Psychedelics, population dynamics, and the generation of experience

Acknowledgements **4**
Prelude **9**
Chapter 1 ..... **15**
The mind manifestors 16
Psychedelic substances 20
The origins of research with serotonin and psychedelics 22
Serotonin in the brain 31
DOI and the medial prefrontal cortex 39
Theories of serotonin and psychedelic action 43
Some necessary intuitions 43
The role of serotonin 50
The effects of psychedelics 53
Chapter 2 ..... **58**
Contributions 58
Introduction 59
Materials and methods 64
Rig 65
Headbar implantation and catheter surgeries 67
Craniotomy surgery 68
Animal handling and habituation 69
Passive stimulation protocol 70
Ephys recordings and LSD delivery 71
Spike sorting 73
Analysis 74
Modulation index 74
Coefficient of variation 75
Fano factor 75
Lempel-Ziv complexity 76
Population dimensionality and entropy analyses 76
Linear Mixed-effects Models 78
Results 80
Single-unit analyses 82
Firing rate modulation 82
Variation metrics 88
Population dynamics and entropy measurements 94
Discussion 102

Firing rate modulation effects.....102
Effects of LSD on spiking rate variability.....106
Population analyses.....107
Limitations of the present study..... 110
Future directions.....111
Interlude.....117
Marian apparitions..... 118
Chapter 3..... 122
Abstract.....123
Introduction..... 123
Real, sensual, objects, qualities..... 125
És com l'espectre d'una flama morta.....130
Soon you will feel that your hand is starting to raise.....140
Generating experiences to meet expectancies.....150
Expectations, missing writers, inferred metaphors, and sociality... 160
The metaphor is like the ghost of a dead hypnosis..... 167
Chapter 4..... 170
Contributions.....171
Abstract.....172
Introduction..... 172
What?..... 176
Extrapharmacological modulation of psychedelic effects..... 176
How?.....184
Labels, pendulums, and neural circuits..... 184
The meaning response..... 186
The experience..... 190
The ability to control experience..... 193
Why?.....196
Alignment and current theories of hypnosis and psychedelics. 197
Psychedelics and phenomenological control through the lens of alignment..... 207
Psychedelics and alignment.....211
Conclusions..... 217
Chapter 5..... 219
Bibliography.....230

Acknowledgements

I must confess that I did not anticipate how overwhelming it would be to set out to acknowledge everyone who has in some way or another contributed to the completion of this doctoral thesis and to my PhD experience more generally. Over the last 6 years, I have interacted and been intellectually influenced by too many people to recount, so I will have to accept, much to my discontent, that this is gonna be an incomplete list.

I want to start by thanking Zach Mainen, who accepted me into his laboratory in early 2020, and who has been my supervisor throughout my doctoral work. Zach has allowed me to follow my curiosity with a degree of intellectual freedom that I will forever be infinitely grateful for, while also challenging me and opening my perspectives on many of the topics that I have engaged with during these years. I will always be intellectually indebted to him, as well as to his exquisite taste in putting together a fantastic group of people which has been incredibly enriching throughout these years.

I also want to thank Daniel McNamee, whose lab I joined in 2022, and who has been invaluable as a co-supervisor ever since. When Daniel joined the institution I was working on a project studying the relationship between serotonin and cognitive maps (not reported here), and his expertise on the topic of cognitive maps was life-saving at that time. He has since been an incredible mentor, offering guidance that I didn't know I needed, and providing much-needed positive reinforcement and encouragement which have exerted a profound positive influence in my experience of the PhD. He has generously shared his time and his curiosity, and has engaged with my work in ways that have deeply enriched it.

Peter Dayan was also incredibly supportive and provided me with invaluable guidance at the beginning of my PhD. He was very influential in my first project at the International Brain Laboratory (also not reported here), and guided me through the difficult process of settling on a project and becoming familiar with the literature: among other things, he pointed me towards Representational Similarity Analysis (RSA) and helped me get familiarized with this method, which was not only very intellectually stimulating but also central in my successful application for a PhD scholarship.

In that regard, I would also like to thank all the institutions that have supported me throughout my PhD. I want to thank the Champalimaud Research center, where I was accepted as a PhD student in 2019, and which has provided me with the security to embark on ambitious and creative projects, and with an incredibly enriching environment full of intellectual stimulation and avenues for collaboration. I also want to thank the NOVA University of Lisbon, the PhD-granting institution where I'm enrolled, and the Fundação para a Ciência e a Tecnologia, the Portuguese entity which granted me with a PhD scholarship in 2021, as well as the International Brain Laboratory (IBL) of which I'm a member since 2020. I would also like to take this opportunity to thank Francisco Clascá and Hiroki Asari, both of whom supervised me in my previous research projects, and without whom I wouldn't be where I am. Paco managed to infect me with his appreciation for the intricate neuroanatomy of the mouse barrel cortex, while being both supportive and open to my ideas during my project in his lab. Hiroki welcomed me in his lab and provided me with all the guidance and freedom that I needed in a critical moment in my career.

