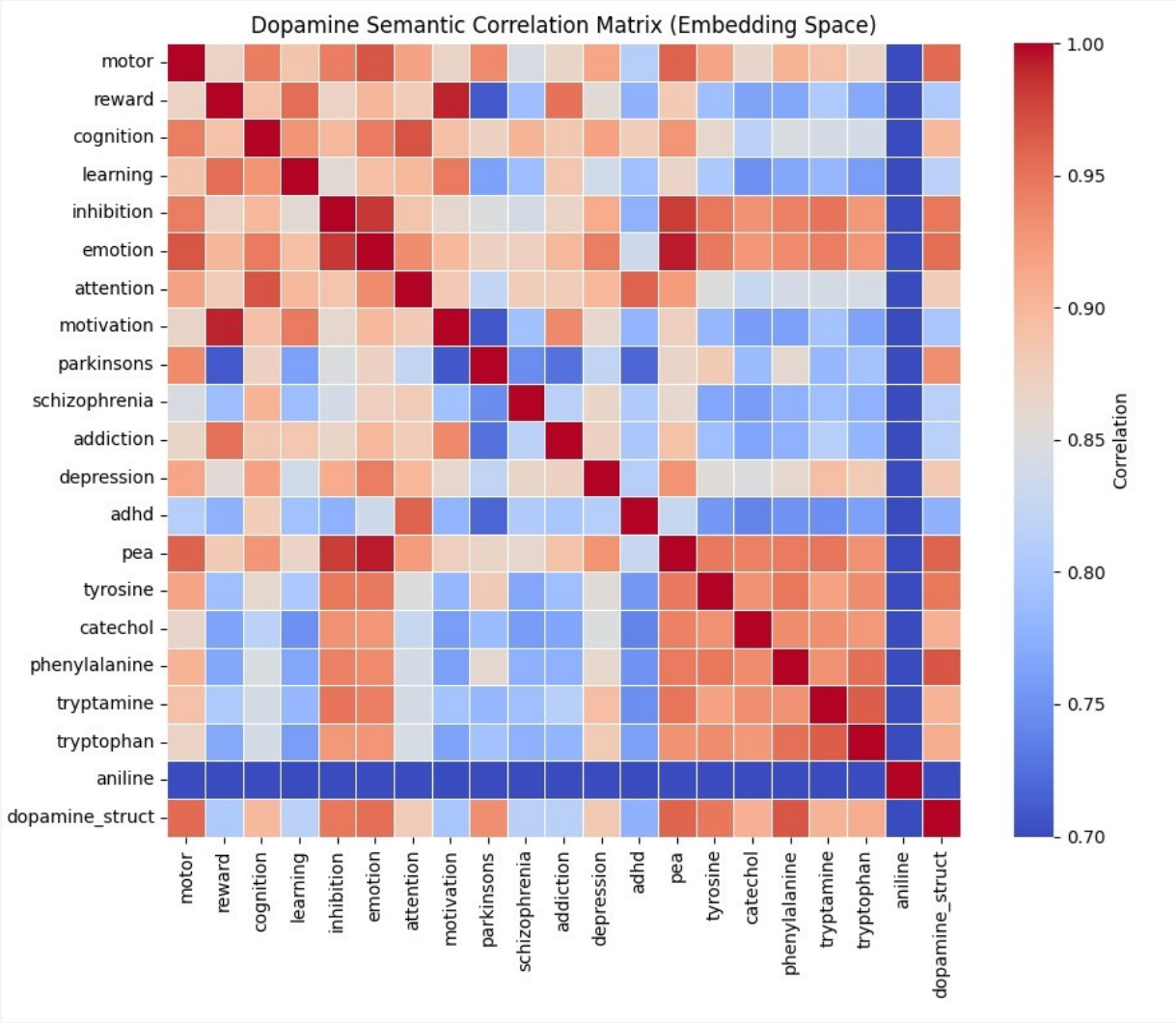




Inhibition appears everywhere because suppression is a general regulatory process, not a core function.

In vertebrates, knowing when not to move is just as important to survival as movement.

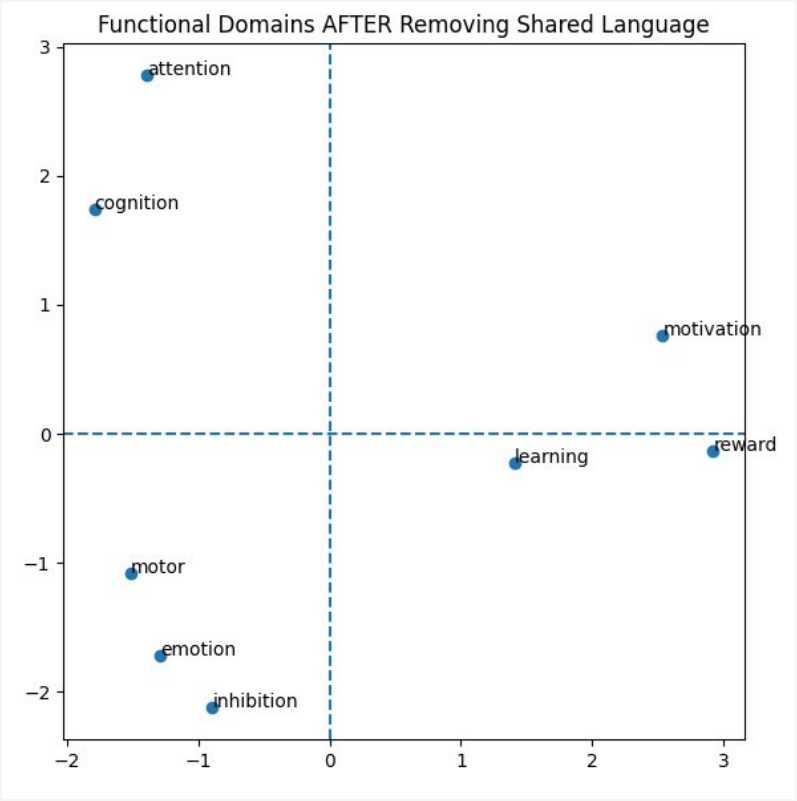
This "stillness" or regulation of movement should be a topic of research study.



Shared high-frequency terms act as a semantic attractor across domains

activity, brain, dopamine, dopaminergic, effects, rats, receptor.

Removing them reveals the true structure

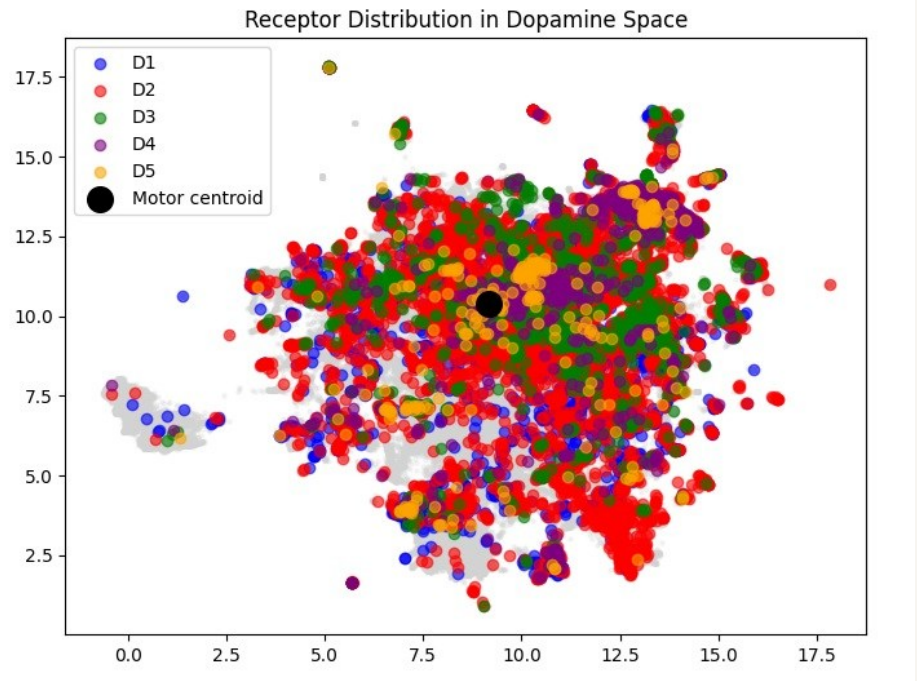


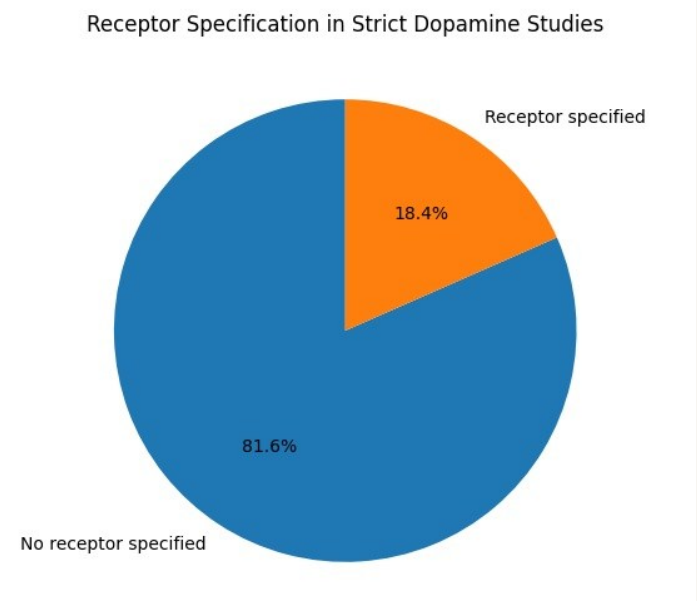
What remains when shared language is removed

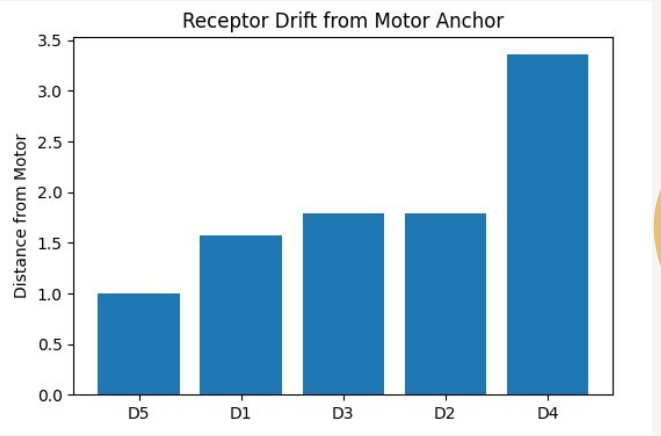
Analysis of shared terminology across dopamine domains reveals extreme semantic compression. In the full embedding space, domains appear artificially close (mean distance = 0.35), but after removing shared language, true separation emerges (mean distance = 3.36). This produces a high Semantic Gravity Index (SGI = 0.897) and near-total variance compression (0.989), indicating that common terms, such as “dopamine,” “activity,” and “brain”, collapse distinct functions into a single conceptual attractor, obscuring meaningful biological differences.

