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ACRONYMS

There'll also be an index of terms, I think, but it's not written yet.

NON-SCIENCE STUFF

FLOSS free/libre open source software

GPL GNU General Public License

GNU GNUs Not Unix

OS open science

FLOSS free/libre open source software

GPL GNU General Public License, the founding document of the Free Software Movement

OS open science

OA open access

IF Journal Impact Factor

WOK *Web of Knowledge*

STEM Science, Technology, Engineering, and Math

Organizations

HEW Department of Health, Education, and Welfare

IRB Institutional Review Board

USPHS U.S. Public Health Service

PLOS Public Library of Science

OKF Open Knowledge Foundation

OECD Organisation for Economic Co-operation and Development

TREND Teaching and Research in (Neuro)science for Development in Africa

Places

FDA Food and Drug Administration

MIT the Massachusetts Instituite of Technology

NIH National Institute of Health

NYU New York University

OEAC Other Euro-American Countries, including Australia, NZ, and Canada

ROW "Rest of World", for what that's worth

BRICS Brazil, Russia, India, China, considered the rising economic and scientific powerhouse countries

ROW "Rest of World", for what that's worth

OECD Organisation for Economic Co-operation and Development

UB FOH University of Botswana, Faculties of Humanities

UOM FOS University of Mauritius, Faculties of Science

UCT COMM University of Cape Town, Commerce

UNAM FHSS University of Namibia, Humanities and Social Sciences

SCI Science Citation Index

WOS Web of Science

SCIENCE

FACS Fluorescence Activated Cell Sorting

GPCRS G-protein coupled receptors

G-PROTEIN guanine nucleotide-binding proteins

RA retinoic acid

5-HT 5-hydroxytryptamine

CNS central nervous system

GDP guanosine diphosphate

GTP guanosine triphosphate

LSD lysergic acid diethylamide

MESCALINE 3,4,5-trimethoxyphenethylamine

OCD obsessive-compulsive disorder

DMT *N*,*N*-Dimethyltryptamine

DOM 2,5-Dimethoxy-4-methylamphetamine

DOI 2,5-Dimethoxy-4-iodoamphetamine

STP Serenity, Tranquility, Peace

PFC prefrontal cortex

LC locus coeruleus

PET positron emission tomography

HTR head twitch response

DEA Drug Enforcement Administration

PPI pre pulse inhibition

MAOI monoamine oxidase inhibitor

HEKS human embryonic kidney 293 cells

1 SCIENCE STUDIES, FEMINIST THEORY, CULTURAL STUDIES

Science is an empowering technology. The sense of systematic inquiry satisfies some deep drive to understand and explain the world around us; "science" is part of a long and storied heritage of bold exploration, innovation, and human ingenuity.

rewrite intro sentence

The classic question in scientific philosophy classes, or history of science classes: "what is science?" While I'd love to spend time ruminating on what the word – or field, or method of knowing, or style of inquiry – is and is not, I move gravitate more quickly towards the practical implications of a science embedded in a culture. For our purposes:

"But boundary crossing in itself is not very interesting for feminist, multicultural, antiracist technoscience projects. Technoscience provokes an interest in zones of implosion, more than in boundaries, crossed or not. The most interesting question is, What forms of life survive and flourish in those dense, imploded zones?"

see Longino?

Science, a systematic enterprise that builds and organizes knowledge in the form of testable explanations and predictions about nature and the universe; *progress*

Science, an international weekly science journal, published by the American Association for the Advancement of Science

Science, a way of exploring the world from a specific cultural/philosophical/technical viewpoint; a practice and culture, but a "culture of no culture": domination and power relations through knowledge

Our second is tongue-in-cheek and the third is certainly controversial, so we'll start with troubling the notion of science as progress and as a systematic truth-building exercise.

Science is, simultaneously and harmoniously, a handmaid to progress and a crucial strut in upholding systematic societal inequities. It is both a compelling, evidence-driven narrative about biological and physical realities and a knowledge necessarily developed in a social context.

rewrite word choice of "progress"?

1.1 BIOPOLITICS OR SCIENTIFIC RESPONSIBILITY?

For the ethical duties and responsibilities of scientists, we have Institutional Review Board (IRB)s to manage human experiments, and the Republican party to manage stem cell and climate science. Ethics are relegated to the limited frame of experimental design and execution. Notions of informed consent, "do no harm", and the humanity of people are what I would call ethical responsibilities, are critical and basic scientific practices.

That is not, however, exactly what this dumb Div III is about.

Take, for example, the well-known Tuskegee Syphilis experiments. In 1932 Tuskegee, Alabama, the U.S. Public Health Service (USPHS) enrolled 400 syphilis-positive black men to observe the "natural" course of untreated, latent syphilis. The study heads began by enticing their participants with explicit promises of free health care and treatment, a promise they never intended to fulfill. To ensure the disease stayed "natural", the USPHS researchers took steps to prevent their subjects from being treated by local physicians. When the draft came through in 1941 and tested for syphilis, the USPHS researchers supplied the draft board

and they were testing with the Wasserman reaction!

with a list of names to be excluded from treatment; the U.S. Army complied. In 1932, no effective syphilis treatment existed, although it was believed that certain mercury ointments could slow its course. Twenty years into the study, when penicillin *had* become established as an effective syphilis treatment, researchers increased their efforts to prevent interference by the outside world and to maintain the course of disease. Halfway through the study, more than 30% of the test group had died *directly* from advanced syphilitic lesions, with many more suffering from secondary complications.[8]

The "study" ceased forty years after it started, in 1972, after a whistle-blower publication in the *New York Times* and Congressional hearings.

In 1973, a year after the cessation of the study, the Department of Health, Education, and Welfare (HEW) released a damning report of the ethical failures over the course of the study. The report focused on the (1) lack of treatment, arguing that once penicillin had been discovered, it should have been used and (2) the "informed consent issue", wherein the report argued men had submitted to *an* experiment, without being told what the experiment entailed. This remains the dominant interpretation:

Wikipedia because it represents dominant views of culture/science

> "...controversial for reasons related to ethical standards, primarily because researchers knowingly failed to treat patients appropriately after the 1940s validation of penicillin as an effective cure for the disease they were studying."
>
> Wikipedia on the Tuskegee Syphilis experiments[76]

To our modern sensibilities, this was a complete ethical failure on the part of the scientists involved, their funding body, and the hospital. The criticism are founded in notions of what a *good* doctor would have done differently.

This is an ethical criticism, and an ethical lesson. It does not account for or consider the deep social structures that *allowed* the Tuskegee experiments to go forward. Doctors and researchers discounted the socioeconomics of black America, arguing that better medical care could not alter the "evolutionary scheme" of things. Researchers never *intended* to treat these men, because in their (white) eyes, black men were a subhuman species. The discovery of penicillin had no bearing on their decision to watch the natural course of death.[8]

All parties were deeply and irrevocably shaped by the anti-back racism in the post-Civil War Jim Crow era that continued, with only slight variation, until the Civil Rights movement. Only deep-seated knowledges about black culture and bodies could enable the Tuskegee Syphilis Study.

Reports were also published every two years by JAMA, so like, this wasn't HIDDEN. Many people saw and discussed this thing.

1.1.1 *Ah a section divider here probably?*

define modern science

Modern scientific systems evolved in an era of Western expansionism and imperialism; the beginnings of biological classifications and phylogenies are rooted in exploratory voyages and specimen collection by Europeans.The Scientific Revolution enabled and fed on the expansion

research scientific imperialism, bioprospecting, new forms

of European powers into new territory.

Discovery of the 'cure' for malaria (by indigenous tribes in the Amazon, transferred to the Jesuit, and eventually the expanding European empires) allowed European nations to make inroads into tropical areas, as their soldiers were no longer dying at the prodigious rates.

Racism – the peculiar brand of American racism, derived from slave-owners desperate to justify their brutality of human bondage – was created through the collusion of science and society, specifically a science that carefully cataloged and characterized the way black men and women differed, and were therefore lesser, than White slaveholders. Darwin's great proposal of evolution let scientists justify the status quo (White men, White Women, Black men, Black women, in that order) as a mere consequence of natural selection.

That was the 40's and 50's – today, we have genetic surveillance.[61]

rewrite genetic surveillance, 1000 genomes project

We have the sciences of homosexuality: if being gay is a genetic inheritance, then we should be careful to screen our pre-natal children and not allow gay men to donate sperm.. If it's cultural, we should be more careful to police the kind of culture we give our children, carefully isolating them in heterosexual spaces. We can cure the queers, if only we knew *why* they were homosexual.

intentionally focused on gay Men because patriarchy

The scientific heritage, the accumulated knowledge upon which we build our futures, is not exempt from criticism more commonly leveled at explicitly political institutions. At the same time, the undeniable power of science and technology to do "good" – hormone therapy for medical gender transitions, Internet communities for otherwise isolated activists, the reclamation of environmental sciences by Native communities, technologies that re-enable disabled bodies, pharmaceuticals that prolong lifespans and raise quality of life, and allow people to take control of their reproductive health* – means we need science to keep pushing. Not to mention the insatiable curiously to understand and the delightful appeal of "basic" research, of discovering something new.

Science is not going away, and nor should it; but to ignore our scientific inheritance, the complicity between science and power, and the role of individual scientists in perpetuating and creating power dynamics is to be neutral in the face of injustice.

1.2 SCIENCE STUDIES

Both my historical time line and ideological foundation for science studies starts with Ludwik Fleck's *Genesis and Development of a Scientific Fact*, first published in 1935 pre-WWII Germany.[27] A practicing syphilis researcher and pathologist, Fleck proposes scientists as the creators of facts, rather than mere observers; or rather, that the act of observing also creates. He describes how certain *styles* of thinking permeate and circumscribe scientific collectives and the people within them. Scientific knowledge is only accepted as true fact once the evidence been thoroughly vetted, trimmed, mediated, and judged acceptable by experts in the field. This is not just the peer-review that drives science, but the presented facts must fit more-or-less neatly into pre-existing structures of thought.