My doctoral trajectory would not have been possible without the countless interactions that shaped it with people from my two laboratories and from the research center at large. I want to start by thanking Guido Meijer, who generously taught me most of the experimental techniques that I know, trained me until I was proficient in doing every step required to perform electrophysiological recordings, and generously offered his help whenever I needed it. In that regard, I also want to thank Dario Sarra, Ines Laranjeira, Joana Catarino, Nicolás Gutierrez, Ana Fernandes, José Teixeira, and Romain Ligneul, all of whom taught me different surgical procedures and in some cases helped me throughout other experimental struggles. I would also like to thank Eric DeWitt, who provided me with high-level guidance throughout the crucial first months of my PhD and leading up to my grant application; Tor and Hanne Stensola, with whom I had many valuable conversations and who engaged with me in critical moments during my PhD; Cindy Poo, who played a crucial role in enabling me to pursue my experimental interests and provided me with much needed help and guidance in different aspects of my projects. I'm also indebted to Razvan Sandru, who suggested that I should write something for a certain call, which ended up being the publication that is now also part of this thesis

(Chapter 3), and who gave me some invaluable advice throughout the writing process.

I want to give a special thanks to Davide Crombie, with whom I have been closely collaborating since his arrival to the lab, and who has radically changed my experience of experimental work. While I've had the privilege of working along with multiple people in the lab, Davide has been the first person with whom I have actually shared a project, in which we are both interested and actively engaged. Collaborating with him is an absolute pleasure, he has given me invaluable advice as a more experienced researcher, taught me a lot about programming and analysis, and I look forward to continuing our collaboration. It was also a pleasure to work alongside Guido while doing IBL recordings, Jose during my cognitive maps project, Ines and Charline Tessereau in my RSA project, and Joana in the current LSD project, as well as sharing a space and interacting with some brilliant experimenters such as Laura Silva, Kcénia Bougrova, Elisabete Augusto, Fanny Cazettes. More generally, being part of two excellent labs in which I have felt comfortable and stimulated has been an incredible experience, and I also want to thank Alireza Tavanfar, Anne-Lise Saive, Charline, Scott Rennie, Magdalena Paluchowska, Quendera, Philippine Decaix, Lydia Fettweis, and Zuza Dedyk, all of whom have gifted me with interesting conversations and exchanges. I also want to extend a special thanks to Sofia Dias and Vitor Roriz, with whom I had the pleasure to interact during their stay at the institute and beyond, and with whom I had some very inspiring interdisciplinary exchanges.

I also want to thank the people from IBL with whom I've interacted throughout the years, while it will be impossible to thank everyone individually, I want to mention Ila Fiete, who helped me throughout my RSA project, and the current Staff members who have supported the psychedelic project that I'm presenting in Chapter 2: especially Steven West, who has provided precious support with all things histology, Florian Rau, who supported me with hardware and software issues during the hardest recording days of the project, and Olivier Winter, who has been incredibly available and supportive in all of my IBL work, and who has been actively interested and involved in my projects, contributing in invaluable ways, including in adapting the IBL spike sorting pipeline to accommodate my different recording datasets.

The experimental projects that I have engaged with rely on the work of myriads of people who I will also not be able to mention here individually. I want to thank all of the involved facilities and platform members, including Margarida Duarte, our colony manager, all members of the rodent platform without whom my experimental work would not have been possible, especially to João Pereira, Bruno Novais, Catarina Carvalho, Dolores Bonaparte, and Rute Marques, as well as the glass wash platform, the software and hardware platform, and the histopathology platform, all of which have contributed and supported my projects in one way or another. I also want to thank Teresa Dias and Penka Girginova, who have helped me with administrative procedures and eased the inevitable pain of bureaucracy.

My PhD would not have been the same without Giorgio Gristina, who has been an incredible classmate, labmate, friend, and intellectual companion, and who has inspired me and accompanied me both in academia and in life, and without Ines Laranjeira, who has also been an invaluable (double) labmate, friend, and intellectual ally, and with whom I've also enjoyed some of the best, endless, conversations inside and outside the lab. I have no interest in knowing how the last 6 years of my life would have gone without their friendship and unconditional support. I also want to thank the INDP 2019 class, with whom I enjoyed a beautiful first year of classes and rotations, and with whom it has been a pleasure to interact over the course of my PhD. Another special thanks goes to Neşe Devenot, whose work has been very inspirational: I've recently enjoyed some incredibly enriching conversations with them, and they generously provided guidance and support about my current dilemmas.

With that out of the way, I also want to thank my friends and family, who have been both a source of infinite support and inspiration, and the reason why these last 6 years have been bearable. I want to thank my mom, who has not only given me unconditional support and love, but also cultivated my curiosity and my drive since early on, always assuring me that I would manage no matter what, and always being involved and present; my dad, who has also always been there, not only cheering for me but also curious to understand what I'm interested in, and eager to participate in my life; and my brother, who is a Frankensteinian combination of a best friend, half of my genes, my partner in crime, my historical comrade, and my inspiration and advisor. I also want to thank my more extended family, both in Madrid and in

Alicante, with a special mention to my uncle Jaime Gosálvez and my aunt Mari-Cármen López, who took the time to steer me into the degree in Biology and who instilled in me the idea that understanding evolutionary theory is crucial for anyone doing research in life sciences, an idea for which I will forever be grateful. I also want to thank my uncle Fernando Castro, who convinced me that I should study a scientific discipline if I wanted to become a philosopher, and who was among other things a very stimulating intellectual influence early on.