Dopamine Receptors Form a Gradient, Not Functional Territories

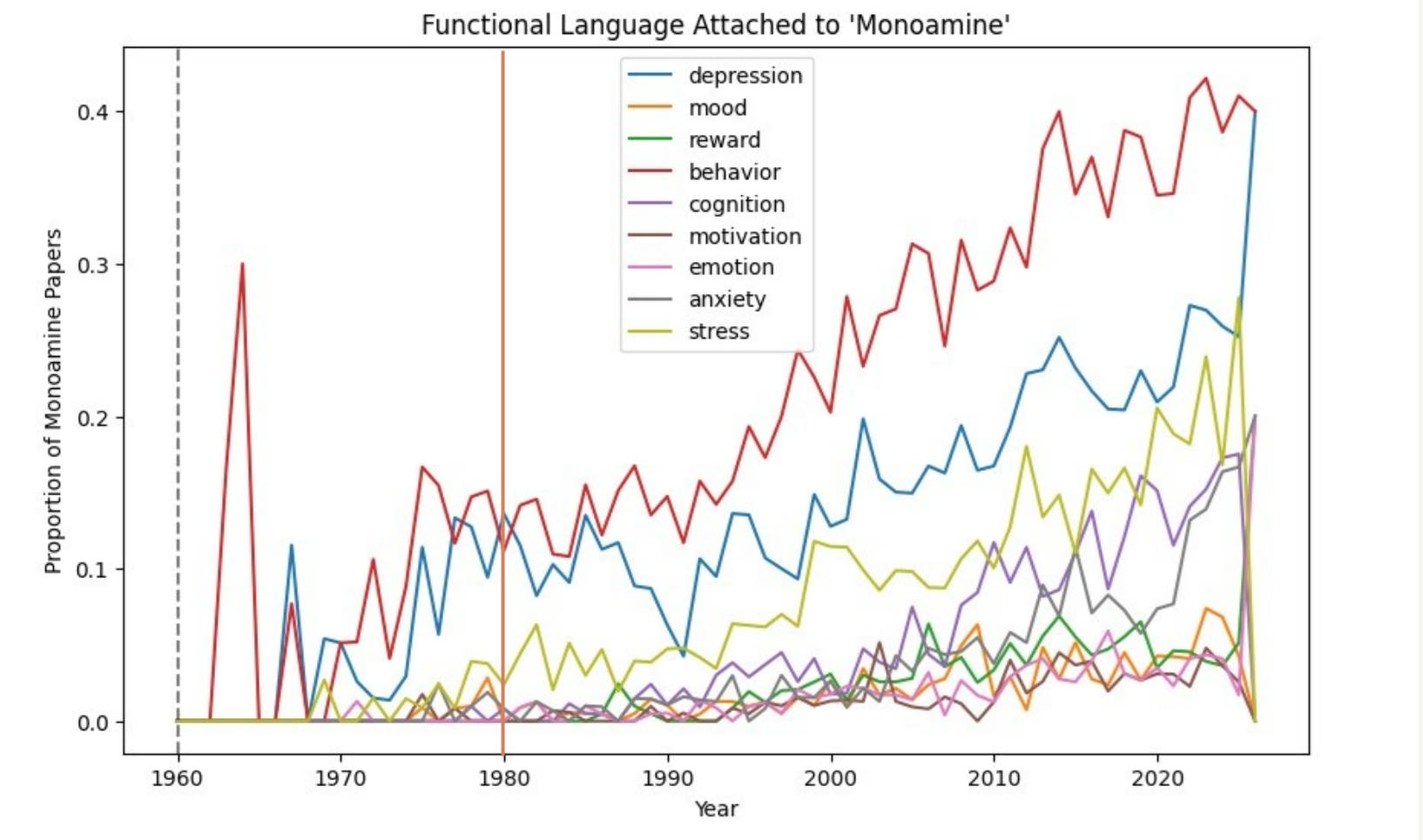
Receptor Findings:
- ~82% of strict studies do not specify receptor subtype
- Receptor-tagged studies cluster together in the same space
- All subtypes remain anchored near motor function
- Differences reflect distance (gradient), not separation (categories)
- No receptor uniquely maps to reward, cognition, or emotion
- Functional claims extend beyond receptor-level organization