Expand historical section of science studies to generate a foundation for current critiques... more explicit Fleck summary w/-page numbers, quotes

"Facts" are then not so much realities of the world but interpretations of it, made by collaboration between individual, collective, and evidence; they only take shape in a matrix of other beliefs and discoveries about

*Given access and governments that don't insist on fucking bullshit lookin' @ you, everybody.

the world. Like a group of people who together produce an idea where the origin is never really clear, scientific facts are held in a common tension, without distinctly available origin stories.

Fleck and Kuhn and many of their concurrent and subsequent philosophers, historians, and sociologists of science offer compelling arguments that science is, yes, evolution, but not evolution *towards* anything.

link P

[[Linking paragraph about how dissatisfying it is to deconstruct science without talking about the *implications* of a value-laden science]]

1.3 FEMINIST THEORY

"...Questioning representation with a vengeance."

rewrite feminist science studies chronology; ways it is or is not western; academic feminism, co-option of grassroots

New ways of knowing overlaps with technology and science studies overlaps with philosophy of science overlaps with uncountable modes andof analysis. What I now call feminist science studies emerges out of academic activists against white supremacy, patriarchy, heteronormativity, and ecological destruction working on ways to critique science as a social institution, and using that critique to forge new ways of asking and answering scientific questions.

Feminist science studies is then at confluence of many ideas, summed in Donna Haraway's 1994 *Cat's Cradle: Science Studies, Feminist Theory, Cultural Studies.*[35]

> **"Cultural studies**... Not culture only as symbols and meanings, not comparative culture studies, but culture as an account of the agencies, hegemonies, counter-hegemonies, and unexpected possibilities of bodily construction... Relentless attention to the ties of power and embodiment... location and knowledge. Unconvinced by claims about insuperable natural divides between high and low culture, science and everything else, words and things, theory and practice.
>
> **Feminist, Multicultural, and Antiracist Theory/Projects**... situated knowledges, where the description of the situation is never self-evident, never simply "concrete," always critical; the kind of standpoint with stakes in showing how "gender," "race," or any structured inequality in each interlocking specific instance gets built into the world–i.e., not "gender" or "race" as attributes or as properties, but "racialized gender" as a practice that builds worlds and objects in some ways rather than others... gender and race are built into practice and have no other reality, no origin, no status as properties ... questioning representation with a vengeance.
>
> **Science Studies**... reflexivity, constructionism... science in the making (not science made), actors and networks... science as practice and culture... the culture of no culture, the nature of no nature... All the disciplines of science studies: history, philosophy, sociology, semiology, and anthropology; but also the formation of science studies out of the histories of radical science movements, community organizing, and policy-directed work. These histories are regularly erased in the hegemonic accounts of disciplinary and interdisciplinary development in the academy and the professions."

-Donna Haraway, *Cat's Cradle*, p. 66-68

So now that we know what we're dealing with (sort of, although it's a slippery web of concepts), that brings us to: so what? Why bother? Why shouldn't we, as one professor urged me, "cut the sociology, focus on the science"?

1.4 WHAT DOES THIS DO IN A PRACTICAL SENSE?

Because I have to at least try to be an Emma Goldman, not Margaret Sanger.

1.4.1 *"Asking Different Questions"*

Feminist science studies both allows and demands practicing scientists engagement with more than "just" science. It lets us ask questions of representation in our labs, our literature, and our students: "Where are the women? *Who* is practicing science, and who is deciding what science is important?" This extends to questioning not just gender, but about race, physical ability, nationalities, and other sociological classifications.

Or should *extend...*

Feminist science studies also lets – and again, demands – that we ask questions on another level about the nature of the knowledge produced. This includes (among many other things),

Representationally weak.

- an examination of the scientific *construction* of race and gender perpetuated by the perceived objectivity of the sciences[28,26,21]
- the deep paradoxes involved in the ab/use of women's bodies in pursuit of reproductive technologies[60,5]
- the shaping of science by gendered and racialized metaphors and languages,[42,48] and the historical complicity between scientific exploration and colonialism, misogyny, and racism (all at once, not as isolated variables)[36,59,63]
- challenging the artificial boundaries between "basic research" and nature/culture to explain a rapidly-growing scientific-industrial complex, and then linking basic research to community activism for women's rights and environmental movements.[69]

It asks us to look at science as a practice inseparable from culture, and what that might mean for knowledge and for scientists as the future producers of that knowledge.

1.5 WHY SHOULD SCIENTISTS CARE?

Because feminist science asks questions that are fundamentally geared towards addressing socialized inequalities in science, it can (and has) help scientists take those inequalities into account. Scientists (in theory) care about helping people. It can't help people if it's racist, misogynistic, and not considerate of how work will be ab/used downstream.

rewrite this? maybe with sources or more emotions

do they though? Still unclear, there's no fucking research

1.5.1 *The point of the thesis*

Scientists should care about where their work is coming from and where it's going, and we *need* good – read: concerned and activist –

people everywhere if we want social progress. This div is (hopefully) a road map and detailed exploration into doing (good) value-laden science. Figure out *how* to apply all of that stuff to everything else I care about: namely, open science, open neuroscience, molecular neuroscience and then write about what did and did not work.

2 SCIENTIFIC STRUCTURES

Here's the thing: science doesn't mean anything until you communicate it to *someone*. Facts only become facts when they're part of a communal decision; more practically, if you "cure cancer", there's not much point unless you get your acclaims, and start pushing your therapy out. The system that has evolved for scientific dissemination today is a network of journals, Internet communications, conferences, emails, and blogs; the rate at which scientific information moves within communities and between scientists and the "public" has increased dramatically, in both speed and scope.

The broad sets initiatives under the open science (OS) umbrella (of which I am a card-carrying member), share a point of view, in which the scientific ecosystem – that network of funding and publishing that underlies the production of knowledge – is suffering from serious problems in dissemination, reproducibility, and efficiency. They propose transparency, greater literature and scientific access, and technological innovation can 'fix' or alleviate those flaws, and improve science as an institution. The "fundamental goals" of open science include:

1. Transparency in experimental methodology, observation, and collection of data.
2. Public availability and re-usability of scientific data.
3. Public accessibility and transparency of scientific communication.
4. Using web-based tools to facilitate scientific collaboration.

Generally, those solutions and/or goals center around digitizing and opening the scientific ecosystem, implementing structures that allow for and incentivize:

1. open access publishing - namely, cost- and licensing-free to full-text published papers and research results
2. open data - publishing raw data pre- or concurrently with paper publication
3. open research - everything else, including, but not limited to:
    a) code distribution - code for analyses, model generation, etc. should be hosted somewhere accessible
    b) lab notebooks - tracing the entire research process with all dead ends and kinks included in an accessible (read: digital) form

There's also a hundred other subcategories on the fringes of those overarching categories new systems of distributed, ongoing, or otherwise "open" peer review; community discussion of publications, billed as an "online journal club"; altmetrics to re-allocate scientific credit away from impact factors towards diverse forms of knowledge transmission.

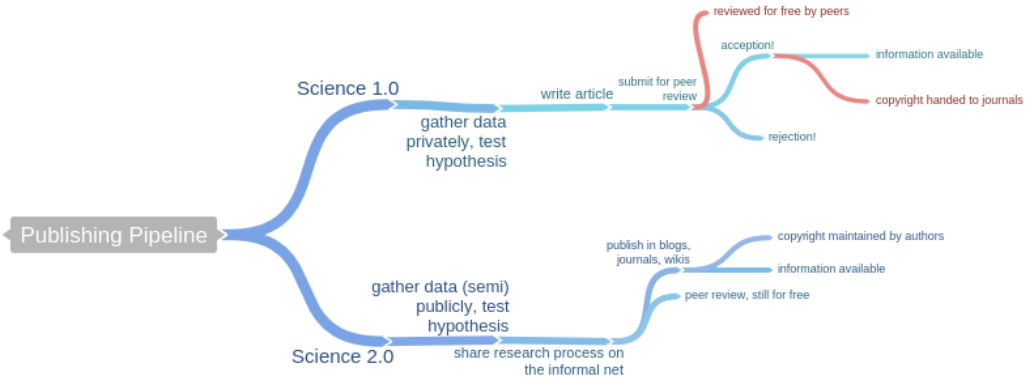


Figure 1: The "classic" current publishing pipeline

2.1 SCIENTIFIC COMMUNICATION WOES

Before we start talking about solutions, it makes sense to identify the problems. To some extent, the OS movement takes these as a given, and move straight to proposing the solution.

2.1.1 *The Publishing Pipeline*

Publishing in a scientific journal, as the main form of scholarly communication for much of modern Western science, is where most attempts to "fix" science start. The path of research to communication is long, torturous, and winding, requiring abridgement, careful scheming, overstatements of effects, prestige calculations.

rewrite publishing pipeline, history of journals

> "Scholarly journals have been at the heart of academic life since the publication of the *Journal des sçavans* and the *Philosophical Transactions of the Royal Society* in the middle of the 17th Century." -Parker 2013 [55]

current goals/what's accomplished w/ publishing

The modern journal article has multiple origin stories, reasons of funding or happenstance.

- In New Orleans, an opening for an asthma grant, so my PI applied to research asthma in the context of serotonin signaling
- an idea, late at night (Otto Loewi, discovery of acetylcholine)
- previously established work by a lab (routine and boring research)
- within the context of a greater project by the PI (re: translational neuroscience lab?)
- a happenstance observation; (see Charney et al., serendipity generally!)