Friends in my different homes have made me feel supported and understood throughout all my adventures in the last few years. I want to give a special thanks to Chiara, Dani, Tomi, Olmo, Claudia, and Amelia, all of whom know me better than myself, continually enrich my life, and have demonstrated to be reliable pillars in my life whenever I need them: all I can wish for is for them to find in me even a fraction of that support and unconditional love when they need it. I will also always be indebted to the inhabitants of the island that have been welcoming me since 1967, my experience of this city wouldn't be the same without them.

Last but not least, I want to thank Stephie, my companion in life. She undoes me in all the right ways, and without her this work wouldn't be what it is today. Together, we have traveled through some of the most beautiful and, at times, the most terrifying landscapes of experience generation. For that, and much more, this work is dedicated to her.

Prelude

"This modest complacency in receiving, or this sparingness in giving, does not, however, befit Science. Whoever seeks mere edification, and whoever wants to shroud in a mist the manifold variety of his earthly existence and of thought, in order to pursue the indeterminate enjoyment of this indeterminate divinity, may look where he likes to find all this. He will find ample opportunity to dream up something for himself. But philosophy must beware of the wish to be edifying."[1]

[1] Hegel, *Phenomenology*

At its core, the present work is structured around two different innovative contributions to the field of psychedelic research: first, results from an experimental project studying the effects of a psychedelic drug in rodents, and second, a set of philosophical and theoretical contributions to the field, centered on the extrapharmacological effects of these substances. While these may seem like unrelated contributions, I will argue that they are intimately connected: they can both be seen as additions to a growing body of publications urging for a critical reappraisal of the status of the field.

I will thus give a perspective of the current state of psychedelic research, specifically focusing on these two interrelated dimensions which I believe deserve urgent attention. Hopefully, this panoramic of the field will underscore the complex nature of psychedelic effects, hinting at how the simplicity of some contemporary theories about the topic may be more symptomatic of our collective desire to understand these substances (and in some instances, to profit from them) than it is of our actual understanding. I will also argue that part of the reason why psychedelic effects are so difficult to conceptualize may be that they seem to influence our ability to transform our beliefs and expectations into lived experiences, which complicates their study in multiple ways. These goals will drive the trajectory of the current work, which can be roughly mapped as follows:

Chapter 1

A general introduction

In the introductory chapter, I will give a brief historical and conceptual overview of the field of psychedelic research with special focus on events and concepts that will be instrumental to

illustrate the points that I mentioned above. The aim of this section is not to provide a comprehensive review of any particular topic (in some instances I will point to such resources for those who may be interested in digging deeper).

I will use the recounting of the history of psychedelic and serotonin research to highlight the following points. First, that the research in these two fields has always been intertwined. This may seem superfluous, but cross-talk between these two fields is sometimes lacking, and can easily lead to avoidable pitfalls, which leads us to the second point: that the name 'serotonin' itself indicates the crucial role of this substance in modulating vascular tonicity. Again, this may seem irrelevant, but an important portion of the human psychedelic research edifice stands on the shoulders of imaging techniques that rely on blood-flow measurements as proxies of neural activity, a foreseeable methodological limitation with consequences that have only recently been systematically investigated.[2] Third, I will emphasize how certain ideas which have been absorbed into modern theories of psychedelics have been present in one form or another since the very inception of the field, calling for stricter scrutiny of their validity. Fourth, I will introduce the relationship between psychedelics, suggestibility and placebo effects, which was also present since the early days of scientific inquiry into these substances, and which is, in my opinion, far from being fully understood.

I will then do my best to provide some basic theoretical concepts to facilitate the comprehension of some contemporary theories of serotonin and psychedelic action. Hopefully, this

[2] Padawer-Curry, *Psychedelic*

chapter will give a good general sense of the complexity of the serotonin system and of its modulation by psychedelic substances, thus providing an appropriate context for the rest of the chapters.

Chapter 2

LSD and population activity

The second chapter will contain some early results from an experimental project centered on studying the effects of LSD in the mouse brain. With high-throughput electrophysiological recordings, high-resolution, high-speed video recordings, and a visual stimulation protocol, we are combining state-of-the-art technologies and approaches in order to interrogate the effects of these substances on neuronal activity in an unprecedented way. Speaking to the complexity of these drugs, we will highlight how the patterns elicited by LSD are not clear-cut, showing complex area-specific effects instead of the high-level, unidimensional modulations of brain activity that some theories propose.

These results highlight the complexity of psychedelic drug effects, and should add to the growing list of calls for caution regarding over-simplification, over-interpretation, and reductionism in the fields of serotonin, psychedelics, and antidepressants research.[3] This chapter will only focus on rodent results from this project, and it's not directly connected to the suggestibility considerations made in the following sections, beyond the fact that those will also highlight certain problematic dimensions of the current state of the field.

---

[3] Hidalgo Jiménez, *Electrophysiological;* Möller, *Is the serotonin;* Drummond, *Navigating;* Devenot, *TESCREAL;* Okay, *Embracing;* Meling, *Mind;* Smausz, *Neural;* Jensen, *Active;* Turner, *Selective;* Hieronymus, *Control;* Laursen, *Impact;* Moncrieff, *What does;* Devenot, *The psychedelic*

Chapter 3

Hypnosis, aesthetics, and sociality

Chapter 3 can be found online as a published standalone philosophy paper.[4] This chapter focuses on the concept of 'phenomenological control', a theoretical framework emerging from the field of hypnosis research. One of the obstacles experienced by anyone approaching the field of psychedelic research is the coexistence of multiple theories and narratives around concepts such as *beliefs, priors, internal models, meaning enhancement,* or *suggestibility,* which have separate but intertwined histories and conceptual backgrounds. While some authors do a better job than others at giving operational definitions of these terms, it is generally difficult to form a general understanding of the field and of how these different concepts interrelate.