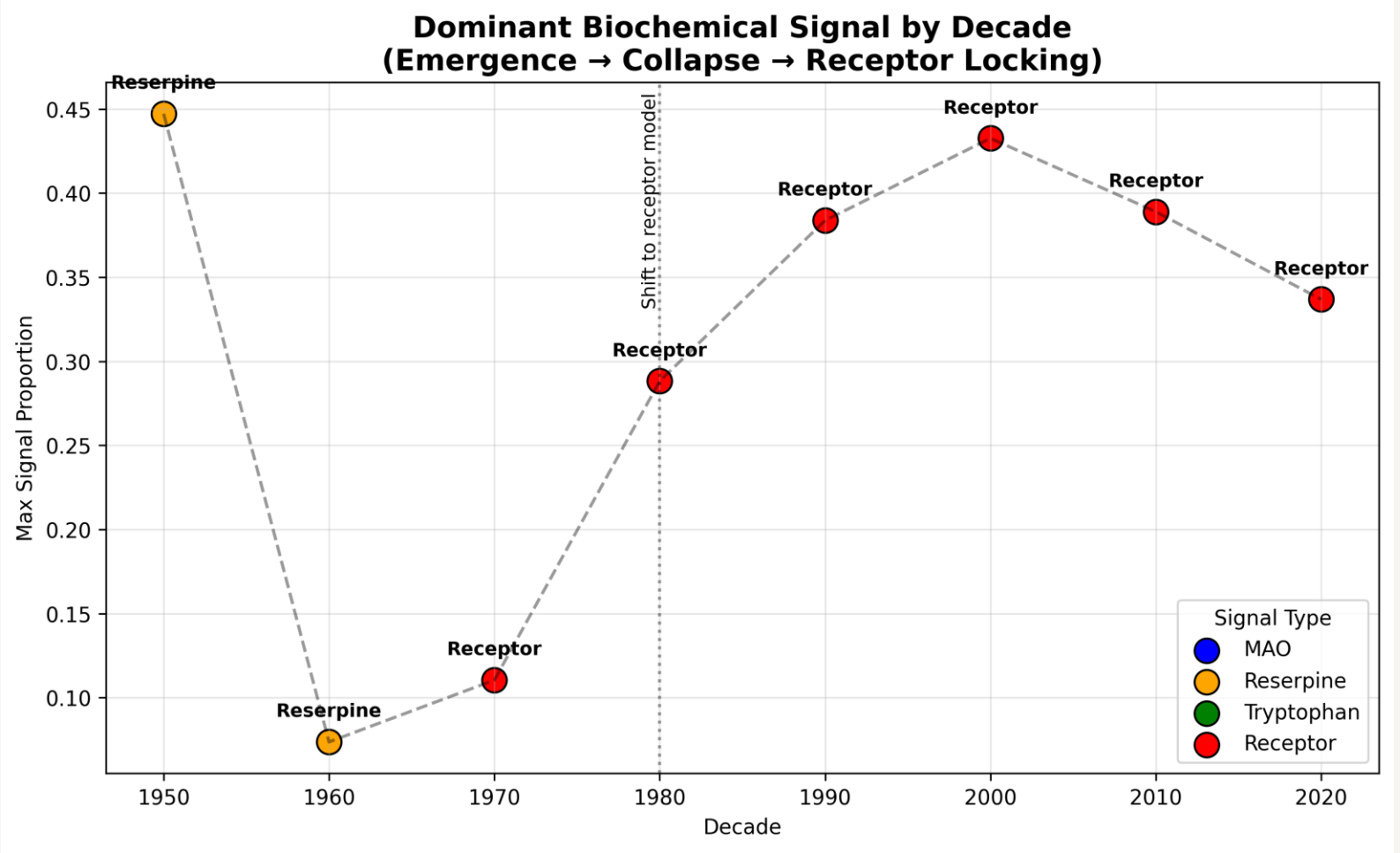




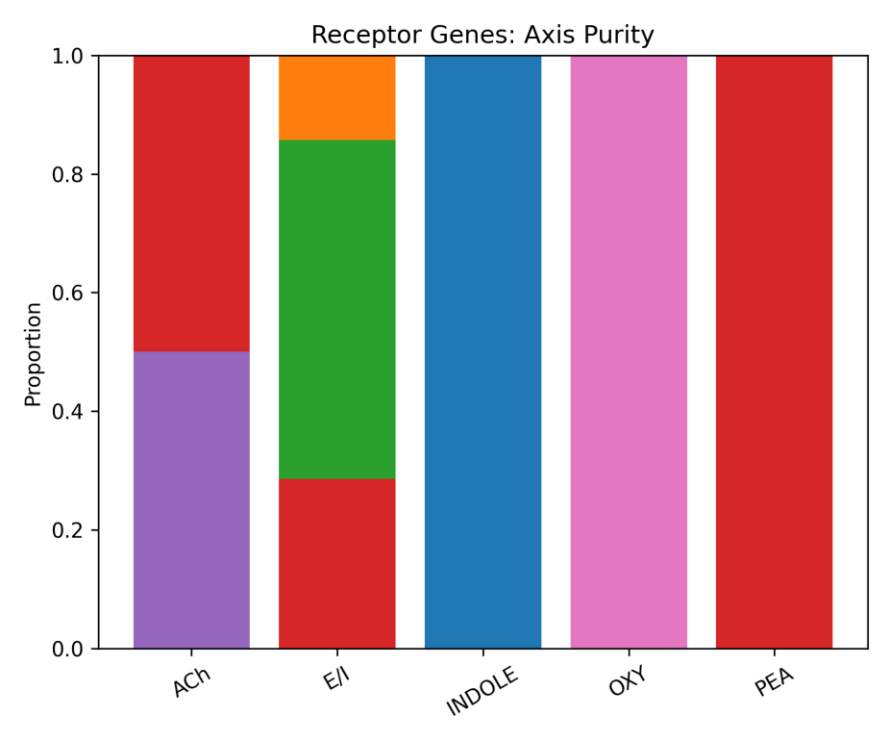
Functions Without Foundation

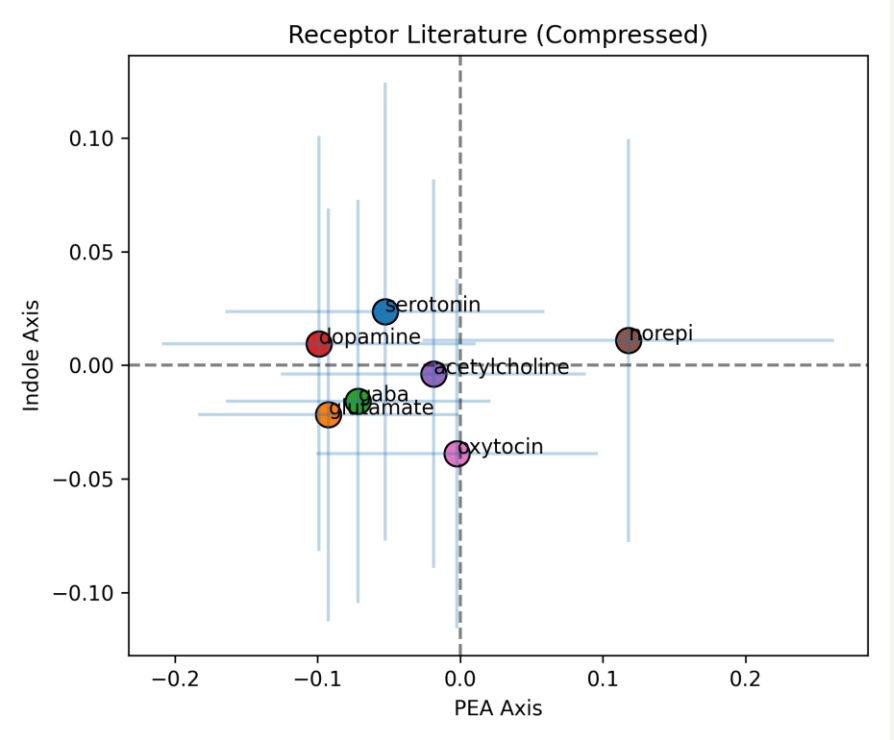


Mechanism Without Foundation



Receptors: chemicals and language



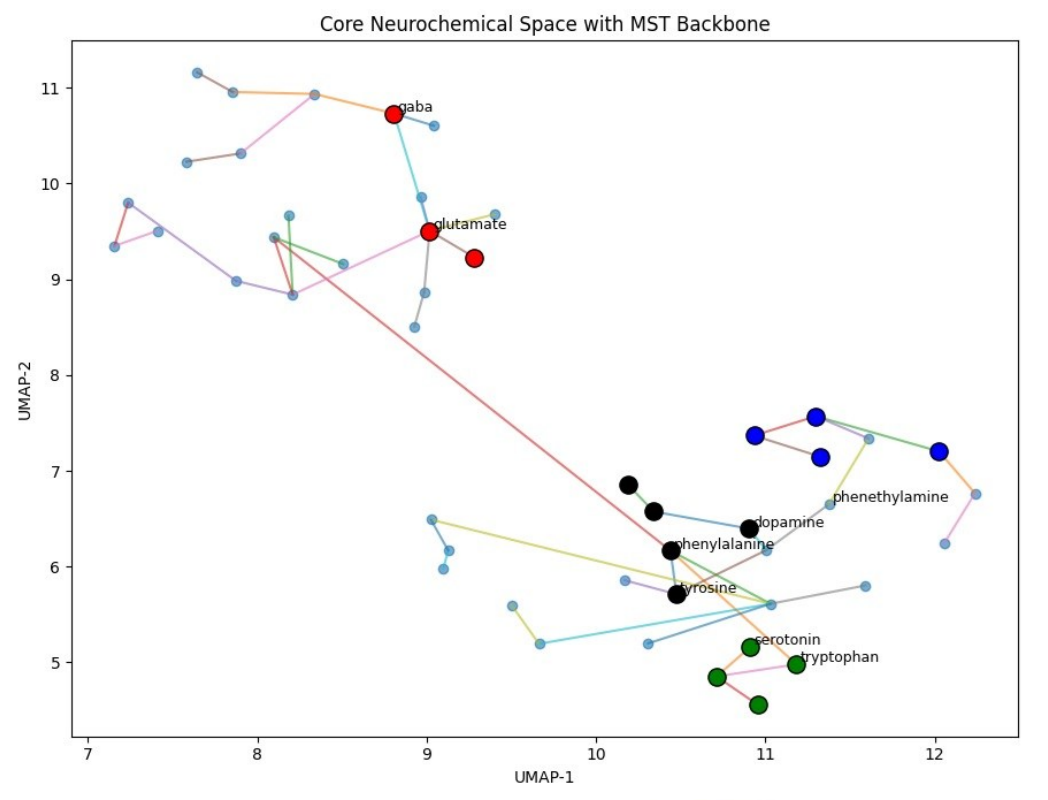


Low entropy → receptor tied to a specific system
High entropy → receptor language spread across many systems
Receptor entropy reflects how non-specific receptor language becomes across neurotransmitter systems.
High entropy indicates shared, overlapping signaling frameworks rather than distinct pathways.

Receptors don't stay specific to dopamine etc., they bleed across systems

Chemistry: What do the molecules say?

Dopamine and chemistry: what do molecules say?



A conserved backbone of chemistry that is stable across time and underlies all neurochemical organization.

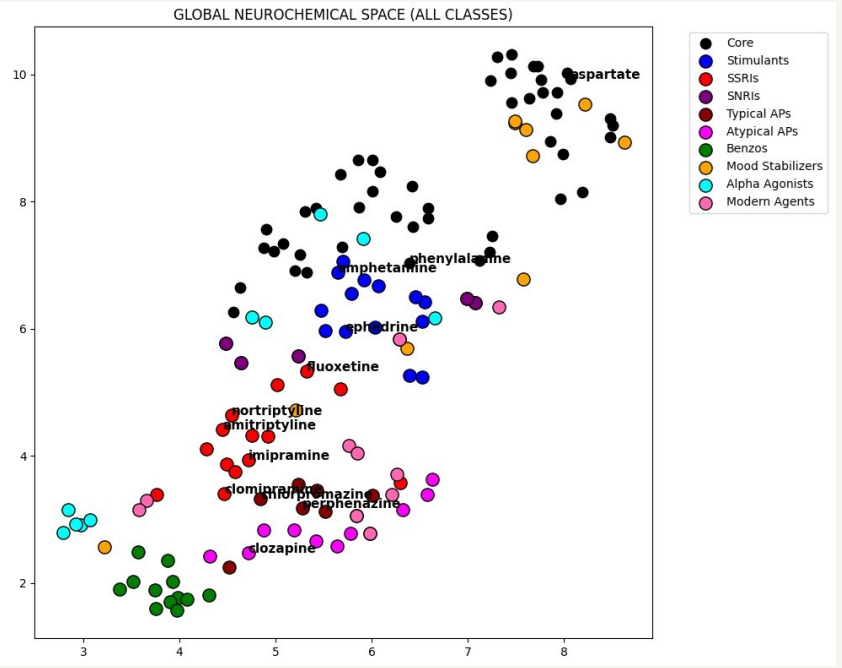
=== TRUNK NODES ===

	name	betweenness
0	phenylalanine	0.690102
17	aspartate	0.546716
23	serine	0.517114
12	glutamate	0.429232
1	tyrosine	0.419981
5	tyramine	0.388529
21	histidine	0.274746
4	phenethylamine	0.259019
14	gaba	0.232192

- **Minimum Spanning Tree (MST):**
The simplest network connecting all molecules based on structural similarity, revealing the core backbone of chemical space.
- **What is a Trunk?**
A set of high-traffic backbone nodes (high betweenness) through which most molecular pathways pass, representing the system's structural highways.
- **Why this matters:**
It shows where molecules actually live and travel in chemical space, before interpretation, highlighting how drugs and neurotransmitters route through shared pathways rather than isolated functions.

The Rise of Dopamine-Targeting Medications — A Structural View

- **Historical Impact**
  - Dopamine-targeting drugs since the 1950s have shaped treatment of Parkinson's disease and psychiatric conditions.
- **What These Drugs Share**
  - Despite different labels (agonists, antagonists, SSRIs, stimulants), most cluster within a **shared chemical pathway**.
- **Structural Reality (the pivot)**
  - Rather than occupying distinct functional regions, these compounds:
  - Align along the **phenethylamine (PEA) axis**
  - Interact with a **common neurochemical backbone**
  - Redistribute activity across the system rather than isolate effects.