Then, after project initiation, scientists collect data, run a set of multiply-envisioned on-the-fly experiments. They "make things work" until there's a data set with evidence for an effect ($p < 0.05$), or that they've successfully answered the question, hopefully with a yes.

rewrite how an idea becomes a paper to be FORMAL

Presumably, then you write the paper – introduction, background, results, discussions, methods, further directions for research – and submit it to a journal of your choice.

linking

Publishers act, although the boundaries are shifting in the digital age, as a clearinghouse and managerial stage. They don't produce the content, make the figures, or draw the conclusions in papers; Journals and their publishing groups provide, to varying degrees: a measure of typesetting and formatting, editorial work, and a distribution system.

although publishers do provide some *value*

Authors/labs submit a manuscript (*gratis*); publishers coordinate the peer review of said manuscript, shipping it out to 1-3 other academics in the field. Those academics review the paper, give feedback, and send it back – also *gratis*. During the months of the process, the submitting author can do nothing else with the manuscript (double submissions being verboten). Peer reviewers send it back with recommendations for publishing, the original writer makes revisions, and the journal agrees to publish it. The submitting lab pays a per-figure and/or per-page fee, signs away their copyright, and the journal takes the final work as its own. Then, those submitting and reviewing scientists pay to access the product of their intellectual labors, having given up the legal right to share that knowledge on their own accord.

find ref for current scholarly system

Pre-Internet, the cost of the journal was tied to the costs of printing and physical distribution. With that barrier out of the way, replaced by digital access, it's hard to see exactly how worthwhile the services of publishers are.

2.2 ACCESS & PAY WALLS

> Under the prevailing subscription-based system, commercial publishers own a monopoly over the distribution of scientific research. They charge authors for the publication of their works, then charge the readers subscription, advertising, and online access fees; in addition they retain the copyright of the articles they publish.
>
> 67

"Primary literature" is the holy grail of contemporary knowledge. 6 pages of double-column size 10 text in *Nature*, *Science*, or *Cell* represent the cutting edge of scientific research; the foundation for future work, and the hallmark of a great researcher.

I've been working from primary scientific literature since my first semester at Hampshire, but it was only a few minutes after my first Google Scholar searches that I immediately slammed up against pay walls to the papers I wanted. So did everyone else I knew. I've spent the past four years of my education begging for paper access from friends at UMass, in pharma, and at MIT.

Nature *is paywalled back to* 1867.

Let's be clear: If I did not have a very good friend at the Massachusetts Instiitute of Technology (MIT), the extreme breadth of sources at the

bottom of this paper would be reduced by at least half. * Even at MIT, there's numerous journals out of reach.

rewrite Data about access & paywalls here

A sense of outrage at these monetary barriers to research that is (a) publically funded and (b) all of the writing/production is done by uncompensated scientists.

Most studies in the U.S. and U.K (the strongholds of scientific research generally) are publicly funded research, in part or in whole. "Taxpayer dollars" fund, via the NIH, much of the high-profile, high-impact research that subsequently appears in journals. Taxpayers – your average layperson, or average scientists – then have to pay *again* for access to the produced knowledge, when they paid to fund it.[67]

The National Institute of Health (NIH) requires funded researchers to deposit after a period of time.

2.3 REPRODUCIBILITY AND RETRACTION

The principle of the elusive scientific method is replication and reproducibility. Researchers document their methods and results to such an extent that any other researcher is able to reproduce their data independently , or, more often, build experiments atop the results of their colleagues (replication).

Like the access crisis, however, there is a perception of a reproducibility crisis in science. Certainly the most high-profile beginning to the discussion was a 2005 article authored by John Ioannidis, provocatively titled *Why Most Published Research Findings Are False*. The paper outlined a statistical estimate on the likely false positive rate in the published bio-medical literature, an estimate eventually clocking in at >50%.[38] The publication caused (understandable) uproar, with a statistical "battle of the titans" ensuing that continues today.[32,39]Statistical debates aside, the gist of the conversations is clear: based purely on statistical considerations, one can expect a percentage of the medical literature to be a false positive (50% according to Ioannidis' calculations, 14% in Jager and Leek's calculations).[39]

find ref for more citations for battle post-Ionnidis publication

rewrite Brief sketch of statistical proof and discussion for falseness

This is not just theoretical number-crunching; the 'crisis' has an enormous business and opportunity cost. Biotech and pharmaceutical companies trying to monetize those discoveries demonstrate the practical scope of the problem. The rate of effective translation from basic research into clinical drug treatments has always been low, but the increasing costs of drug development and renewed focus on research reliability has prompted drug companies to join the conversation with data.

lol @ pharma and cultures of molecules/reductionsm with regard to increasing Food and Drug Administration (FDA) restrictions

The in-house target validation studies run by most bio-medical companies provide a unique data set on the reproducibility of bio-medical research. Amgen's researchers attempted to reproduce the results of 53 high-profile 'landmark' cancer studies over 10 years; results could only be recapitulated in 6 of the cases, an 11% success rate.[6] Researchers at Bayer tracked the fate of 67 validation projects; in 2/3 of the cases, the validation data was so inconsistent with the published literature that the project was significantly delayed, or more commonly, entirely terminated.[58]. At Bayer, this did not correlate with fields, experimental conditions, model systems, or journal impact – it's just that most research could not be reproduced at industrial labs.

Both sets of studies were largely based on oncology-directed data

This gets back to local biologies? But in the sense of localized non-controllable environments

To temper those sample sizes, two labs (in Berkeley, CA, and Boston, MA) collaborating on a Fluorescence Activated Cell Sorting (FACS) project, discovered that even with identical protocols, they had consis-

*Data forthcoming.

tently different results. In a laborious year-long process, the two labs (or rather, the primary researchers in both labs) isolated the difference in their experimental results to the speed of agitation at one step of the organ isolation process. While the results initially *seemed* irreproducible and incommensurable, their end conclusion was principically that biological research is at such a level of complexity that even minor changes from lab to lab in the microenvironment can "break" an experiment.[37]

RETRACTION We can explain away the lack or replication with varying degrees of success. Where the literature really gets into trouble is retraction – that is, journals and authors withdrawing published articles, articles that have already been deemed acceptable by peer-review and editorial mandate. Pulling an represents an enormous reputation cost to both journal and author; retraction often leads to firing (or mandatory stepping down) of the editor, and in the longer-term, a distinct downward trend in the citation rate of the author's former papers. Retraction is serious business for everyone involved, which makes the relatively increasing incidence all the more concerning. In 2008, Cokol, Ozbay, and Rodriguez-Esteban concluded that[†]

> "...in the period between 1990 and 2006, we found a significant increase (r = 0.55, p = 0.02) [in retractions]...From these observations, we conclude that retraction rates are still on the rise.
>
> Cokol et al.[15]

This trend begs for an answer, which is as of yet still in flux. Some propose the pressure to publish, increasingly important to funding and hiring decisions, hits researchers in a vulnerable spots – pressures to publish increase scientific bias[23]

> "[Two viable interpretations] The first interpretation implies that increasing competition in science and the pressure to publish is pushing scientists to produce flawed manuscripts at a higher rate, which means that scientific integrity is indeed in decline. The second interpretation is more positive: it suggests that flawed manuscripts are identified more successfully, which means that the self-correction of science is improving."
>
> Cokol et al.[15]

Intriguingly, and perhaps tellingly, not only are the rate of retractions increasing, but they're increasing in the journals we respect the most. In a 2011 *Infection and Immunity* publication, Fang and Casadevall found a "strikingly robust" correlation between a journal's "retraction index" and its impact factor (Figure 2). [25]

That might not mean the rate of fraud is increasing – rather, the rising retraction rate might actually be due to an increased awareness and responsiveness to misconduct, rather than increased misconduct itself.[24]

[†]Publishing in *EMBO*, a European journal, plausibly explaining why U.S. metric fiends hadn't caught on to it.

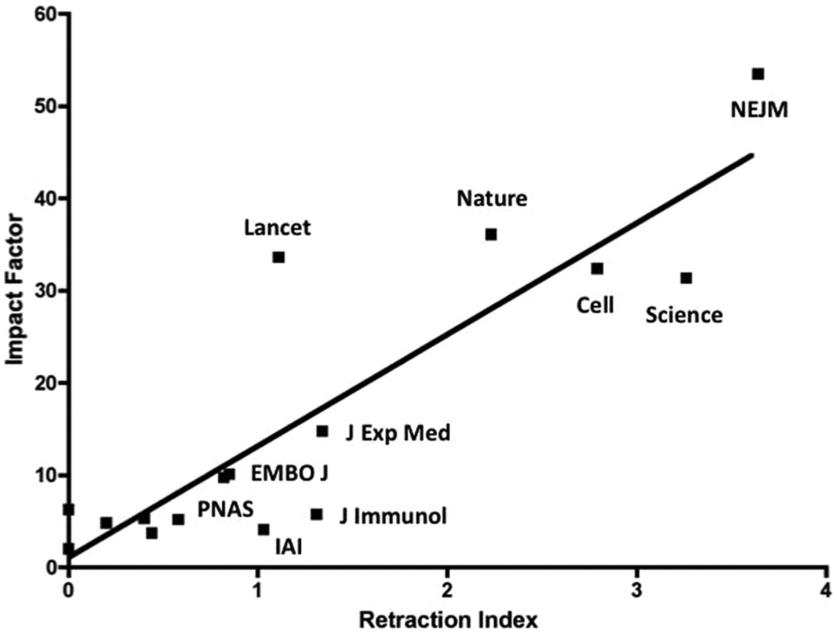


Figure 2: "Correlation between impact factor and retraction index. The 2010 journal impact factor...is plotted against the retraction index as a measure of the frequency of retracted articles from 2001 to 2010."[25]

Grieneisen and Zhang examined not just numbers of retractions, but *why* articles were being retracted. Of the 4,449 retracted articles found in 42 of the largest bibliographic databases from 1928-2011, retractions were due to:

47% alleged publishing misconduct‡

20% alleged research misconduct

stack to >100% because more than one reason is often cited

42% the usage of questionable data or interpretations

Of the alleged research misconduct, fifteen individuals accounted for >50% of the retractions. WhileGrieneisen and Zhang admit the growth in retractions by a factor of 11.36 deos exist (excluding repeat offenders, adjusting for literature growth), they assert that research misconduct of the fraud variety underlie most retractions; i.e. the retraction rate is likely due to social factors, not changes in rigor or intentional deception.[33]

Summary re: conflicting evidence ,but there is *concern*, which is more the point.