With no aspiration to provide the ultimate unifying theory of psychedelics, this chapter will hopefully give some useful definitions and serve as an introduction to the concept of phenomenological control, which will be proposed in the following chapter as a new conceptual lens through which to interrogate the nature of extrapharmacological effects in psychedelic drugs.

Chapter 4

The 'what', 'how', and 'why' of psychedelic extrapharmacological effects

In Chapter 4, I will use the concept of phenomenological control to unify some research threads concerned with extrapharmacological effects of psychedelics. I will first give a general overview of the

[4] Arlandis, *Hypnosis*

different ways in which such effects have been characterized, and propose phenomenological control as a conceptual framework to put these into perspective. Then, taking advantage of the possibilities of this framework, and in light of some of the ideas presented in the previous chapter, I will suggest some alternative ways in which psychedelic drugs may be modulating phenomenological control. Lastly, I will introduce the idea of 'alignment' as a normative hypothesis to situate these effects, with the main objective of highlighting some silent assumptions that are common in the field, and which I believe should more actively be scrutinized (e.g. the assumption that brains evolved, exclusively or predominantly, to perform optimal inference).

Chapter 5

Conclusions and discussion

In this brief final section, I will provide some closing remarks and a high-level wrap-up of the work developed in the previous chapters.

Chapter 1
A general introduction

The mind manifestors

> My thesis is that the psychotomimetics have a large place to play in psychiatry. [...] It is absurd then to label them generically psychotomimetics. I make several suggestions, have you any other ones? If you have please send by air express [...]. The name should have a clear meaning, be reasonably easy to spell and pronounce and not be too like some other name. Psychophrenics had to be abandoned and so did psychoplastics. Psychorhexics and psychohormics are doubtful. So far psychodelics-mind manifestors seems the most promising, psycholytics-mind releasers is doubtful because lysis in medicine is now associated with dissolution rather than release. Euleutheropsychics, though accurate and euphonious is too much of a mouthful. Psychodelics seems unambiguous, not loaded with old associations and clear.[5]

This passage was written by Humphry Osmond, the British psychiatrist who coined the term 'psychedelic', in a letter sent to Aldous Huxley in 1956. The neologism was formed by joining the Greek words *psykhē* (mind) and *dēloun* (make visible, reveal, manifest), and it remains the most widely used term for these substances to this day. The idea that psychedelic drugs have the capacity to expose the secrets of the mind was popular then, and it has remained popular until today, both in underground psychedelic culture and in the scientific field of psychedelic research. In a sense, this thesis can be thought of as an exploration of the question: to which extent has research with psychedelic substances improved our understanding of the mind?

I believe that psychedelic substances can be a great tool in the quest for understanding the intricacies of brains and minds from a neuroscientific and psychiatric perspective, and I will mention some

[5] Bisbee, '*Psychedelic*', 262

ways in which they have already been used successfully in that way. I also believe that one of the clearest conclusions that emerge from looking at the history of psychedelic research is that we have since the beginning of this scientific field invested these substances with our hopes and wishes for them to be a turning point in our understanding of the human psyche.

The psychedelic field is somewhat unique in that it reunites some contextual factors that rarely coincide in other fields of research: they have a very substantial presence in our collective imaginary, the main outcome measures in clinical trials are often subjective in nature, and their recent boom in popularity has turned the attention of big investors towards the field,[6] introducing a dimension of economical interests into the research[7]. This combination of factors may be particularly problematic if we consider the possibility that one of the main effects of these substances could be that of increasing suggestibility, as will be discussed later on.

At the time when the letter above was written, 'psychotomimetics' was the most common label utilized to refer to this class of substances, alluding to the alleged ability of these substances to induce psychosis-like states in subjects. In this passage, Osmond argued that these drugs would have a much larger role to play in psychiatry, and asked Huxley to help him out in deciding which new term to coin in order to substitute this, in his view, outdated and inadequate one. The letter then goes on with Osmond explaining to Huxley his progress in writing a paper about these substances:

---

[6] Ioannidis, *Why Most;* Most factors proposed by that article as leading to decreased likelihood of a scientific finding being true apply to most research with psychedelics: small studies, small effect sizes, vague outcomes, great financial interests, extremely popular field…
[7] Devenot, *TESCREAL*

> After renaming them I end by 500 words of shewing the part which they must play in changing our outlook on the world. I use here the idea that in a rapidly changing world the assumed perceptual framework may not be inconvenient, but actively dangerous. We dare not allow this fiction which is in part a social construct exert the tyranny which it has done in the past. We have got to develop a social psychology of change. It seems likely that love, charity, compassion are the only real transdimensional factors which will transcend sociological and dimensional barriers. It means in effect that we have to exalt the mystic's intuitions as being vitally necessary tools for our survival. So clearly have the[y] put these things that their instructions almost amount to blue prints. Blue prints in the hands of apes!
>
> I end: "The psychodelics which we possess will one day seem as crude as our ways of using them yet even they can help us to extend our experience far beyond our present ability. Whether we use them for good or for ill, whether we use them with skill and deftness or with blundering ineptitude, depends not a little on the courage, intelligence and humanity of many of us here today. Have we a chance to assist *homo faber*, the cunning, foolhardy tool maker, merge into that other creature whose presence we have so brashly presumed, *homo sapiens*, the wise, the understanding, the compassionate."[8]