Most drug classes cluster along a shared phenethylamine (PEA) pathway rather than forming distinct functional regions.

=== GLOBAL TRUNK ===

	name	path_dominance
78	ephedrine	0.370455
67	amphetamine	0.348849
61	imipramine	0.339936
48	fluoxetine	0.303089
85	perphenazine	0.302846
59	amitriptyline	0.299485
0	phenylalanine	0.293667
60	nortriptyline	0.293543
62	clomipramine	0.288386
82	chlorpromazine	0.274540
89	clozapine	0.235054
17	aspartate	0.231532

As drugs accumulate, the core structure is not replaced, it is reweighted.

Dopamine: A Node in the Axis, Not the Driver of the System

What the Chemistry Shows

•Dopamine is structurally positioned within the phenethylamine (PEA) / catecholamine axis. It occupies a local region, not a central controlling position in the global space

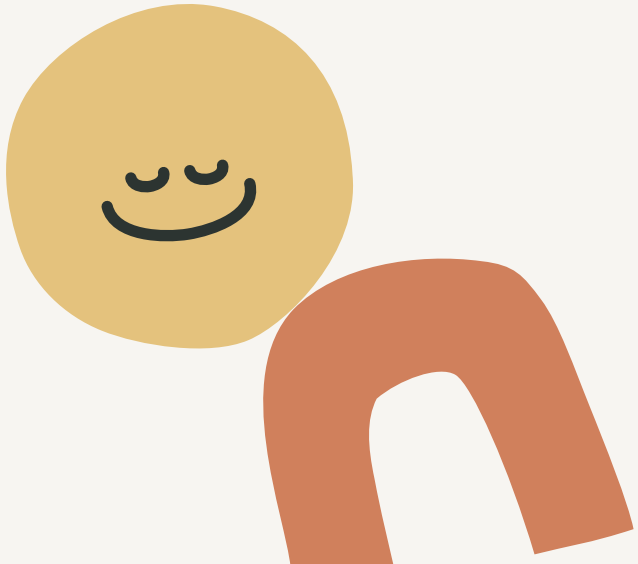
What the Network Shows

Core structure is defined by stable trunk nodes (e.g., phenylalanine, tyrosine). Dopamine participates in this system but does not dominate connectivity or routing

What Changes with Drugs

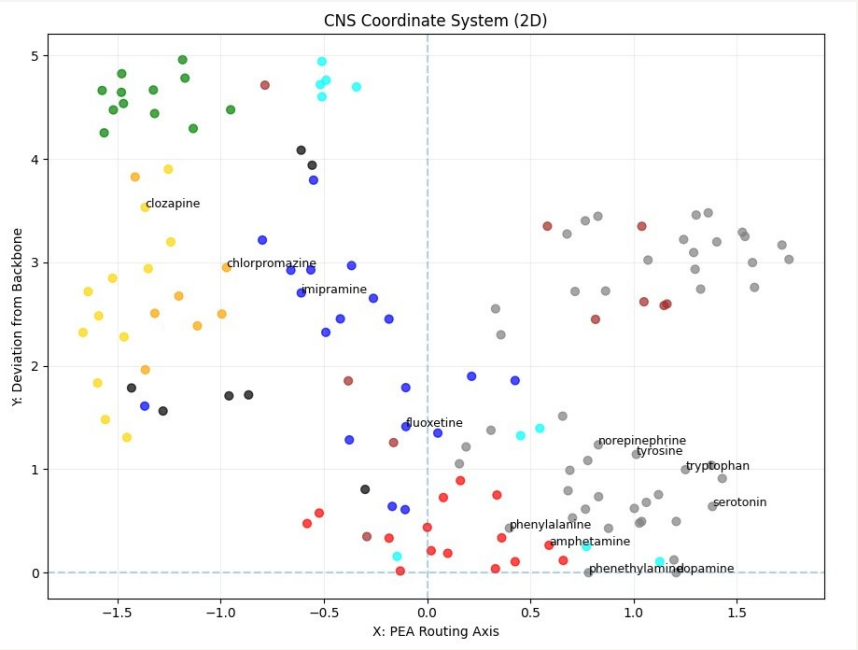
•Clinical compounds cluster along the same axis

•They reweight pathways rather than create new ones



```
=== CLOSEST TO PEA AXIS ===
                name  dist_to_pea
79   pseudoephedrine     0.000000
127      methyldopa     0.571429
81       mephedrone     0.636364
77      armodafinil     0.666667
76        modafinil     0.666667
75        bupropion     0.675000
57       milnacipran     0.727273
58  levomilnacipran     0.727273
48       fluoxetine     0.739130
73  methylphenidate     0.739130
74          cocaine     0.740000
117   carbamazepine     0.742857
65     trimipramine     0.750000
63      desipramine     0.750000
118   oxcarbazepine     0.767442

=== FARTHEST FROM PEA AXIS ===
                                name  dist_to_pea
139                      amantadine     0.964286
120                      topiramate     0.931034
129                     brimonidine     0.923077
138  dextromethorphan hydrobromide     0.921875
137                dextromethorphan     0.920635
50                       paroxetine     0.919355
126                      tizanidine     0.915254
93                     paliperidone     0.909091
92                      risperidone     0.906667
99                    brexpiprazole     0.906667
95                     aripiprazole     0.905405
104                     clonazepam     0.896552
128                   apraclonidine     0.895833
98                     iloperidone     0.891892
94                     ziprasidone     0.890625
```




```
=== EFFECT SIZE (vs GLOBAL MEAN) ===
              count    mean_z     max_z     std_z  effect_vs_global
class
ssri             19  0.232095  0.844366  0.342205          0.107370
typical_ap        7  0.225872  0.697153  0.311365          0.101147
stimulant        15  0.203021  0.919825  0.346936          0.078296
benzo            12  0.138370  0.352030  0.147021          0.013644
core             48  0.103686  1.000000  0.190418         -0.021039
atypical_ap      12  0.103209  0.521981  0.194762         -0.021516
modern            7  0.026228  0.113862  0.040353         -0.098497
mood_stabilizer  10  0.025080  0.112852  0.042020         -0.099645
alpha_agonist    10  0.011504  0.091797  0.029142         -0.113221

=== PERMUTATION TEST ===
Observed top mean: 0.7404
Random mean: 0.1237
p-value: 0.0
```

How 721 drugs changes the trunk.

```
TOP CONNECTIVITY CNS:
                                drug  connectivity  is_trunk
90                       methcathinone      0.021358         1
562  3,4-methylenedioxymethamphetamine      0.017128         1
194                      benzylamine      0.016921         1
107                     succinic acid      0.016697         1
353                         methylone      0.016611         1
54                       mephedrone      0.016574         1
14                      methamphetamine      0.016316         1
13                       amphetamine      0.016269         1
175                          cumene      0.016130         1
518                phenylpropionic acid      0.016099         1
```

Dopamine is part of the system, not the system itself.

Reductionism and Semantic Artifacts: Sources of Drift, and Opportunities for Reconfiguration

What We're Seeing

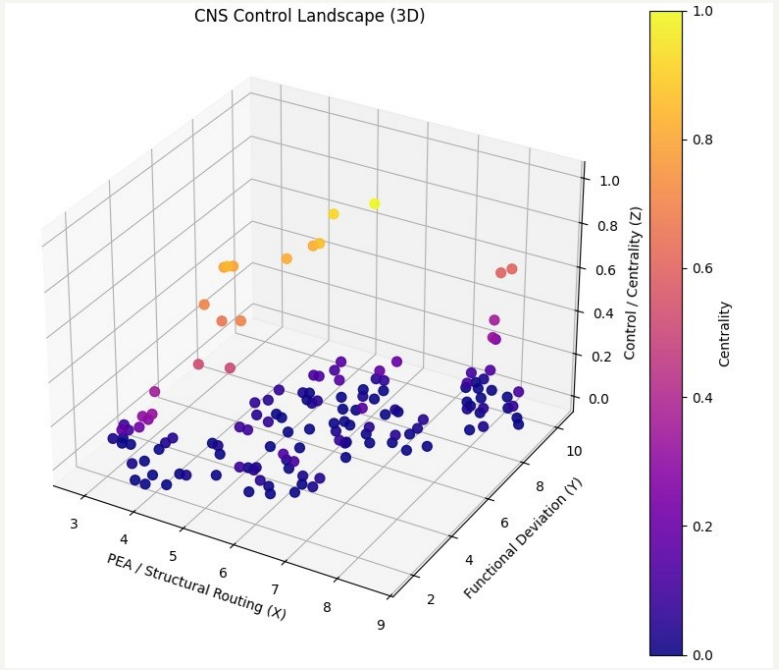
- Functional labels (reward, motivation, salience) cluster in overlapping regions
- Genetic, clinical, and pharmacological findings often do not align cleanly
- Small shifts in language produce large shifts in interpretation