2.3.1 *Statistical Failures: Underpowered and Badly Analyzed Data Sets*

everybody is bad at statistics, our stuff is underpowered and selective etc., we don't report data so we can't actually check how much statistics are being done

> *Power failure: why small sample size undermines the reliability of neuroscience* –Button et al.[11]

‡Peer review and citation RINGS. People making up email addresses. What a fuckin' world.

> *Puzzlingly High Correlations in fMRI Studies of Emotion, Personality, and Social Cognition* (originally *Voodoo Correlations in Social Neuroscience*) – Vul et al.[72])
>
> *Willingness to Share Research Data Is Related to the Strength of the Evidence and the Quality of Reporting of Statistical Result*s – Wicherts et al.[75])

2.3.2 *File Drawer Problems, Negative Results, Publication Bias*

> Publication bias occurs when results of published studies are systematically different from results of unpublished studies... Empirical research consistently suggests that published work is more likely to be positive or statistically significant (P,0.05) than unpublished research [according to a cited 1993 study??].
>
> 18,41

What happens when something doesn't work? When do we keep pushing, and how do we say "*This* disproves our hypothesis"?An experiment that is *not* working that *should* work (with regards to the current literature) lays its blame on reagants, on the technical skill of those involved, on the time of year[§], as seen in – everywhere but the "science" (i.e. the realities of the world).A 1991 *Lancet* issue is usually cited as the first publicaiton to directly point at the issue. Easterbrook, Gopalan, Berlin, and Matthews reviewed a set of clinical research trials, concluding:[19]

> "Studies with statistically significant results were more likely to be published than those finding no difference between the study groups... Studies with significant results were also more likely to lead to a greater number of publications and presentations and to be published in journals with a high citation impact factor. An increased likelihood of publication was also associated with a high rating by the investigator of the importance of the study results, and with increasing sample size."

The tendency is ften called the "positive publication bias", but it's might be more accurately described as bias towards *interesting* results: a high-profile study refuting another high-profile study in a positive-negative loop is just as exciting as the first positive results were.[46]

The positive is not limited to clinical trials or the eternal scapegoat of psychology: animal research, and fields like ecology, molecular biology, and physics show a similar (if decreasingly prevalent) bias.

find ref for on statistics abuse inbiology, ecology, and physics. And math, if it exists? questionable

One effect of this is the file drawer effect: many studies in a given research area may be conducted but never reported, leading to a set of journal articles wholly unrepresentative of the actual state of affairs. An extreme example: if the null hypothesis is "true", but the 5% of studies that by *chance* show a statistical significance are published while the rest of abandoned data stays in a theoretical file drawer, useless to everyone but the carpenter ants.

The tendency towards significant results come from a combination of social factors and the inherent chance involved in testing biological systems. Scientists are extremely loath to submit a paper with

[§]Of course, the time of year *is* a meaningful factor, re: Otto Loewi and acetylcholine in frogs

negative results.[54] Journal editors, especially those in high-impact journals, are less likely to accept them. are more likely to recommend a positive-results paper be published, award positive-results papers better methodological scores, and are more critical and detect more errors in papers with non-significant results.[22] Negative results also garner more requests for additional data points and statistical analyses than identical papers with significant results.[62] Readers are less likely to be interestedinterested in hearing about therapies that *don't* work

According to Ioannidis, negative papers are most likely to be suppressed when:[38,78]

- studies conducted in a field are smaller
- effect sizes are smaller
- there is a greater number and lesser preselection of tested relationships
- there is greater flexibility in designs, definitions, outcomes, and analytical modes
- there is greater financial and other interest and prejudice
- more teams are involved in a scientific field in chase of statistical significance

Whatever the reason, the current journal system, the de facto dissemination system for scholarly production, is not representative of the research that's actually happening. Researchers may spend years trying to duplicate results, since the papers of failures to replicate weren't published. Meta-analyses, papers that use the entirety of collected data in a field to compare results, can only draw on the published data, which has a distinct bias towards significance.

2.4 IMPACT FACTORS & GATEKEEPING

> "Does the pressure to publish in prestigious, high-ranking journals contribute to the unreliability of science?"
> Brembs, Button, and Munafò

Citation is the metaphorical currency of science because it leads to real currency!

find ref for citation as currency of science

Nominally, choosing papers to read and base future work on is based on relevance and applicability of the literature. There is, of course, a deluge of literature, and it's nigh-impossible to keep up with the flow of information. One technique employed by scientific audiences in deciding where to invest their reading time is the prestige rank of a journal; similarly, when choosing which journal will be the most beneficial venue for their work, those same rankings come into play.

> "Most researchers acknowledge an intrinsic hierarchy in the scholarly journals ("journal rank") that they submit their work to, adjusting not only their submission but their reading strategies accordingly."[9]
>
> "The citation game has created distinct hierarchical relationships among journals in different fields."[78]

Presumably physics and plants as well, but it seems like Nature *mostly does bio? I have literally no idea*

Qualitatively, the top of the biology journal hierarchy is the *Cell*, *Nature*, and *Science* triumvirate; journals that are instantaneously recognizable and eminently reputable. To get a *Cell* paper is to be immediately taken a little more seriously. ¶

Quantitatively, the journal hierarchy is represented by the Journal Impact Factor (IF), calculated for journals by publishing house? mass-media company Thomson-Reuters, specifically their *Web of Knowledge* (WoK) citation network. The IF was originally proposed as one metric of many to track scientific productivity: a simple mathematical formula reflecting the number of citations of a journal's material divided by the number of citable materials published by that same journal. || 44

$$\text{Impact Factor} = \frac{\text{number of citations}}{\#\,\text{citable materials published}} \tag{2.1}$$

> "The original intention for the use of the impact factor was to allow comparison between the citation rates of journals... This has proven invaluable for researchers and librarians in the selection and management of journals." 44

That's all well and good, but like with many metrics, it's applied with a widening and indiscriminatory brush. IFs have evolved from one metrics of citation rates to one approximating journal quality overall, on the premise that a higher citation rate of papers indicates higher quality papers. 44From there, the journal IF serves as a marker of quality on individual papers and researchers. Eugene Garfield, the first one to describe an IF type system, considers these applications an abuse of a simple equation. Likely yes, but it nonetheless has serious consequences for the scientific ecosystem of research, hiring, grantsmanship, and publishing.

Metrics immediately lead to gaming the system.

2.4.1 *choose their acceptances*

> ... Editors make estimates of likely citations for submitted articles to gauge their interest in publication. 78

Journal editors and publishing administrators shape what we see and pay attention to; peer reviewers have to maintain impartiality when reviewing the make-or-break publication of their competitors.

Who thought this would go well?

Scientists, especially high-profile and competitive ones, choose carefully which journals they'll submit to. It's a game of saying is this research trendy *and* of high enough quality *and* an original idea *enough* to make it in this high-impact journal or another? A manuscript submission takes months and in the intervening time, the manuscript can't be sent out anywhere else. This means choosing a too high impact journal is a loss of months of publication time; but publishing in a less-cited journal can have serious consequences on tenure decisions, grant applications, and other administrative gambols.** It also sets up a

¶Sources are: my life, everybody's life, a lot of blog posts, general atmosphere. Like, if I see a *Nature* headliner, I'm more likely to be excited and impressed.

|| insert time (2 years) and other data

**There's a number of sources denying that IFs are specifically counted in any of these. But they're certainly powerful tokens in the scientific imaginary, from which reviewers of any kind are hardly exempt.

choice along the lines of relevance: should one publish in a high-profile, non-specific journal

> They powerfully discriminate against submission to most journals, restricting acceptable outlets for publication.

Moreover, impact factor trumps audience: while a field-specific journal might make your research more visible to people who could use it, it won't have the same on-paper look as a **CNS journals!** (CNS journals!) publication.

effects on the kind of research that gets done and accepted

2.4.2 *Fraud in High Impact journals*

> "What is obvious from this equation is that the impact factor depends crucially on which article types Thomson Scientific deems as "citable"—the fewer, the better (i.e., the lower the denominator, the higher the impact factor).
>
> . . . Because a journal's impact factor is derived from citations to all articles in a journal, this number cannot tell us anything about the quality of any specific research article in that journal, nor of the quality of the work of any specific author. These points become particularly evident by understanding that a journal's impact factor can be substantially affected by the publication of review articles (which usually acquire more citations than research articles) or the publication of just a few very highly cited research papers.
>
> The PLoS Medicine Editors 2006[70]

3 MOLECULAR PSYCHEDELICS

3.1 PSYCHEDELICS & PHARMACOLOGY

Culturally significant and an touchstone for identity at my (soon to be) alma mater, hallucinogens – psychedelic hallucinogens, drugs inducing a profound qualitative perceptual change – exist in the public and scientific eye as small molecules. They entered the modern scientific frame with with Albert Hoffman's 1938 synthesis of lysergic acid diethylamide (LSD) from ergotamine, a isolated compound from the rye fungus ergot and his accidental discovery, some years later, of the compound's ability to induce profound psychological effects.

In the years since Hoffman's synthesis and 'accidental' discovery, the broad class of drugs exemplified by LSD have been, variously: implicated in CIA coverups and brainwashing; a foundational symbol of counter-culture movements; effective treatment for alcoholism, obsessive-compulsive disorder (OCD), and depression; the inspiration for a number of scientific breakthroughs; as a field of battle for the rights of indigenous rights .

The current shamanistic traditions we know they come from – ayahuasca in the the past and present Amazon river basin, ergot-containing drinks for ancient Greek philosophers. etc.

originally plants and complexes

research native histories of drugs

The current manifestations represent a lineage of psychedelic use predating written history on all inhabitated continents: cave paintings in Europe[2], archeological evidence from the desert southwest of what is now Texas and Mexico[10,20], and more evidence woo

these drugs have been around a hella long time, and it's only just now that Western science/culture is beginning to treat them as a potentially meaningful therapeutic substance.