Here, Osmond reveals some of his beliefs about the potential of psychedelic substances beyond having 'a large place to play in psychiatry'. These beliefs have undoubtedly influenced the trajectory of the field thus far, and I think it's important to keep in mind that they pre-date all modern studies with psychedelics. If we want to develop a rigorous scientific understanding of psychedelic drugs and their effects on humans, we should strive to continuously question our beliefs and

[8] Bisbee, '*Psychedelic*', 262

stay alert to the ways in which we may be distorting reality to fit into our preconceived ideas or intentions.

When discussing modern theories of psychedelic action later in this section, we will explore the REBUS model and the 'cognitive flexibility' framework, which are very much still alive in the psychedelic field, and which go in line with Osmond's conviction that psychedelics 'must play a part in changing our outlook on the world'. We will later discuss how, contrary to these long-held beliefs, the possibility is now emerging that the opposite may be true: psychedelics may *reinforce, amplify,* and *perpetuate* our views about the world. According to the 'strong priors' theory of hallucinations, for instance, this may be one of their central mechanisms of action.

Osmond's remark about the possibility of using these substances for good or for evil seems particularly timely nowadays, when the overall narrative pendulum of psychedelic research seems to be leaning towards an optimism that could be harmful in certain ways: not only have concerns been raised regarding the lack of information and research concerning the adverse effects of psychedelics[9], there are also growing concerns regarding the harms that may result at wider socioeconomic scales[10].

To what extent have Osmond's ideas been confirmed over the last 70 years? Is it still true that the word 'psychedelics' is not "loaded with old associations"? Which of Osmond's ideas are actual properties of these substances, and which ones are just beliefs being projected onto them? These are some questions to keep in mind while reading the following chapters.

But before that, let's take a step back. What are psychedelic substances, really? What do we know about them? In this section we will

[9] Evans, *On Minimizing;* Meling, *Mind*
[10] Devenot, *The Dark*

take a panoramic view of the current state of the art in psychedelic research. Because the so-called ‘classic psychedelics’ all share an affinity for certain serotonin receptors, and because research with psychedelics has always been intertwined with our understanding of the serotonergic system, I will use this introduction to give a glimpse at the history of these two fields and the complexity of the underlying biology.

The intention of this introduction is not to give an in-depth course on the neuroscience of serotonin and psychedelics: when appropriate I will point to the abundant resources that exist for those who wish to delve deeper into these topics. Rather, I will use this introduction to draw a birds-eye view of some historical topics that I consider to be relevant to understand the field today, as well as to give a general sense of the serotonergic system and the physiology of psychedelic drugs in the brain, which I believe will be important in order to contextualize some of the most popular contemporary theories in the field.

Following this introductory chapter, in **Chapter 2**, I will present the results from an experimental project centered on the effects of lysergic acid diethylamide (LSD) on the activity of populations of neurons throughout multiple structures in the mouse brain. After that, **Chapters 3 and 4** will focus on the topic of suggestibility, which I believe is understudied and misunderstood (albeit crucial) in the field of psychedelic research.

Psychedelic substances

Psychedelics are a heterogenous class of substances characterized by their ability to cause profound acute alterations in subjective experience in humans. They are sometimes divided between ‘classic’ and ‘atypical’, with the classic psychedelics always presenting some level of direct agonist activity in different serotonin receptors. The

2a serotonin receptor sub-type (5-HT2AR) has been identified as being particularly relevant for the subjective effects of these substances.

Many of these molecules are found naturally in fungi, plants, and animals, while many others can only be produced in a laboratory. There are recorded uses of psychedelics by humans dating back thousands of years, and a multitude of known cultures in which psychedelics played or still play a central role in ritualistic practices[11]. Scientific interest in these molecules has existed since at least the early 20th century. While initially they were often considered merely as a possible experimental tool to induce 'chemical psychosis', interest in their therapeutic potential has increased, perhaps climaxing over the last decade in what has been referred to as the 'psychedelic renaissance'. Currently, they are being researched as treatments for depression and other anxiety disorders, substance abuse, post-traumatic stress disorder (PTSD), and other conditions.

It is important to note that, from a chemical perspective, the term 'psychedelics' doesn't refer to one structurally well-defined class of molecules, but rather it refers to at least two, usually more, classes of molecules, depending on the authors and their operational definition of the term. While most authors agree in grouping 'classic' psychedelics (LSD, psilocybin, DMT, Mescaline, 5-MeO-DMT, and others) together and as coming from the chemical families of tryptamines, phenethylamines, and lysergamides, some authors consider MDMA, Ketamine, Ibogaine, or Salvinorin (which don't belong to those families) as 'atypical' psychedelics.