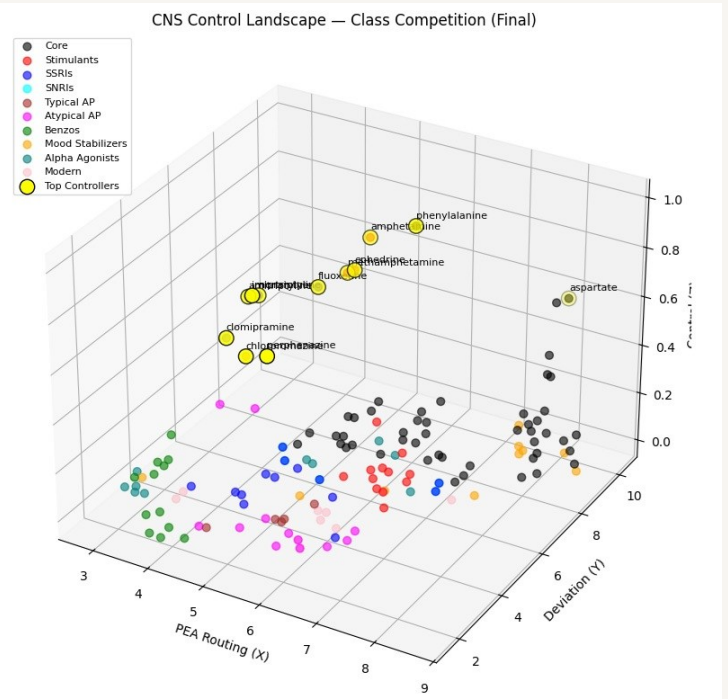
Why This Happens

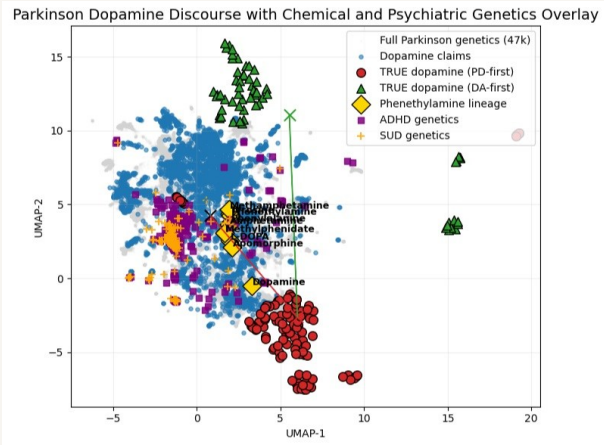
Shared terminology acts as an attractor (dopamine, receptor, activity, etc.)
Reduction to single mechanisms obscures network-level structure
Different fields (genetics, psychiatry, chemistry) operate on misaligned coordinate systems

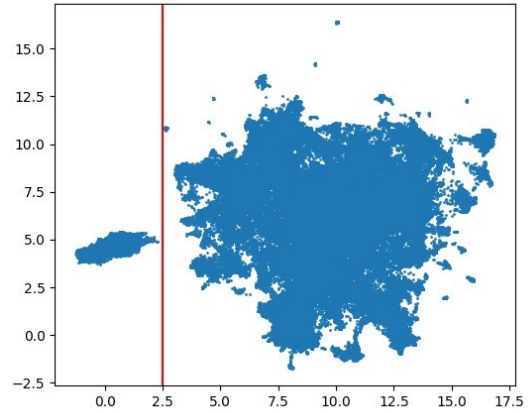
Result

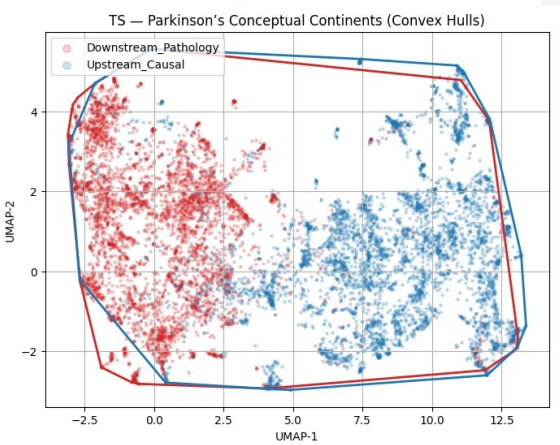
Inconsistent findings across studies
Difficulty replicating functional claims
Overextension of single molecules into multiple roles











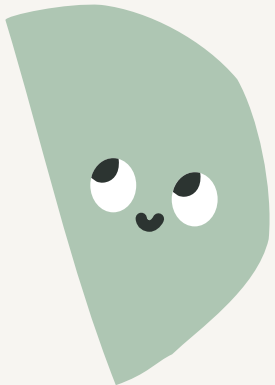
A Path Forward: Reconfiguration

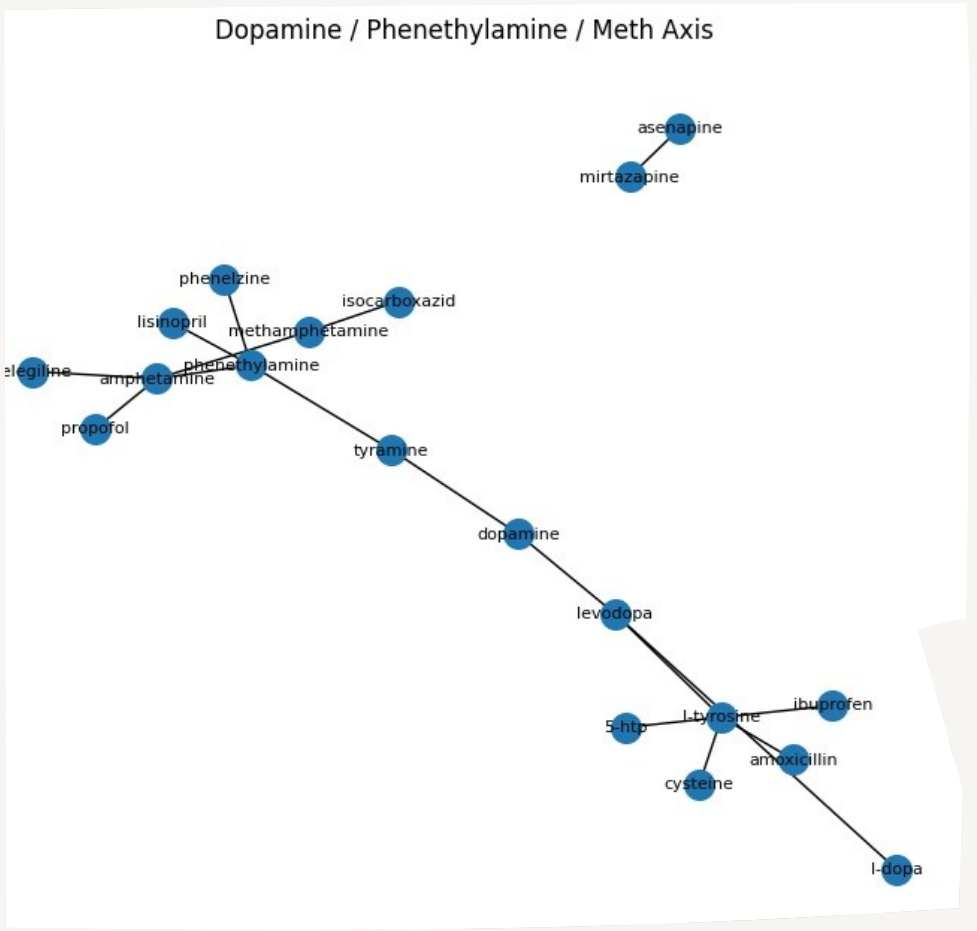
- Anchor interpretation to structural coordinates (axes)
- Separate signal (chemistry) from overlay (language)
- Evaluate function as position within a system, not isolated labels

Dopamine: A node in a larger system

Stimulants show greater structural similarity to phenethylamine than to dopamine, indicating that their chemical scaffold aligns with the phenethylamine backbone rather than dopamine itself.

Structure points to phenethylamine.
Interpretation points to dopamine.





- meth ↔ PEA: **0.321** (higher)
- meth ↔ dopamine: **0.135**
- amp ↔ PEA: **0.400**
- amp ↔ dopamine: **0.176**

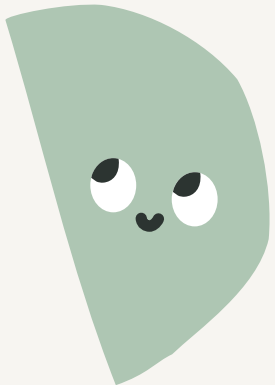
Dopamine Centrality Emerges from System Composition

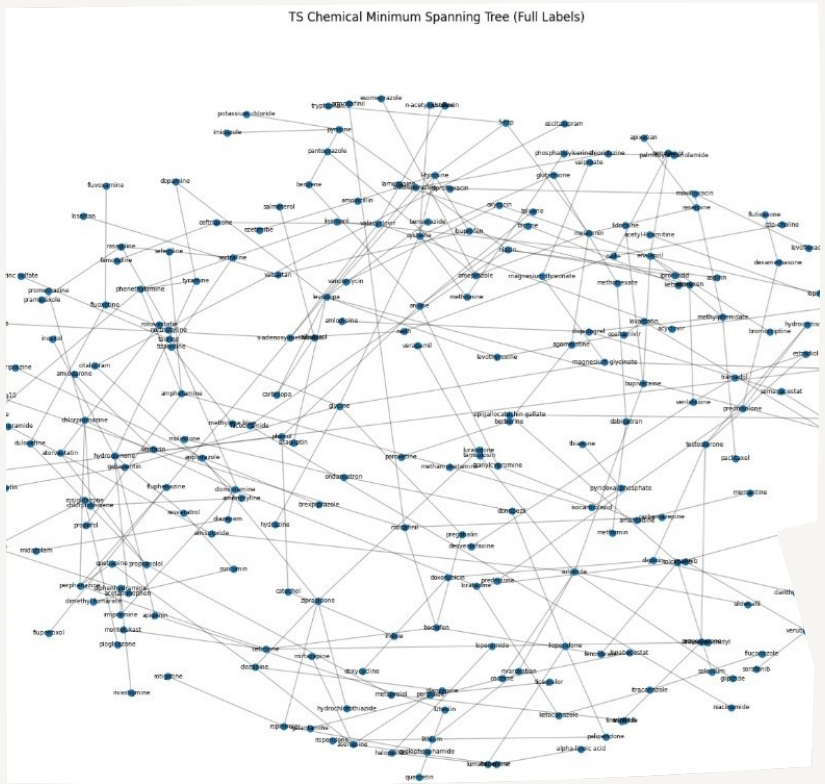
Across 238 compounds, spanning CNS-active and general medications, a consistent biochemical backbone emerges.

Core nodes (tyrosine, tyramine, levodopa) organize connectivity, while dopamine participates without dominating.

Dopamine's centrality is not inherent; it emerges under specific structural conditions.

We didn't discover dopamine as the driver of behavior—we assigned it that role.