In my own experience and those around, they're either positively life-changing; or not. Some functionally similar signaling mechanism interacts with environment and person to crate this completely unique experience. Part of what's incredible about really any drug experiences is the alterning of how you think – it's a paradigm shift in the most literal sense of the word

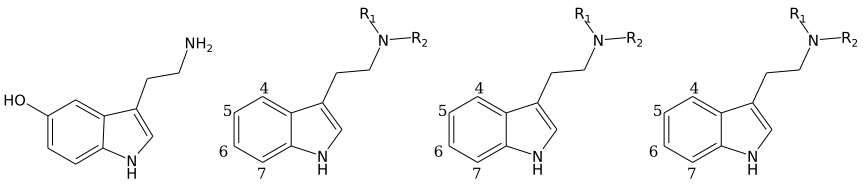
3.1.1 *A brief history of scientific psychedelics*

Discovered in Switzerland, underwent furious experimentation until they became a Schedule I drug (i.e. no medical usage and dangerous), and have recently started to re-emerge in the scientific literature at specific labs.

rewrite scientific history of psychedelics

3.1.2 *Consciousness-raising molecules?*

One small piece of the psychedelic puzzle is understanding what happens on a molecular level to induce both short and long term perceptual changes.



(a) Serotonin (b) Tryptamines (c) ergolines[[not actually] (d) phenethylamines [eventually]

Figure 3: Chemotypes of 5-HT$_{2a}$ agonists[52]

Of course, the single-cell and smaller level changes are only one level of the alteration in experiences, and only make meaning in the context of networks of neurons, brain regions, the body, and the environment.

but they're still cool and I still like them. Saying this but in academic language.

3.2 THE CLASSICAL PSYCHEDELICS

For the sake of simplicity, "hallucinogens" here mean serotonergic psychedelics

Serotonergic hallucinogens are classified according to their chemical structure, addictive potential, lethality or lack thereof, and the ineffable desire of humans to classify everything. They are non-addictive drugs, and users become tolerant after a single effective dose, and must wait some weeks before the drugs are effective again.They are biologically non-lethal, i.e. unlike other common recreational drugs methamphetamines or opiates, an overdose does not affect critical lower-level biological functions like breathing.

find ref for receptor binding affinity

too snarky?

rewrite for clarity

find ref for drug lethality

The drugs that fit these admittedly-fluid criteria are the classical psychedelics, the most well-known perhaps being the synthetic LSDLSD has natural analogues in psilocybin, produced by a genus of mushrooms; mescaline, produced in several species of New-World cacti; and among others.The chemical analogues are numerous and endlessly permeable; while most are used as hyper-selective 5-HT$_{2a}$ agonists, they have also percolated out as recreational drugs.

New World?

rewrite for clarity

rewrite hyper selective?

Chemically, they resemble the endogenous serotonin, and fall into one of three main chemotypes.Tthe tryptamines, which closely resemble serotonin, ergolines related to LSD, which can be considered to be rigidified tryptamines, and the phenethylamines (see Figure 3).[52]

should note somewhere that LSD is less popular than ever haha molly haha

is there space for anecdotal *voices here?*

Psychological Effects

write re: scales of consciousness

- wooieoeuoo pretty colors and stuff!
- non lethal, non addictive
- a qualititively different experience than day-to-day life; a "noetic" perception that the user knows isn't real to the external world, but accepted as 'real' to their internal life
  - "or teaches them an alternate reality"

per herb

- radical life changes (pollan article, end of life, terminal illnesses, compulsions, traumatic life events)
- but also not always? ~~~~~drugs~~~~

Why Receptors?

Biology's point of entry into molecule-body interactions starts with receptors. Cell-surface receptors bind the molecule and transmit a signal, or act as a channel to allow direct access to the intracellular milieu; alternately, signalling molecules diffuse through the cell membrane and then find intracellular receptors. Measuring and quantifying molecule-receptor interaction lies at the heart of pharmacology. I know this seems like an obvious statement/paragraph but it'll be cleaned up later and it's important to ME. #feminism

ignores transport of the drug to the brain, ingested, diluted and digested

rewrite this awkward sentence

All of the classical psychedelics share a binding affinity for the 5-HT$_{2a}$ receptor normally targeted by 5-hydroxytryptamine (5-HT). LSD and ergoline analogues also bind to some dopamine receptor subtypes and 5-HT$_1$ receptors, while a phenethylamine like 2,5-Dimethoxy-4-iodoamphetamine (DOI) binds seemingly exclusively to the 5-HT$_{2a}$ and 5-HT$_{2c}$ receptors. This shared affinity between the three classes for a single receptor subtype and the subsequent signalling pathways is well-established as the essential component of psychedelic signaling.s[31] (other citations later)

5-HT also has an affinity for the 5-HT$_{2a}$ receptor, but 5-HT hardly results in an alteration of the conscious state.

Drugs have different effects than the things they mimic! Amazing. But even cooler, different drugs have different durations and experiences. The user-reported differences between drug trips can then be explained at least with a model that relies on 5-HT$_{2a}$ activation, tempered by modulatory effects of dopamine and 5-HT$_{2c}$receptor activation.

Different experiential drug effects are attributed to differences in intracellular signaling cascades, as well as modulation by other receptors and neuron-neuron interaction.

consequence of this theory –> idea of a therapeutic "magic bullet"

According to classical concepts of pharmacology, different ligands should only modulate the *quantity* of a signal, but not the *quality*.[71] The 5-HT$_{2a}$ receptor receptor fails to adhere to said concepts: there is evidence for ligand-specific intracellular effects on second messengers, transcription factor activation, receptor de/sensitization, internalization, and recycling, among and other effects on the intracellular environment. In the case of the psychedelics, there are distinct *hallucinogenic* downstream effects in the form of transcriptomic "fingerprints"[30], and specific and preferential activation of second messengers[31,45].

find ref for the 100 other studies of these effects

Because biology focuses on the receptor-ligand interactions as the site of action, and downstream effects as the consequence, this is where we pick up. Our area of interest becomes very narrow: the elucidation of the intracellular signaling pathways activated by the stereoelectronic perturbation and conformational movement of specific amino acid residues at the shared binding site of psychedelic hallucinogens, ideally while maintaining the most *in vivo*-like intracellular environment possible. The grand goal remaining, of course, to explain how a small molecule can (sometimes) irrevocably shake loose long-held notions of self and meaning.

Receptors of interest address the 5-HT$_{2c}$, 5-HT$_{1c}$ and dopamine involvement

3.3 THE 5-HT$_{2A}$ RECEPTOR

Why the 5-HT$_{2a}$ receptor is implicated. Also outline the order of this section? 5-ht receptor, localization of receptor, animal studies...then neuroanatomy, then biased signalling?

maybe LSD as fundamental to discovery of serotonin/receptors?

In humans

There is an extremely strong correlation between 5-HT_{2A}R affinity and hallucinogen potentency in humans, as measured by subjective reports post-trip. 5-HT_{2a}R antagonists "ameliorate" (or reduce, mitigate, dampen) both the subjective psilocybin experience and block effects on a variety of neurophysiological measures. In positron emission tomography (PET) studies of binding, the intensity of a psilocybin experience directly correlates to the level of 5-HT_{2A}R occupation.

antagonists *ketanserin:5-$HT_{2A/C}$ risperidone:5-HT_{2A}/D_2*

differences between PET and fMRI re: Halberstadt and activation areas?

Unfortunately, the Schedule I status of most known hallucinogens precludes or severely restricts the human element of experimentation; research on the psychedelics is just now picking up[53,57]

in animals

Psychedelic studies in animals, one could argue, somewhat defeats the point of a consciousness-altering drug experience. Mice, rats, and rabbits can't report back on their changing views on life, the Universe, and everything; it's unlikely that they'll come to terms with their looming decapitation. That said, we can still decapitate them.

> "Importantly, although there are some exceptions, almost all the behavioral effects of hallucinogen studies in laboratory animals are mediated by the 5-HT_{2A} receptor... 5-HT_{2A} activation is sufficient to produce hallucinogen-like stimulus effects."[34]

by measurement of behavioral effects

In mice, rats, and rabbits, there are a few mostly-reliable behavioral proxies for hallucinogenic potential. Administration of drugs with known human hallucinogenic potential (typically LSD or DOI) reliably induce several behaviors.

Drug discrimination The most common animal model relies on training rats (and less often, mice or monkeys) to discriminate between a known hallucinogenic drug and a vehicle control; by pressing one lever or the other, the rat "tells" the experimenter "I think this was the training drug" or "I think this was nothing."[51] With this, animals can reliably discriminate between drug and control at low dosages that otherwise fail to elicit other overt behaviors; with a more sensitive set-up (drug-drug-vehicle), rats will also reliably discriminate between LSD and its non-hallucinogenic counterpart, lisuride.

But seriously, do you think rats try to keep it together?

Drug discimination is by far the most subtle of the responses; most of the rest require much higher doses of drug administration to elicit responses.

I know this is true for HTR, but maybe not the rest? research.