---

[11] While it is tempting to make up for the tendency to erase indigenous and countercultural wisdom from modern psychedelic narratives by bringing our attention to those, we will limit the scope of our analysis to the history of scientific research with these substances, which we believe is the immediate context necessary to understand some of the critiques that will be presented later on. Devenot, *Dark Side*

Given that serotonergic activity seems to be crucial for both the acute subjective effects and the long-term therapeutic effects of psychedelics, understanding how these molecules affect the brain will likely go hand in hand with developing a deep understanding of the physiological functions of the serotonergic system, a highly complex neuromodulatory system which has posed significant challenges to researchers studying its functional roles. Because of its central role in understanding psychedelics, we will go through some basic aspects of the serotonergic system and its scientific history alongside that of psychedelics. This will serve as context when considering the current state of research on psychedelics. We will start by discussing the origins of serotonin research, which were intertwined with research on psychedelics from early on.

The origins of research with serotonin and psychedelics

The term Serotonin was coined in 1948[12] by a team of researchers that had set out to study the biochemical factors involved in the etiology of hypertension. It had been known for a long time that upon clotting of blood, a substance would appear that had vasoconstrictive properties. Led by Irvine Page[13], at the time the Director of Research at

[12] Rapport, *Serum*

[13] In his book *Serotonin* from 1968, Page described having some conflicting feelings about their discovery of Serotonin. While it catalyzed his success as a researcher, he felt that it did not bring him closer to developing treatments for hypertensive patients. In the book, he made some interesting statements, such as “Thus, the past 20 years have been extraordinarily productive, resulting in thousands of papers (on serotonin), and even a great deal of valuable information”, ”I noted that serotonin had replaced epinephrine as a sure road to tenure for the pharmacologist”, ”The great variety of suggested roles (for serotonin) can be said to be a tribute to man’s ingenuity and his unquestionable willingness to write papers”, or ”Clearly, this field has fallen heir to the current disease of science—too many journals, too many meetings and too little worth

the Cleveland Clinic, and spearheaded by the organic chemist Maurice Rapport and the biochemist Arda Green, the team initially set out to discover endogenous factors that could contribute to the development of hypertension, and for the first time in 1948 reported the discovery of Serotonin. Later on in that same year, when describing the crystals they had isolated from blood serum, Rapport would write: “we would like provisionally to name [it] serotonin, which indicates its source is serum and its activity is one of causing constriction.” [14]

Later on, I will discuss how the meaning of the word Serotonin itself highlights an important limitation in our ability to study Serotonin and serotonergic agents in humans: results from studies using functional magnetic resonance (or any other technique that measures blood flow as a proxy for neural activity in the brain) are confounded by the ability of these molecules to bind to serotonin receptors expressed in blood vessels and cause vasoconstriction[15].

It was only in 1949[16], while Maurice Rapport was working in his new position in Columbia University, that the chemical structure of serotonin was determined to be 5-hydroxytryptamine (5-HT), and in 1951 it was synthesized for the first time in a laboratory. In 1952[17], it was determined that a compound discovered by the italian pharmacologist and chemist Vittorio Ersparmer in 1935, originally named enteramine, was chemically identical to serotonin. In that sense, the first researcher to discover serotonin was Ersparmer, who was interested in how certain amines found in the skins and intestinal tracts of a variety of species had

---

talking about.” His dissatisfaction with the field of Serotonin research is symptomatic of the difficulties that have plagued this literature since its origins. Even today, results in the field often seem contradictory, and despite repeated modeling efforts the Serotonin system is still not as well understood as other neuromodulatory systems.

[14] Whitaker-Azmitia, *The Discovery*

[15] Padawer-Curry, *Psychedelic;* Padawer-Curry, *Investigating*

[16] Rapport, *Serum* (2)

[17] Ersparmer, *Identification*

the ability to induce contractions of smooth muscles. He first discovered enteramine when studying the ability of an acetone isolate derived from enterochromaffin cells (enteroendocrine/neuroendocrine cells, i.e. specialized cells found in the intestinal tract which receive neuronal inputs and induce the secretion of certain hormones into the bloodstream) of the gut to induce the contraction of smooth muscle in rat uterus.

As it turns out, 90% to 95% of Serotonin in our bodies is estimated to be produced by enterochromaffin cells in our gut, which likely explains why it was first discovered in the gut, and why it took 18 more years for it to be found in the brain [18]. For a long time, it was considered that enteric serotonin could not affect brain activity, and that these two serotonin systems would be functionally isolated, due to the inability for serotonin to freely cross the brain blood barrier (BBB). However, different research threads point at multiple ways in which enteric serotonin and central nervous system (CNS) activity are connected[19], for instance, through the influence of microbiota on precursor metabolism which can affect central serotonin levels, through serotonin's role in the enteric nervous system, which interacts with the CNS in multiple psychiatric disorders[20], or through the Vagus nerve, which upon signaling from gut-derived serotonin has been shown to modulate the activity of structures in the central nervous system such as the nucleus tractus solitarius (NTS), the dorsal raphe nucleus (DRN), or the locus coeruleus (LC)[21].