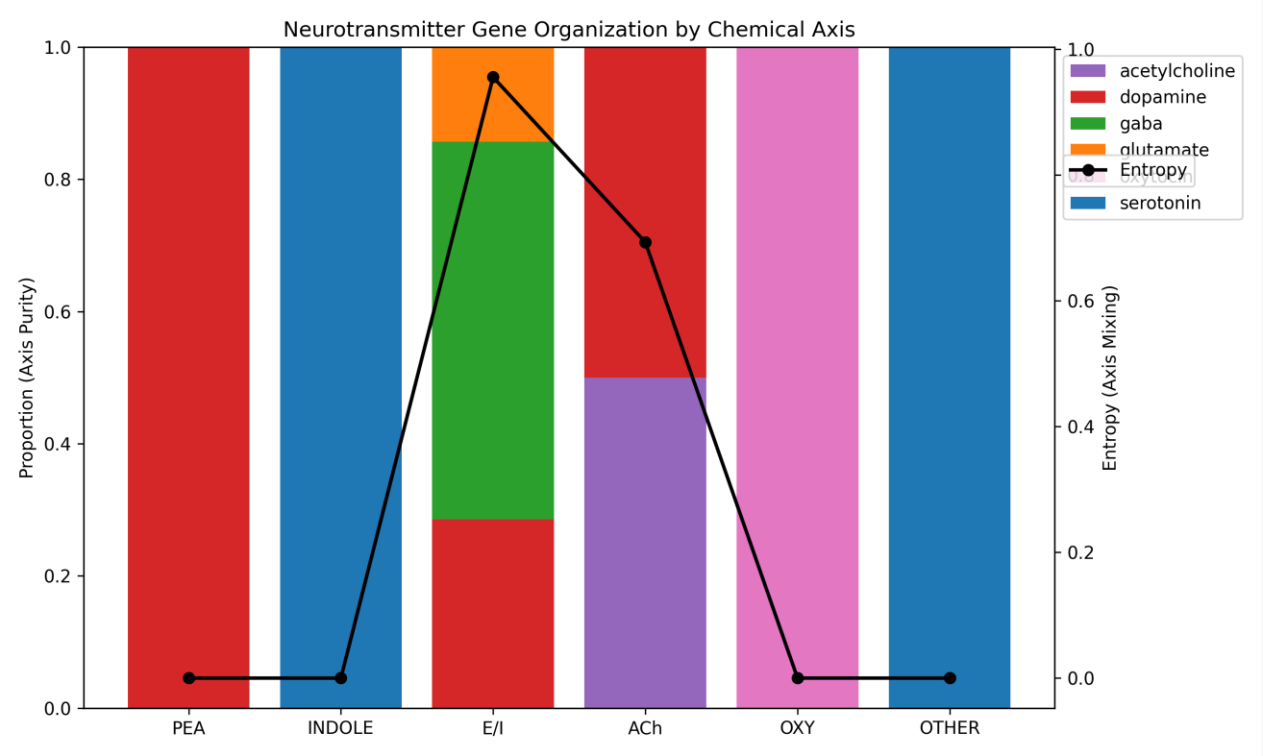




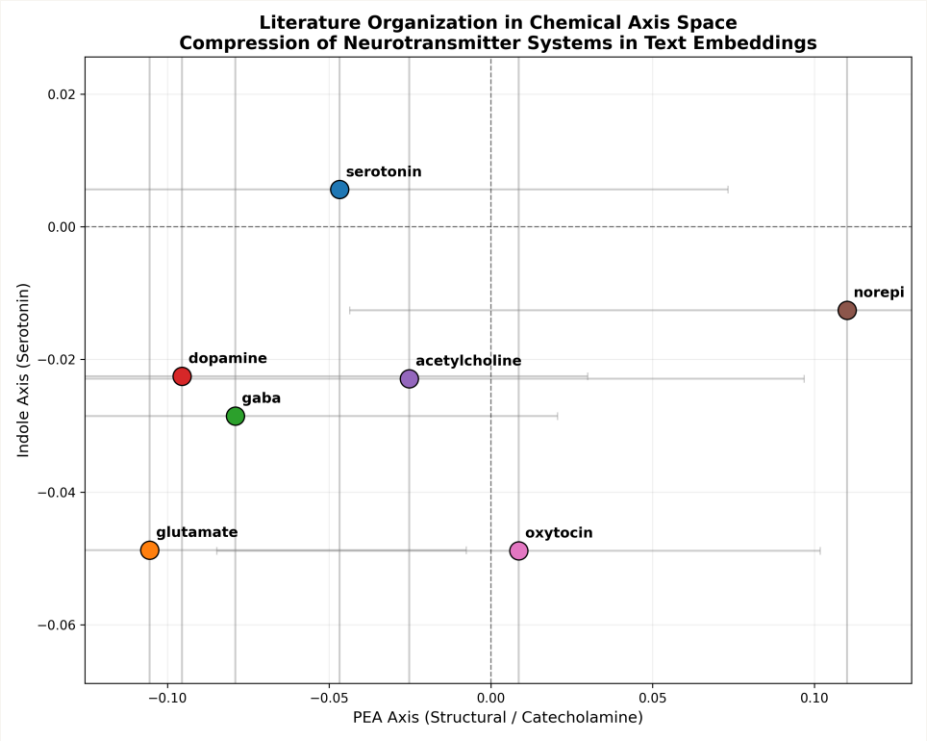
=== TOP BRIDGE (TRUNK) NODES ===

	drug	betweenness
194	l-tyrosine	0.623150
182	glycine	0.532039
183	cysteine	0.528463
61	levodopa	0.507616
237	tyramine	0.502002
155	baclofen	0.499285
168	pregabalin	0.464350
236	dopamine	0.451834
158	cetirizine	0.441572
20	perphenazine	0.402131
235	phenethylamine	0.346599
81	enalapril	0.302689
80	lisinopril	0.287349
16	chlorpromazine	0.264321
229	hydroquinone	0.215762
95	ibuprofen	0.156476
227	phenol	0.149324
12	clomipramine	0.137238
96	naproxen	0.133734
32	quetiapine	0.133734

Genetics: chemicals and language



Entropy reflects how "pure" a neurotransmitter system is at the genetic level.
Low entropy systems map cleanly to chemical origins;
high entropy systems reflect functional mixing across pathways.



The literature does not preserve chemical structure; it compresses systems into a shared functional space.

Finding the paradox:

=== TRUNK NODES ===

	name	betweenness
0	phenylalanine	0.690102
17	aspartate	0.546716
23	serine	0.517114
12	glutamate	0.429232
1	tyrosine	0.419981
5	tyramine	0.388529
21	histidine	0.274746
4	phenethylamine	0.259019
14	gaba	0.232192

=== BENZO TRUNK ===

	name	path_dominance	is_benzo
1	tyrosine	0.427309	0
0	phenylalanine	0.389246	0
5	tyramine	0.355165	0
42	phenol	0.334782	0
17	aspartate	0.316774	0
4	phenethylamine	0.308847	0
44	aniline	0.303112	0
53	oxazepam	0.240758	1
23	serine	0.239041	0
12	glutamate	0.222385	0

=== MOOD TRUNK ===

	name	path_dominance	is_mood
17	aspartate	0.447760	0
0	phenylalanine	0.415688	0
1	tyrosine	0.325580	0
23	serine	0.294682	0
12	glutamate	0.249060	0
5	tyramine	0.239427	0
27	leucine	0.186521	0
21	histidine	0.175948	0
4	phenethylamine	0.168390	0
14	gaba	0.158913	0

=== STIM TRUNK ===

	name	path_dominance	is_stim
0	phenylalanine	0.454786	0
48	amphetamine	0.353913	1
17	aspartate	0.345915	0
23	serine	0.247951	0
12	glutamate	0.192689	0
21	histidine	0.163075	0
1	tyrosine	0.158778	0
52	phentermine	0.135576	1
59	ephedrine	0.121364	1
44	aniline	0.119381	0

=== ALPHA AGONIST TRUNK ===

	name	path_dominance	is_alpha
0	phenylalanine	0.461779	0
1	tyrosine	0.369048	0
17	aspartate	0.346491	0
21	histidine	0.303023	0
5	tyramine	0.285009	0
23	serine	0.267387	0
12	glutamate	0.236842	0
4	phenethylamine	0.158169	0
20	histamine	0.150846	0
14	gaba	0.140508	0

=== TYPICAL TRUNK ===

	name	path_dominance	is_typ
1	tyrosine	0.410901	0
0	phenylalanine	0.402952	0
17	aspartate	0.342942	0
5	tyramine	0.330975	0
4	phenethylamine	0.272100	0
42	phenol	0.268868	0
44	aniline	0.261749	0
23	serine	0.255678	0
12	glutamate	0.243187	0
43	catechol	0.189029	0

=== SNRI TRUNK ===

	name	path_dominance	is_snri
0	phenylalanine	0.418646	0
1	tyrosine	0.385087	0
17	aspartate	0.356335	0
5	tyramine	0.312170	0
23	serine	0.264800	0
12	glutamate	0.253205	0
4	phenethylamine	0.208569	0
21	histidine	0.190988	0
14	gaba	0.152668	0
44	aniline	0.150735	0

=== TOP 25 TRUNK NODES (BETWEENNESS) ===

	name	betweenness	degree
11	dmt	0.662921	4
60	phenylalanine	0.585518	5
23	tryptamine	0.511610	3
59	serotonin	0.496629	2
21	5-htp	0.493383	2
36	tryptophan	0.489638	2
41	imipramine	0.407241	3
1	5-meo-dmt	0.362297	3
27	clomipramine	0.323845	4
19	l-tyrosine	0.313858	3
73	venlafaxine	0.299376	3
86	l-dopa	0.280899	2
7	dopamine	0.271660	3
62	tramadol	0.265668	2
0	dextromethorphan	0.257928	4
47	clozapine	0.244444	5
12	amphetamine	0.222971	3
88	tyramine	0.216979	2
72	phenethylamine	0.208489	5
16	hydrocodone	0.187765	4
42	selegiline	0.145069	2
58	methadone	0.127091	3
76	lorazepam	0.125843	2
44	clonazepam	0.107615	3
32	armodafinil	0.087141	4