Head twitch response The head twitch response (HTR) consists of 5-11 shakes of the head (in mice) and trunk (in rats), like that of a wet dog. It is not hallucinogen-specific, inducible by 5-HT precursors and drugs that increase 5-HT release, but the HTR is reliably induced by hallucinogenic and reliably *not* induced by non-hallucinogenic 5-HT_{2a}R agonists.

rewrite differences between organisms in HTR

Prepulse inhibition of startle

> "Prepulse inhibition (PPI) refers to the phenomenon where a weak prestimulus presented prior to a startling stimulus will attenuate the startle response; PPI is often used as an

detail: or by blocking with ketanserin/antagonist simultaneously? think so, find ref

> operational measure of sensorimotor gating, and reflects central mechanisms that filter out irrelevant or distracting sensory stimuli."[34]

Interval timing Temporal perception is seriously disturbed by hallucinogens, as any recreational, spiritual, or lab participant could subjectively inform you. In rats and mice, temporal perception can be assessed, again, by training regimens of teaching rats to press levers after certain time intervals have elapsed, or in response to long- and short-duration stimuli. DOI affects performance in both types of trials, while 5-HT_{2a} antagonists rescue the DOI-induced loss-of-function.

find ref for subjective differences in time

ketanserin, volinanserin

exploratory/investigative behavior *nutshell:* measuring the quantitative and qualitiative spatial and temporal structure of activity (Behavioral Pattern Monitor, BPM) indicates hallucinogens induce neophobia and specific locomotive/exploratory effects; lisuride vs. LSD induce different behavioral footprints, and as per usual, 5-HT_{2a} antagonists reduce those effects.

rewrite exploratry/investigative behavior in animal models

differences in indoleamines and phenethylamine reaction in rats and mice?

tolerance studies

nutshell version: Ergolines, phenetheylamines, and tryptamines show intense and rapid cross tolerance (with the exception of DMT); this tolerance correlates with a significant decline in the density of 5-HT_{2a} receptors and desensitization of the receptors in transfected cell lines.

define desensitization/mechanism

3.4 NEUROANATOMICAL DISTRIBUTION

rewrite literally all of this section to be more concise and because I hate neuroanatomy

> "[The 5-HT_{2a} receptor] is expressed in regions of the brain believed to be involved in cognitive processes such as the prefrontal cortex, specifically in pyramidal neurons and interneurons. "[49]

3.4.1 *locus coeruleus*

role of the locus coeruleus; source of noradrenergic projections; responsive to (novel or arousing) sensory stimuli; HC enhance responsiveness such that innocuous stimuli drives response; response mediated by 5-HT_{2a}

3.4.2 *Prefrontal cortex*

in vitro Almost all prefrontal pyramidal neurons express the 5-HT 2A receptor, with the receptor localized primarily to the proximal apical dendrites.[16] Approximately 20-25% of the interneurons in the prefrontal cortex (PFC) express 5-HT_{2a}Rs mRNA, largely to be basket and chandelier cells.[34]

rewrite localization of 5-HT_{2a}Rs on neurons

> " Previous studies have shown that activation of 5-HT_{2a}Rs in this region results in a robust increase in spontaneous glutamatergic synaptic activity, and these results have led to

research relevance of basket/chandelier cells?

> the widely held idea that hallucinogens elicit their effect by modulating synaptic transmission within the PFC. Rather, they [our data] suggest that 5-HT_{2a}Rs facilitate intrinsic networks within the PFC. Consistent with this idea, we locate a discrete subpopulation of pyramidal cells that is strongly excited by 5-HT_{2a}Ractivation."[7]

rewrite with my very own words

write re: fMRI, PET data? human-level science, generally, in terms of activation patterns and interactions with other structures

in vivo

interactions with other structures

write interactions with other structures?

3.4.3 *Visual Cortex*

Visual cortex does stuff because visuals! but I haven't written about it yet

3.5 FUNCTIONAL SELECTIVITY & THE 5-HT_{2A}R

introduce terms of biased signalling/functional selectivity etc

3.5.1 *G-protein coupled receptors*

GPCRs are a extremely diverse class of heptahelical transmembranes signaling proteins, . Approximately 30-40% of pharmaceuticals target 7% of GPCRs[29]; as a class of proteins, they are prolifically expressed across cell types and species. Ligand binding to a the extracellular terminal of GPCRs initiates a conformational change in the protein that transmutes through the membrane to interact with a heterotrimeric guanine nucleotide-binding protein (G-protein) complex on the intracellular side.

The G-protein complex consists of a modular configuration of an α-, β-, and γ-subunit.[74] In the inactive receptor, all three subunits associate; the α-subunit maintains a bound guanosine diphosphate (GDP). Ligand binding induces a conformation shift in the receptor and consequently the bound G-protein complex In the classic model of signaling, this leads to the exchange of the α-bound GDP for guanosine triphosphate (GTP), followed by dissociation of the α-subunit and $\beta\gamma$-complex* from each other while remaining anchored to the membrane. They are free to diffuse laterally and initiate signaling cascades, until termination of signaling by the innate GTPase activity of the α-subunit. The resulting GDP-bound α-subunit re-associates with a $\beta\gamma$-complex to reform the G-protein complex. (See Fig. 4 on the facing page)

The classical model is complicated by lines of evidence that suggests activation can trigger a conformational change without subunit dissociation. However, even without that additional variable, the already established highly-modular structure of the G-protein complex gives it an immensely versatile psition; the subunit variations are crucial to tuning, modulating, and transmitting extracellular signals.

rewrite G-protein complications, also find ref

*The γ-subunit is extremely unstable alone, and is thus almost always found in and exerts effects as part of a dimeric $\beta\gamma$-complex.

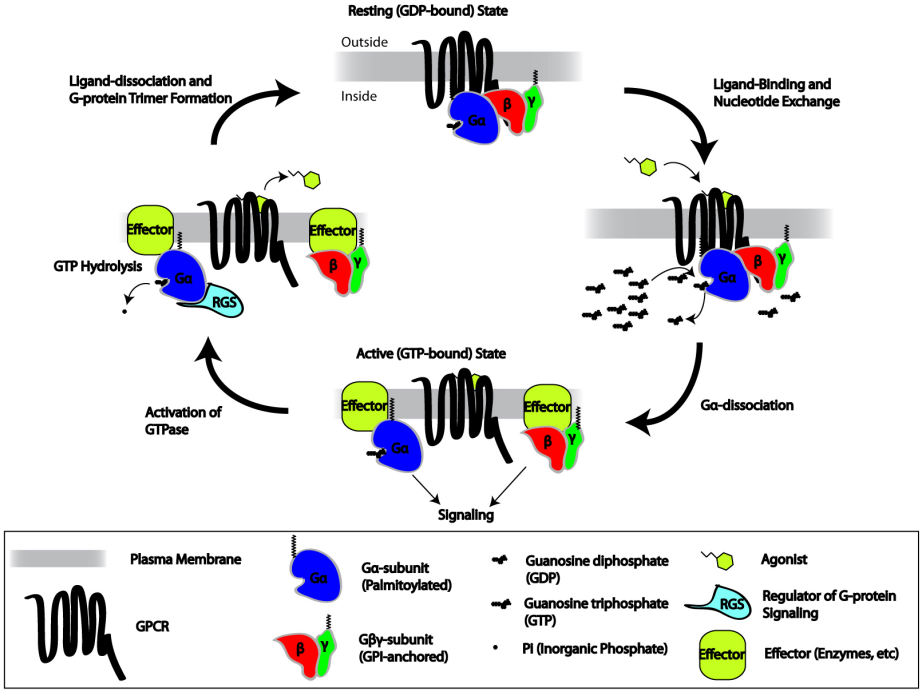


Figure 4: stole from Wikipedia, the general active-inactive cycle of GPCRs

α-SUBUNIT There are sixteen α-subunit genes, and for much of the research on GPCRs, the α-subunits were considered the active functional unit of the α-β-γ complex. The α-subunits that define the basic properties of a heterotrimeric G protein can be divided into four families, $G_{\alpha s}$, $G_{\alpha i}/G_{\alpha o}$, $G_{\alpha q}/G_{11}$, and $G_{12}/G_{\alpha 13}$.

more here probably, i.e. what the canonical couplings and functions are, but not in *too* much detail

βγ-COMPLEX The βγ-complex of mammalian G proteins is assembled from a repertoire of 5 β-subunits and 12 γ-subunits.[12]

and yet-undiscovered units

> "The βγ-complex was initially regarded as a more passive partner of the G protein α-subunit, thought only to act as a negative regulator. However, it has become clear that βγ-complexes freed from the G protein α-subunit can act as mediators of signalling in their own right."[17]
>
> "In the inactive state, the GDP-bound Gα subunit is associated with the obligate Gβγ dimer, which slows the rate of spontaneous GDP release by Gα acting as a guanine-nucleotide dissociation inhibitor."[12]

3.6 5-HT$_{2A}$ SIGNALING

3.6.1 *Canonical pathways*

The canonical α subunit: $G_{\alpha q/11}$

The 5-HT$_{2a}$R couples to $G\alpha_{q/11}$ and an unexplored βγ-complex.

> "The 5-HT 2A receptor couples to Gq and activates phospholipase C (PLC) signaling, resulting in the hydrolysis of

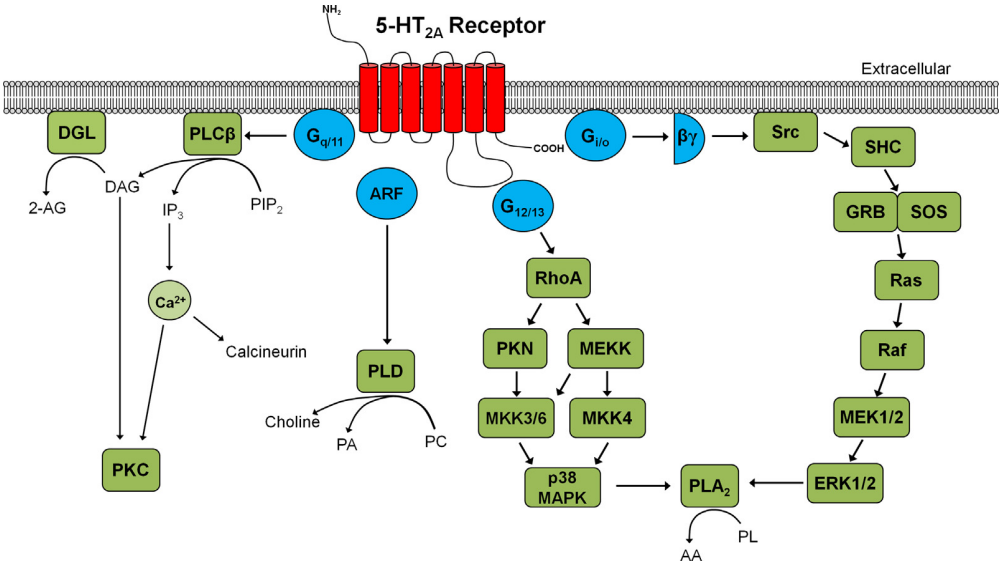


Figure 5: 5-HT$_{2a}$ pathways, fig 4 from Halberstadt, 2015[34]

> membrane phospholipids to inositol triphosphate (IP 3) and diacylglycerol,and mobilization of intracellular Ca $^{2+}$...
>
> There is evidence that 5-HT 2A is coupled to several non-canonical signaling pathways, including beta-arrestin-2, Src (potentially involving G i/o-associated G subunits), extracellular-regulated kinase (ERK), p38 mitogen-activated protein (MAP) kinase, phospholipase A 2 (downstream from ERK 1,2 and p38 MAP kinase), Akt, and phospholipase D (dependent on the small G protein ADP-ribosylation factor-1 (ARF1))". [34]

3.7 EVIDENCE FOR BIASED SIGNALING

The weight of evidence for the psychological effects of psychedelics implies activation of the 5-HT$_{2a}$ receptor is crucial; that does not explain how or why. While other receptors have a sort of tuning effect on the quality, duration, and intensity of the drug experience, 2aR activation is the "root note" of a whole chord of potential experiences.