It was only in 1954 that serotonin was first reported as a neurotransmitter. Betty Mack Twarog, a researcher at Harvard who was interested in certain properties of mollusc muscles and in how these

[18] Twarog, *Serotonin*
[19] Del Colle, *Novel*
[20] Chen, *Regulation*
[21] Hwang, *Interaction*

could be modulated by neurotransmitters, demonstrated that serotonin was the neurotransmitter they had been trying to identify while studying the relaxation of muscles in the edible mussel, *Mytilus edulis*. By the time these results were published in 1954, Twarog had also found serotonin in the mammalian brain[22]. In his 1968 book, Page, who was collaborating with Twarog at the time, wrote:

> When cerebral metabolism or "brain chemistry" was being established as a field worthy of study, serotonin played an extraordinary role. It will come as a surprise to younger readers that even as late as 1937 many scientists were dubious as to whether "neurochemistry" was indeed a discipline. If I had to select a single effect resulting from the discovery of serotonin, I would unhesitatingly suggest its influence in shaping investigators' ideas on cerebral activity.

Since we are discussing Serotonin now with the goal of contextualizing psychedelic research later on, some points in which research with serotonin and psychedelics started to connect for the first time are worth mentioning. LSD, a classic psychedelic which we will discuss extensively later on, was first synthetized by Albert Hoffman in 1938, and its effects in humans were first experienced by him in 1943 (first accidentally on April 16th, and then, three days later, on April 19th, intentionally[23]). The first interaction between serotonin research and psychedelics happened through this molecule.

Dilworth Wayne Wooley, again, while working on elucidating the dynamics of contractions in the rat uterus (same as Ersparmer), demonstrated that serotonin's ability to induce contractions in the smooth muscles of the uterus could be counteracted by the application of LSD,

---

[22] Whitaker-Azmitia, *The Discovery*
[23] Hoffman, *LSD*; Lee, *Acid*

and mimicked by bufotenin (also known as dimethylserotonin, a tryptamine psychedelic found in some plants, fungi, and animal species). As part of his theory of 'antimetabolites'[24], he proposed that LSD could be an antimetabolite of serotonin[25] as early as in 1954, and ultimately developed a theory about serotonin's involvement in mental illness[26]. I think it's important to highlight that within a decade of the term Serotonin appearing, the molecule had been characterized, discovered in multiple tissues of different animals including their brains, connected to psychedelic substances, and *through* this connection with 'psychotomimetics', linked to mental health conditions.

Wooley also hypothesized that serotonin might play a role in brain development, based on his observation of the similarity between serotonin and the family of the auxins, a group of plant hormones which have crucial roles in regulating development and growth patterns in plants. While a chemical similarity is probably not a good proxy for predicting whether a given molecule will have similar functions in such distant taxa, he turned out to be right in that regard: serotonin does play a crucial role in the development of the nervous system in the embryo[27]. Not only that, it turns out that serotonin itself is also present in plants [28], as was originally reported by Bowden *et al.* in 1954 [29]. Since then, serotonin has been demonstrated to participate in processes at all stages of plant life, from germination to vegetative growth and survival

---

[24] Wooley, *A biochemical.* "It is now well known that several classes of drugs are related chemically to individual hormones and other essential metabolites. In fact, a major part of the pharmacological effects of these drugs is attributed to a specific interference with the biological functioning of these metabolites to which the drugs are related structurally. That is, the drugs are antimetabolites".
[25] Wooley, *A biochemical*
[26] Di Cyan, *The biochemical*
[27] Sodhi, *Serotonin*
[28] Erland, *Serotonin*
[29] Bowden, *5-hydroxytryptamine*

mechanisms [30], sometimes, perhaps coincidentally, in direct collaboration with auxins[31].

Even though the work of Timothy Leary, a psychologist from Harvard who decided to study psychedelics after a personal experience with psilocybin in 1960[32], and who perhaps brought these substances to the attention of the mainstream public, is often portrayed as the one pioneering the study of psychedelics in humans, there were a multitude of studies in fields as varied as medicine, psychology, or espionage, happening already in the 1950s. Among these, I want to highlight the work of Henry Knowles Beecher, whose work on the fields of anaesthesiology, psychedelics, and ethics of research radically changed our understanding of the placebo effect and led him to take a central role in popularizing double-blind, placebo-controlled, randomized trials (RCT).[33] This historical figure brings to the fore a connection between psychedelics and placebo effects that will be crucial for our discussions in later chapters.

Beecher's work on anaesthesia led him to conclude that the experience of pain can be decomposed into at least two parts: the tissue injury itself, and the meaning assigned to the injury by the subject. His

---

[30] Erland, *Serotonin*
[31] Wan, *Involvement*
[32] Mashour, *From LSD*
[33] See Kaptchuck, *Powerful* for a relevant discussion about placebo effects and the RCT: "these powerful placebo effects... can produce gross physical change, [which] include objective changes at the end organ which may exceed those attributable to potent pharmacological action"; "This new concept of placebo was much larger both in meaning and power than its predecessor. It incorporated many contributors to health outcomes such as natural history, routine medical and nursing care, and the "art" of medicine that had once been clearly distinct from the deception of an inert pill."; "The placebo effect also includes another often overlooked consequence of research activity. It is modified by consequences due to the context of the RCT itself. Issues such as the method of recruiting patients, manner of giving informed consent, procedures for blinding, vehicle of delivery (colour of pills, pills vs injection), provider characteristics, provider verbal attitudes, and physical setting of the environment have been insufficiently studied."

observation that soldiers in World War II needed lower doses of anaesthesia than civilians with equivalent injuries in the hospital led him to this conclusion. One contemporary interpretation of the effects of psychedelics is that they act as 'meaning enhancers'[34], and Beecher's work with LSD, which was carried out after he developed an interest in the aforementioned nuances in pain management, and which led him to conclude that these substances may be reflecting or enhancing the pre-existing state of mind in the subject consuming them (as opposed to them simply leading to psychosis-like symptoms, as was often argued at the time) pre-date [35] Timothy Leary's 'set and setting' paradigm, which then became a fundamental motto in psychedelic research and culture, and which has survived until today. We will discuss these topics and their relevance for contemporary research on psychedelics in later chapters.