=== ATYPICAL TRUNK ===

	name	path_dominance	is_atyp
1	tyrosine	0.427309	0
0	phenylalanine	0.389246	0
5	tyramine	0.355165	0
42	phenol	0.320755	0
17	aspartate	0.316774	0
4	phenethylamine	0.308847	0
44	aniline	0.303112	0
43	catechol	0.256904	0
45	indole	0.244155	0
23	serine	0.239041	0

=== MODERN AGENTS TRUNK ===

	name	path_dominance	is_modern
0	phenylalanine	0.493304	0
17	aspartate	0.357534	0
1	tyrosine	0.321859	0
23	serine	0.275650	0
12	glutamate	0.249060	0
5	tyramine	0.228481	0
56	bupropion	0.184994	1
21	histidine	0.182527	0
52	cariprazine	0.173128	1
14	gaba	0.158913	0

=== TOP STRUCTURAL NODES ===

	name	path_dominance	is_ssri
5	tyramine	0.432110	0
1	tyrosine	0.422028	0
0	phenylalanine	0.363054	0
17	aspartate	0.282984	0
55	desvenlafaxine	0.275291	1
61	imipramine	0.256556	1
65	trimipramine	0.246096	1
23	serine	0.215326	0
12	glutamate	0.197552	0
4	phenethylamine	0.184994	0

The chemical trunk is stable in structure, but unstable in identity.

=== TOP 25 TRUNK NODES (BETWEENNESS) ===

	name	betweenness	degree
11	dmt	0.662921	4
60	phenylalanine	0.585518	5
23	tryptamine	0.511610	3
59	serotonin	0.496629	2
21	5-htp	0.493383	2
36	tryptophan	0.489638	2
41	imipramine	0.407241	3
1	5-meo-dmt	0.362297	3
27	clomipramine	0.323845	4
19	l-tyrosine	0.313858	3
73	venlafaxine	0.299376	3
86	l-dopa	0.280899	2
7	dopamine	0.271660	3
62	tramadol	0.265668	2
0	dextromethorphan	0.257928	4
47	clozapine	0.244444	5
12	amphetamine	0.222971	3
88	tyramine	0.216979	2
72	phenethylamine	0.208489	5
16	hydrocodone	0.187765	4
42	selegiline	0.145069	2
58	methadone	0.127091	3
76	lorazepam	0.125843	2
44	clonazepam	0.107615	3
32	armodafinil	0.087141	4

91 – core, DOA, CNS

=== TRUNK NODES ===

	name	betweenness
0	phenylalanine	0.690102
17	aspartate	0.546716
23	serine	0.517114
12	glutamate	0.429232
1	tyrosine	0.419981
5	tyramine	0.388529
21	histidine	0.274746
4	phenethylamine	0.259019
14	gaba	0.232192

128 core

=== TOP BRIDGE (TRUNK) NODES ===

	drug	betweenness
194	l-tyrosine	0.623150
182	glycine	0.532039
183	cysteine	0.528463
61	levodopa	0.507616
237	tyramine	0.502002
155	baclofen	0.499285
168	pregabalin	0.464350
236	dopamine	0.451834
158	cetirizine	0.441572
20	perphenazine	0.402131
235	phenethylamine	0.346599
81	enalapril	0.302689
80	lisinopril	0.287349
16	chlorpromazine	0.264321
229	hydroquinone	0.215762
95	ibuprofen	0.156476
227	phenol	0.149324
12	clomipramine	0.137238
96	naproxen	0.133734
32	quetiapine	0.133734

238 mixed

=== TOP 25 BY BETWEENNESS ===

	drug	betweenness	degree
0	succinic acid	0.643612	7
1	diphenylmethane	0.530163	6
2	caproic acid	0.511711	4
3	phenylpropionic acid	0.510050	4
4	phenethyl alcohol	0.486938	2
5	benzyl alcohol	0.486634	2
6	benzylamine	0.479381	4
7	butyric acid	0.456615	3
8	valeric acid	0.453664	2
9	amphetamine	0.438857	4
10	3,4-methylenedioxymethamphetamine	0.438278	4
11	methamphetamine	0.435355	5
12	methcathinone	0.433116	4
13	methylone	0.412874	4
14	mephedrone	0.406842	2
15	pseudoephedrine hydrochloride	0.349244	3
16	hexanone	0.348520	4
17	cyclizine	0.332908	4
18	cumene	0.332820	3
19	diphenylpyraline	0.328634	3
20	beta-alanine	0.327005	5
21	heptanone	0.325984	2
22	melperone	0.301022	5
23	gamma-aminobutyric acid	0.298587	3
24	beta-alanine hydrochloride	0.297794	2

1189 mixed

138 CNS

TOP CONNECTIVITY CNS:

	drug	connectivity	is_trunk
90	methcathinone	0.021358	1
562	3,4-methylenedioxymethamphetamine	0.017128	1
194	benzylamine	0.016921	1
107	succinic acid	0.016697	1
353	methylone	0.016611	1
54	mephedrone	0.016574	1
14	methamphetamine	0.016316	1
13	amphetamine	0.016269	1
175	cumene	0.016130	1
518	phenylpropionic acid	0.016099	1

721 mixed

=== GLOBAL TRUNK ===

	name	path_dominance
78	ephedrine	0.370455
67	amphetamine	0.348849
61	imipramine	0.339936
48	fluoxetine	0.303089
85	perphenazine	0.302846
59	amitriptyline	0.299485
0	phenylalanine	0.293667
60	nortriptyline	0.293543
62	clomipramine	0.288386
82	chlorpromazine	0.274540
89	clozapine	0.235054
17	aspartate	0.231532

What we call ‘neurotransmitter systems’ are not structural centers, they are regions of convenience within a larger chemical network

The trunk doesn’t reveal what matters; it reveals what connects.

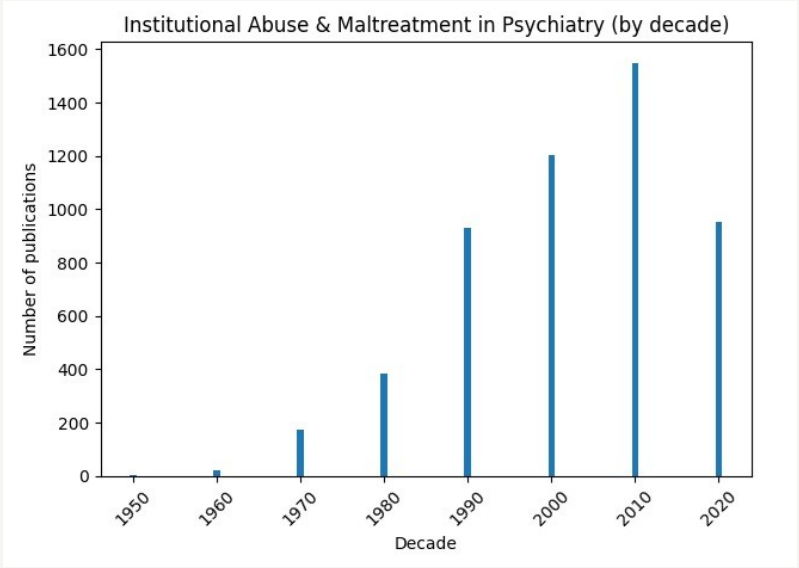
Dopamine’s Legacy and Future Directions

Motor Function and the PEA / Catecholamine Axis

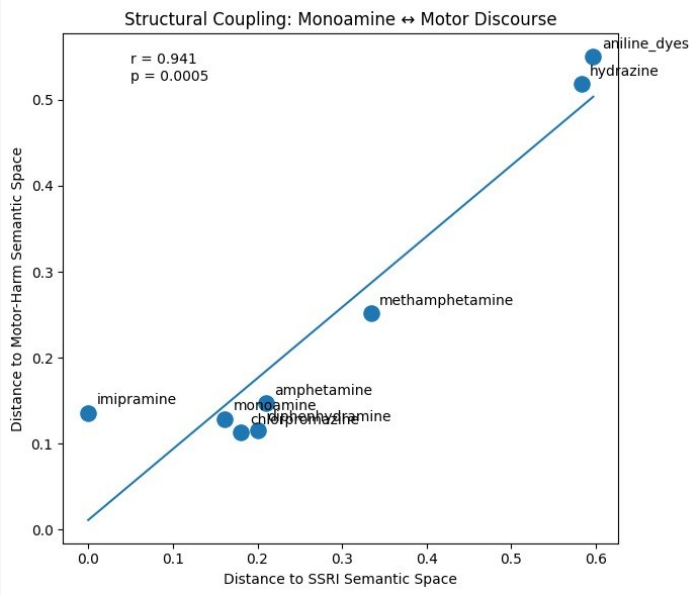
•Motor effects are consistently reported across compounds aligned with the phenethylamine (PEA) / catecholamine axis
(PEA → dopamine → norepinephrine)
•This axis regulates both:
- movement initiation
- movement suppression (“stillness”)

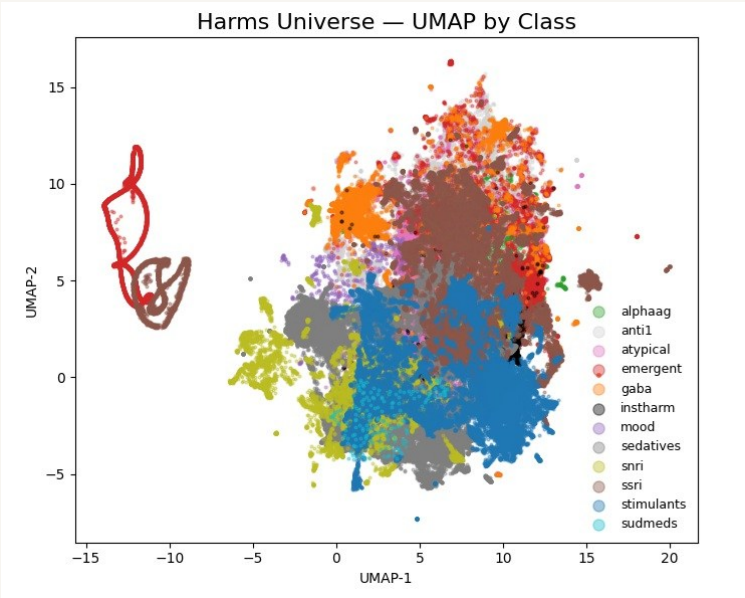
•Compounds interacting along this pathway frequently produce:
- motor activation
- motor disruption
- or dysregulation