While the interaction of different neurons and receptor activation are and the emergent properties thereof are worth exploring, I'm a molecular biologist, and we focus on single-cell effects. Of these, there's evidence that the direct intracellular cascades play a role in mediating hallucinogenic effects in the immediate response, in the duration of the trip, and in the longer-term psychological changes as measured by gene and structural changes.

transition to evidence at different levels for biased signalling's involvement. This WHOLE SECTION is quotes from abstracts because that's my writing process or whatever. Basically really drafty and I know that.

> The first is at the receptor/effector level. It has been demonstrated that some hallucinogens, such as LSD, activate different signaling cascades than 5-HT. For example, at the 5-HT$_{2C}$ receptor, 5-HT binding produces a strong phosphoinositide hydrolysis response, a rise in intracellular calcium levels and phosphorylation of the receptor itself. LSD pro-

duces robust phosphoinositide hydrolysis, however there is no concomitant rise in intracellular calcium and only limited phosphorylation of the receptor[49]

3.7.1 *Binding Events*

internalization & recycling

de/sensitization

"Waning responsiveness to continuous or repeated stimulation constitutes the phenomenon of desensitization, which pervades biological systems... Agonist-induced desensitization involves phosphorylation of G protein-coupled receptors by two currently recognized classes of serine/threonine protein kinases...

GRK-mediated receptor phosphorylation facilitates the binding of an inhibitory arrestin protein to the phosphorylated receptor, an event which substantially impairs receptor signaling."

downregulation of receptor production

structural regulation

"Taken together, the present work elucidates novel roles for PSD-95 in regulating the functional activity and intracellular trafficking of 5-HT 2A receptors and possibly other GPCRs."[77]

"The interaction of the 5-HT 2A and the 5-HT 2C receptor with specific sets of PDZ proteins may contribute to their different signal transduction properties."[4]

3.7.2 *Electrophysiological events*

3.7.3 *Signalling events*

second-messenger activation

"While lisuride and LSD both act at 2AR expressed by cortex neurons to regulate phospholipase C, LSD responses also involve pertussis toxin-sensitive heterotrimeric G i/o proteins and Src."[31]

"Alternatively, the reason why lisuride fails to recruit G i/o may have nothing to do with functional selectivity, and could be a consequence of its low intrinsic efficacy at 5-HT 2A."[34]

BETA ARRESTIN INTERACTIONS

"ß-arrestins are intracellular proteins that bind to heptahelical receptors and represent a point where such divergences in ligand- directed functional signaling could occur... we compared the endogenous agonist, serotonin, to the synthetic 5-HT_{2A}R hallucinogenic agonist (DOI), in mice lacking ß-arrestin-2, as well as in cells lacking ß-arrestins. In mice,

we find that serotonin induces a head twitch response by a ß -arrestin-2-dependent mechanism. However, DOI invokes the behavior independent of ß -arrestin-2.

The two structurally distinct agonists elicit different signal transduction and trafficking patterns upon activation of 5-HT_{2A}R, which hinge on the presence of ß-arrestins."[65,64,66]

receptor reserves

rewrite in your own words

"NIH3T3 cells stably expressing the rat 5-HT_{2a}R were used to measure agonist-induced pathway activation. We determined the potency and intrinsic activity of each compound to activate either the PLA 2 pathway or the PLC pathway. Furthermore, the data support the hypothesis of agonist-directed trafficking in NIH3T3–$5HT_{2A}$ cells because **structurally distinct ligands were able to induce preferential activation of the PLC or PLA 2 signaling pathway.** From these data we conclude that structurally distinct ligands can differentially regulate 5-HT_{2A} receptor signal transduction."[45]

NIH3T3: Swiss mouse embryo, hypertriploid karyotype

Transcriptomic signalling

"We also found that DOI, LSD, and lisuride each induced distinct transcriptome fingerprints in somatosensory cortex that were absent in 5-HT_{2A}R null-mutants".

mice, XY karyotype

Moreover, DOI and LSD showed similarities in the transcriptome fingerprints obtained that were not observed with the behaviorally inactive drug LHM. Our results demonstrate that chemicals acting at the 5-HT_{2a}R induce specific cellular response patterns in vivo that are reflected in unique changes in the somatosensory cortex transcriptome."[30]

HEKs human embryonic 'kidney' cells, XX karyotype

Morphological plasticity

Activation of the 5-HT_{2a} by DOI causes a transient increase in spine size in cultured cortical neurons[40]

karyotype not specified

3.7.4 *long-er term changes*

on what time scale?

Receptor modifications

"The receptor binding experiments suggest that phosphorylation of G 11 on serine 154 reduces coupling of 5-HT_{2a} receptors, whereas DOI causes down-regulation of 5-HT_{2a} in addition to the phosphorylation-induced uncoupling of $G_{\alpha 11}$ to 5-HT 2A receptors...

These data suggest that DOI causes phosphorylation of G q/11 in vivo and could thereby contribute to the desensitization of 5-HT 2A receptors."[68]

gene expression

Both single-doses and chronic administration lead to long-term changes in gene expression and plasticity in the mammalian brain[50,47]

3.8 MODEL SEROTONIN SYSTEMS

Those signaling pathways have been investigated in a variety of systems. This is by no means a comprehensive overview, but studies on hallucinogens have occurred in a number of different systems.

1. Humans: with psilocybin, LSD, and MDMA
    a) fMRI, EEGs,
    b) interviews of subjective experience
2. Rats: LSD + many other drugs
    a) global RNA extraction to look @ gene transcription
    b) staining to see receptor expression
3. primary neurons? (pretty sure)
4. Oocytes with mGlu & 2a receptors: LSD, lisuride, psilocin
    a) to study signaling & colocalization
5. CHO cells expressing a fluorescent 5-5-HT_{2a} receptor and variants

Obviously, 1 is the most full bodied "system", but we can't look at short term neuronal changes, and imaging studies have all the flaws of imaging studies.

rewrite neuroimaging sucks

2 has problems. Largely cost, and scale, and I can't use them at Hampshire, and it's harder to study specific receptors in specific cells on a tiny temporal basis.

3 are expensive and hard to maintain and dumb.

(4) and 5 both suffer from what seems to me fatal flaws – cells express different internal proteins and matrices. Undifferentiated cell lines won't have the same signaling pathways set up to receive signals from a receptor; what's the point in studying signaling pathways, receptor dynamics, or gene transcription in a set of cells that likely is incapable of accurately reproducing the full breadth of signaling pathways

3.8.1 *Frustrations with model systems?*

differences between mouse, human, and rat

3.9 PROJECT OUTLINE

1. Clone the receptor from rat cDNA into a plasmid that is also expressing a large fluorescent protein (GFP), an antibiotic resistance gene, and promoter region to force expression of the DNA.
2. Transfect HEKs to test expression of the construct, and then into P19 mouse stem cells
3. Induce neuronal-like differentiation into the transfected P19s, and see if the cell is capable of reconstructing a dendrite with localized serotonin receptors

3.9.1 *Why am I doing this @ Hampshire?*

Because I wanted to write a div about more than "just" science, I opted to work at Hampshire. Our money and our model systems are limited; I also won't be getting DEA approval, so I can't work directly with psychedelic drugs.

3.9.2 *Resources*

P19 stem cells, which are known to differentiate into relatively poorly-characterized neuron-like cells when cultured with a micro-molar concentrations of retinoic acid (RA).

The trick for us, however, is not just the production of neuronal cells, but neurons expressing the 5-HT_{2a}receptors, with the machinery of GPCRs fully intact and functional.

as far as cancerous, genetically manipulated, and traumatized rat cells can be "normal"

3.9.3 *P19s*

P19s are derived from embryonal teratocarcinoma cells, from behind the testes of XY-karyotype mice. They are immortal and easy to maintain, retaining pluripotency under normal cell culture conditions. With RA application and minor modification of culture conditions, P19s differentiate into central nervous system (CNS) cells, including glia, neurons, and fibroblast-like cells.[3] Studies of this differentiation pathway have elucidated a number of genes important for neural development,[73] and they're an established model system for exploring embryonic differentiation of neuronal cells.

3.10 A BRIEF HISTORICAL FORAY INTO OTHER KINDS OF USES???

Mayans and the Inca and merchant men, oh my.

4

RECONSTRUCTIVE NEUROSCIENCE

What I cover – or have done – with my year of Division III is specific to me. My interests in open access (OA) and open science comes from conversations about software freedoms and technology my first few weeks on campus; I started with psychedelics because they lay so cleanly at the intersection of my personal experiences and what biology can answer. I started with feminist theories and ways of (re) constructing the world with academic feminism because the disconnect between my labwork and the social movements that constitute our lives made a gap so great I thought I might fall into it.

These links are inherent to the particular shape and path of my life; they are an accidental and serendipitious collaboration of topics. The previous godawful pages is one way of slicing a knowledge system that prioritizes certain kinds of knowledge distribution and making, certain kinds of structural/layered analysis, and specific biological phenomena.

This chapter is more of a clean-up than anything new; ideally, the previous pages have both informed and consciously shaped that information flow. Gender is no longer an additional layer of analysis; it was always there. Access to literature and code were/are fundamental parts of writing this; who wrote my software and what choices they made, and what values they did/not consider have already shaped the rest of this piece.

4.1 PSYCHEDELICS AND ME (WOO)

Writing about psychedelics draws on two conflicting desires.

One — to be scientific, cite my sources, to draw entirely on clean-cut, statistically significant research

Talking about the subjective experience of psychedelics seems a slippery anecdotal path, unless I'm drawing on the qualitiative interviews and quantitative brain-imaging studies performed at the Vollenweider lab in Zurich, or the accounts of LSD and psilocybin as psychotherapy adjuncts at New York University (NYU) and Johns Hopkins University. To use sources from outside the peer-reviewed literature doesn't just feel academically unsound, it cuts at some essential notions I maintain about the necessary qualities of controls, peer review, and a sense of separation between experimenter and experimentees.

find ref for studies

two — acknowledge and *explicitly* draw on personal stories of drug experiences in a way the research literature does not

In reality, I've learned much more about drug experiences and the communities – and current usage – that surrounds them from the Erowid vaults, and from voluntary stories, and from conversations.

standpoint theory — seeing from the bottom is the "better" or more objective viewpoint. Correlates roughly to the "lived experience" of grassroots feminist organizing.

In the case of OA, even writers saying "Access isn't an issue" cannot convince me because for *me*, access is an issue – and knowing that means I am more prone to being critical and more qualified to provide counterpoints to statistical arguments with observations about behavior about me and my institution. An elementary application of standpoint theory, with regards to access.

But realistically, the underlying drive and much of the underlying research with psychedelics *isn't* peer reviewed. - I *know* that they can induce things, both good and bad, that are life shaping, and I *know* that drug-users are still in our world, they're just processing it differently. With that knowledge, gleaned from personal experiences and shared from others, is something I bring to case studies, lends support to discussions of addictions, means I can draw on flesh-deep knowledge to fill in the outlines made by science. but that's not something I can *say* in a scientific paper.

The *experience* of psychedelics is also, of course, not something that should enter Scientific Writing from a personal point of view; but just as familial or personal experiences with cancers inspire research into the biological underpinnings, psychedelic researchers don't just happen upon these drugs.

shame There's also a distinct feeling of shame, to some extent "Well, yes, I'm at Hampshire College, and I'm really interested in the biology of psychedelics, because wow, drug trips!" Interacting with drugs means tie dye prints and smoky dorm rooms, or out-of-touch artists and creatives. Psychedelics mean emotions and subjectivity; the personality of the user is closer to the surface than most sciences. Serious scientists should restrain themselves to less squishy areas, at least if they want to stay serious.

sharing experiences people want to share these experiences. Making LSD a primary component of how I introduce my interests has garnered incredible stories, of bad trips and good trips and revolutionary life-changing experiences. My circles are far from devoid of drug users; I do go to Hampshire. I regret not formally interviewing people about how they interact with drugs and incorporating those stories into this section. For better or for worse, drug use – and psychedelics specifically – have and continue to shape the people and relationships around me.

4.1.1 *Hallucinogens*

I'm a little conflicted about the relevance of this section, but I also am really *excited about it, and the possibilities for re-envisioning how I could do cultural molecular neuroscience.*

site of reductionism?

Psychotropic drugs have a rich and important history of spiritual and mental use in nearly every human culture. It seems that any and every culture has sought new insights and views with the help of native pharmacological agents. Although largely reduced now to their chemical structurein the labs funded by the NIH, most of the compounds derive from different cultural traditions. Peyote (active ingredient: mescaline)* has historically been used by the Native American church, a right they

*A comparison of the plant/spiritual context to the chemical structure should go here to demonstrate how we separate them out. With an analysis of the rights of traditional groups to use those drugs [re: NA church lawsuits], and also the danger of deforestation and environmental destruction to *traditional* methods of harvesting plants – making them only available with clinical approval – and chemical synthesis methods, which probably contribute to pollution and destruction.

successfully fought for in court. Ayahuasca (active ingredient: DMT combined with a monoamine oxidase inhibitor (MAOI)) is a traditional South American drug.

Talk to Otto's friend about his experiences? And access?

Source for ergot and historical significance

Locating drugs how presumptuous to take drugs from indigenous cultures and push them into the laboratory. Is plasticity and all of the signaling mechanisms relevant if the experience isn't included? Hallucinogens are notoriously sensitive to situation – or rather, individual interpretations of a situation. The quality (and thus long term effects) of a psychotropic experience is created through the *interplay* between environment and individual; like facts, it doesn't wholly reside in either, or even at the mere intersection. Trying to pull that out in a lab environment, is, as Fleck describes, not just a translation of information from one knowledge realm to another, but a full fledged transformation such that the ayahuasca in the lab is only nominally related to ayahuasca in (shamanistic) practice.[†]

4.1.2 *Colonialism, Women, and Western Knowledge*

Religion/Recreation Psychedelic use in Mexico was pushed down by the Spanish conquerors; it existed in small, isolated villages. In the 50s and 60s, the first (white, male, and then white, female) pilgrims from the United States made their way to isolated Mexican villages to first take drugs in the spiritual shamanic context, and then started using them recreationally, for days at time.

Now, ayahuasca experiences can be bought and sold in South America – which turns out to be okay, from an appropriative standpoint, because those services were always part of the indigenous economy. The Western/Northern feminist trope is to instantly assume indigenous businesses are violations, which seems like another recreation of the noble savage.

Women As per LondaSchiebinger's *Feminist history of colonial science*, women often held botanical and plant knowledge because of the distribution of gender roles. When colonialism showed up in the Americas and in Africa, the subsequent destructin and theft of that knowledge fell/was principally from *women*.

4.2 FEMINIST SEROTONIN STUDIES(?)

*****theoretically I think all of this should be included in the...serotonin section, bc embedded-ness? Phamarcology of serotonin/depression, 5-HT2a is affected by race/gender/socioeconomics/different & localized biologies******

4.3 TURTLES ALL THE WAY DOWN

"Neuroscience" as a discipline constructs a history tied to Galen and Aristotle and ancient Sumerian hieroglyphs,[1]. realistically, "neuroscience" isn't a discipline, but rather a heterogeneous mush of an extremely broad range of nearly unrelated subfields. That said, neuro-

Disciplines aren't real, basically.

[†]Anne Fausto-Sterling, and many others, talk about knowledge outside the academy – communal, social, and indigenous knowledges.

science, the field, was deliberately named, funded, and institutionalized to lie at the intersection of complementary disciplines – "interdisciplinary" from the start.[1]

4.3.1 *Interdisciplinary studies*

Need to define scientism/find description from Crit Neuro. Also page numbers.

- In *Critical Neuroscience*,Choudhury and Slaby[14] propose "interdisciplinary" as a code word for scientism(which I recall as being a bad thing)
- Situating the brain/cognition within a culture is an expanding trend (which I should be happy about). The large problem is that when "culture" and its importance are talked about in scientific settings, culture is a fixed quantity with Right responses. Hispanic medical patients require an interpreter; cases of Vietnamese epilepsy require a cultural translation between spiritual/traditional Vietnamese and doctors with curative drugs.
- Epigenetics – the metaphorical and physical incorporation of social effects into the genome, is a way of explaining what culture does for human development, creating a narrative of "soma to society". But incorporating social factors as a genomic part of humans also creates new "at risk" populations, making the epigenetic traces of historical marginalization into fundamental parts of those groups that need fixing.[43,56]

4.3.2 *Molecular and genetic reductionism*

"Reductionism" is a bit of a catch all term that I should probably explore more. The Western scientific traditions is entirely focused on reducing systems to their smallest working unit,, with the intention of finding out one "answer" and threading it into many other answers to form a kind of tapestry of knowledge. The reduction and simplification of systems roughly correlates with the notion of "pure" sciences, pure being perceived as better, "harder", and (incidentally, of course) more masculine. In the biological sciences, and in the neurosciences, reductionism is:

- generally a trend in the biological sciences – maybe due to perception of increased objectivity/hardness (a la physics and chemistry).
- Somewhat inherent to "neuroscience", since the ultimate goal is to reduce function/cognition to a set of circuits/cells/meaningful small and completely circumscribed/understood units.
- Where does it come from?
  - What goals are there and how does reductionism accomplish them for us? What is good and not good about applications to neuro? Can and should cell studies be used to "answer" or explore questions about cognition? What do we lose when we "solve" disease in vitro?
- Personalized medicine; or personalized neuroscience is still a way of reducing the individual to the cellular and genomic information, without accounting for personhood. Personalized medicine"

is not actually personalized; it's genomic. Relying on genetic information to give meaningful information about health care and responses is hardly specific to an individual's needs and abilities, as we'd like a feminist science to be.

4.4 INFORMAL AND FORMAL KNOWLEDGES

The re-introduction of psychedelics into the clinic is also paired with a systematic devaluing of recreational users, and a low-key but distinct disdain for traditional usages (at least in the formalized literature).

In reality, however, hallucinogens have amazingly well-documented and supportive informal communities. Taking psychotropics is, for many, a spiritual and deeply-prepared for experience. Users are often hyperaware of the chemical effects, interactions with medical conditions or other drugs, how to set scenes, how to guide their mental state in meaningful ways – in short, expert and specific knowledge more typically associated with discerning scientists than hippies in the woods.

But hippies in the woods may know a lot more about how to *use* those drugs than scientists who have never experienced them and treat them solely as tools in a molecular toolkit.

4.5 CONCLUSION

Div is hard but I guess okay in the end, also what will I do with the rest of my life?

Sorry, current reader, this doesn't exist yet <3

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