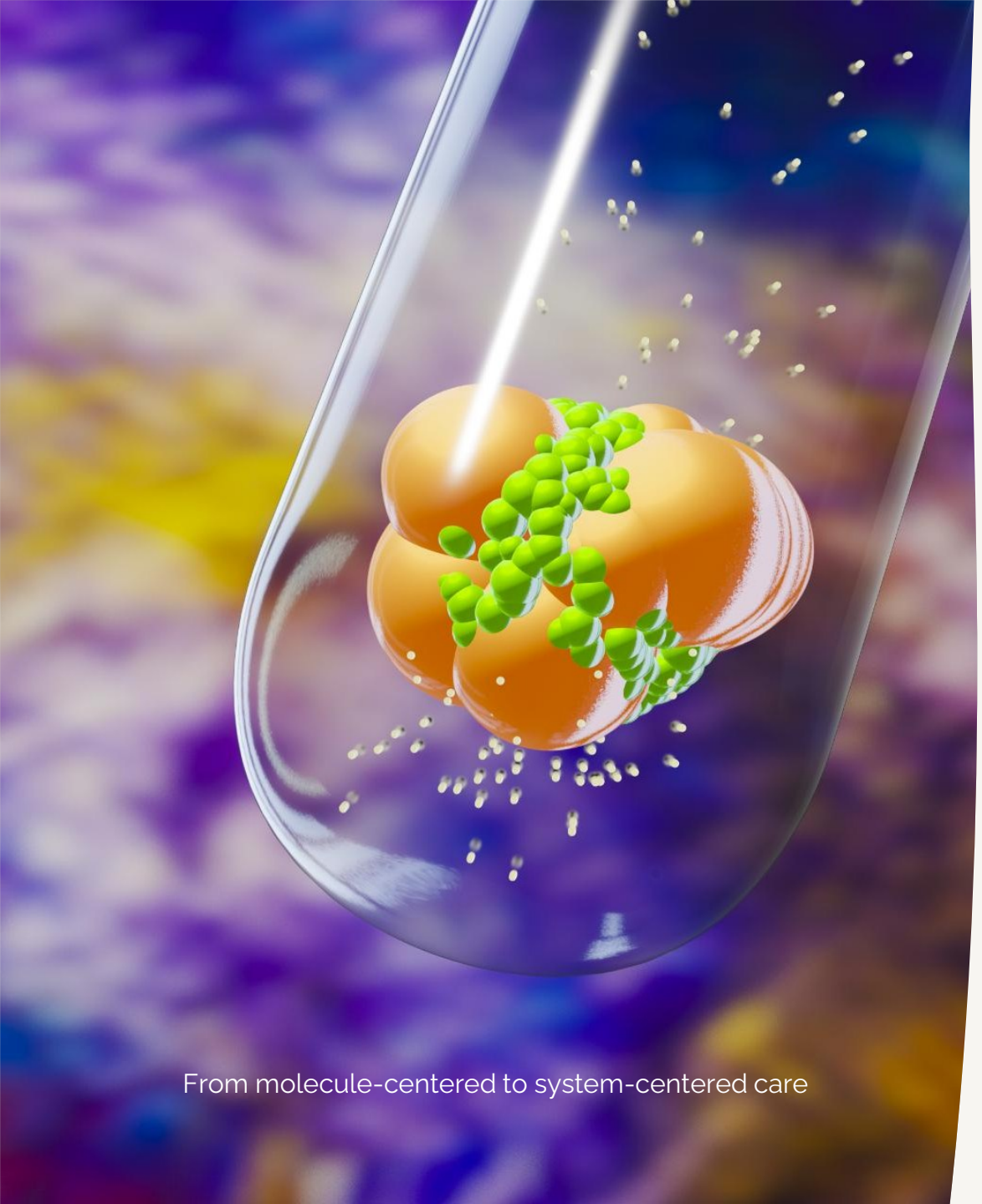
Reports of institutional and treatment-related harms have increased over time.
This reflects both expanded use of interventions and improved reporting.
However, variability in measurement and underreporting remain significant challenges.



Motor regulation—not reward—is the most consistent biological anchor across this system.







From molecule-centered to system-centered care

Implications for Neuropsychiatric Practice

System-Based Therapeutic Approaches

- Clinical effects emerge from modulating networked biochemical systems, not single molecules
- Interventions targeting the PEA/catecholamine axis influence motor regulation and related functions

Rethinking Personalization

- Individual variability reflects system configuration, not just receptor subtype differences
- Effective treatment may require targeting pathways and network balance, rather than isolated targets

Measurement and Interpretation

- Many studies lack precise receptor or system-level specification
- Clinical interpretation is influenced by incomplete or inconsistent measurement frameworks

Clinical Reality (the anchor)

- Pharmacological effects often reflect redistribution of activity across systems
- Side effects, including motor and behavioral changes, are expected outcomes of system perturbation

The chemistry didn't emerge from psychiatry.
Psychiatry emerged from the chemistry.

Chemical Lineage Precedes the Story

Established Chemical Foundations

•Core compounds in the phenethylamine/catecholamine pathway (e.g., phenylalanine, phenethylamine, tyrosine, dopamine, norepinephrine) were identified decades before modern psychiatric frameworks
•These molecules form a stable biochemical lineage that persists across time

Temporal Gap

•Key compounds predate psychiatric application by 4–50 years
•Clinical models were built after the chemistry was established

Interpretation vs. Structure

•These systems were not discovered through psychiatry, rather, psychiatry was built on top of them.

Conclusion: What did dopamine show us?

What Holds (Biology)
•Dopamine is consistently aligned with motor regulation
•It operates within the PEA/catecholamine axis
•It is biologically real and functionally important

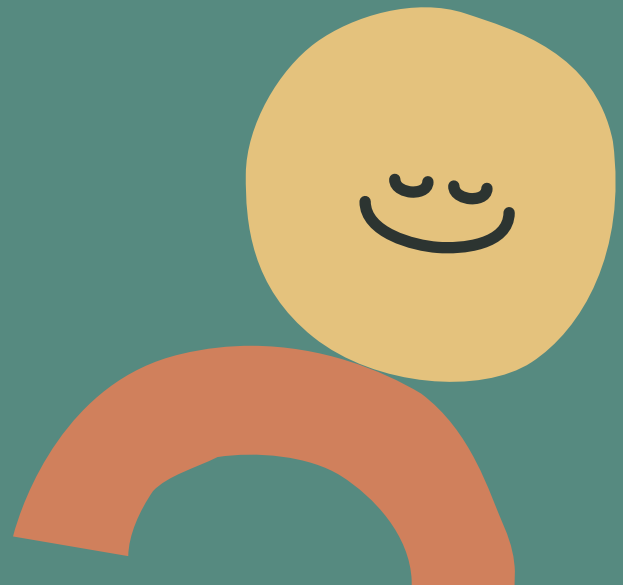
What Emerged (From Data)
•Dopamine is not structurally central
•Its "importance" emerges from scale- and system-context
•It functions as a participating node, not a controlling center
•Many effects reflect network interactions, not isolated action

What This Means (Going Forward)
•Move from molecule-centered → system-centered models
•Interpret clinical effects as system perturbations
•Improve measurement of pathways, not just receptors
•Remain open: much is still unknown

Dopamine's role in motor function is clear and well supported.
The expansion into reward, cognition, and emotion is far less consistent at the level of direct evidence. Many of these domains, however, share a common feature; action, suggesting that the apparent diversity of function may originate from a single underlying motor axis. Dopamine is a node in a lineage—not a trunk of the system.

Next: Does serotonin follow the same rules?

Thanks for your attention!



Phenylalanine
What it is: Essential amino acid
Origin: Natural (dietary proteins)
Entry point into catecholamine chemistry
Tyrosine
What it is: Amino acid derived from phenylalanine
Origin: Natural metabolism
Precursor to dopamine
Phenethylamine (PEA)
What it is: Simple endogenous amine
Origin: Natural trace amine
Backbone of stimulant drugs
Tyramine
What it is: Decarboxylated tyrosine
Origin: Fermented foods (cheese, wine)
Early link between diet and physiology
Tryptophan
What it is: Essential amino acid
Origin: Natural (diet)
Entry to indole/serotonin chemistry

Tryptamine
What it is: Simple indole amine
Origin: Natural metabolism
Backbone of serotonin and psychedelics
Serotonin
Dopamine
Catechol
What it is: Benzene with two hydroxyl groups
Origin: Plant metabolism + industrial synthesis
Core motif of dopamine/norepinephrine
Phenol
What it is: Aromatic alcohol
Origin: Coal tar, early antiseptic chemistry
Early medical + industrial chemical
Aniline
What it is: Aromatic amine (benzene + NH_2)
Origin: Coal tar dyes (19th century dye industry)
Starting point for many synthetic drugs
Benzene
What it is: Basic aromatic ring (C_6H_6)
Origin: Coal tar, petroleum refining
Foundation of modern organic chemistry
Indole
What it is: Fused aromatic ring system
Origin: Coal tar + plant metabolism
Core of serotonin, psychedelics
Hydrazine
What it is: Reactive nitrogen compound (N_2H_4)
Origin: Industrial chemistry (rocket fuel, dyes)
Led to early MAO inhibitors (e.g., iproniazid)