Important to note is that Beecher was a U.S. Army Lieutenant Colonel, whose experiments with LSD were largely funded by the Army, and whose interest in the ethical aspects of research likely stemmed from the problematic psychedelic experiments that he witnessed and carried[36], which were guided by the U.S. Army's interest in using psychedelic drugs for their potential for 'mind control' and 'brainwashing'[37].

While the current work is not meant to provide an in-depth dive into the history of research on serotonin or psychedelics, I considered it relevant to provide an overview of these initial stages of research in these fields, because I believe that multiple topics that are still crucial

---

[34] Hartogson, *The Meaning*
[35] Mashour, *From LSD*
[36] It's unclear to which extent Beecher was involved in the MKULTRA project which famously carried a multitude of highly unethical experiments involving psychedelics and non-consenting subjects. Mashour, *From LSD*
[37] Mashour, *From LSD*

today can already be seen emerging in these events from over seventy years ago.

One of the important dimensions is the etymology of the word serotonin itself: it was discovered in the context of its ability to modulate the tone of circulatory vessels, and this constitutes a fundamental confound affecting all research carried out in human subjects using fMRI and other related techniques that use blood flow as a proxy for neural activity. This limitation will serve to contextualize the importance of modern high-throughput electrophysiological research in animals, of which the experiments described in Chapter 2 are one instance. Likewise, it will inform the considerations made in Chapter 4 about the relevance of suggestibility in the realm of psychedelic research: because of the indirect and hard to interpret nature of studies centered on data from indirect measurements (such as fMRI, which again constitutes a very substantial and influential chunk of the totality of psychedelic research in humans), psychedelic research is particularly vulnerable to overinterpretation and overtheorization, a reality that can be understood as a peculiar type of multi-layered phenomenon: some dominant theories of psychedelics point at their ability to potentiate the beliefs of the subjects undergoing a psychedelic experience, and at the same time, it seems like the psychedelic research field at large has sometimes had a similar effect in the psychedelic research community.

In that regard, we have also touched upon the intimate relationship between serotonin, psychedelics, and the phenomena related to ‘meaning’ or placebo (placebo is sometimes referred to as meaning-response). The fact that from the very beginning psychedelics were seen as having the potential to elucidate mechanisms underlying mental health and disease, and the fact that they led to realizations as important as that of the need for double-blind, placebo controlled studies, highlight this fundamental relationship between psychedelic

drugs and meaning assignment, which will be discussed from different angles in Chapters 2, 3, and 4. Likewise, the aforementioned interest of the U.S. Army in these substances as potential 'mind control' drugs is important, considering the intimate relationship between suggestibility and psychedelics that will also be extensively discussed in Chapter 4.

Lastly, we have also glanced over the complexity of serotonin as a molecule with a variety of physiological roles: serotonin is only two synthetic steps away from the amino acid tryptophan[38], and attesting to its vicinity to such a ubiquitous molecule is its presence in animals, plants, fungi, bacteria, and archaea[39]. With most of our serotonin being produced in the gut, it likely plays an important role in gut microbiome-host communication[40], while also having both peripheral and central nervous system effects spanning most aspects of our physiology: from vasoconstriction, temperature regulation, and reproductive functions to pain signaling, aggression, or mental health. The ubiquitous presence of this molecule, as well as the extreme complexity of its physiology, should be kept in mind when discussing the myriad of theories that have attempted to unify different aspects of its physiology under a single explanatory framework[41]. While striving for unification and all-encompassing theories can be productive in the scientific endeavor, I will argue that it is also sometimes equally important to remain aware of the dangers of over-universalization. On that note, in the next section we will go through an overview of some aspects of the physiology of serotonin, specifically regarding its roles as a neuromodulator influencing

[38] Tryptophan availability in the diet is believed to influence serotonin signaling. In humans, tryptophan is an essential amino acid (i.e. it cannot be produced endogenously to cover physiological needs) and blood tryptophan levels can vary quickly throughout the day. Experiments with tryptophan depletion have correlated low levels of tryptophan with increased impulsivity, altered social cognition, and acute depressive relapse. Ligneul, *Serotonin.*
[39] Erland, *Serotonin*
[40] Del Colle, *Novel*
[41] Oakley, *Embracing*

perception, behavior, and cognition, concluding with an overview of the different theories that have been put forward as models for serotonin's role as a neuromodulator over the last few decades.

Serotonin in the brain

The term 'neuromodulator' is used to describe a specific subclass of neurotransmitters with certain characteristic properties. Neurotransmitters are usually defined as molecules which are secreted by a neuron and have an effect through binding to receptors in the target cell. The target cell is usually a postsynaptic neuron, a gland, or a muscle cell, and the effect of the neurotransmitter binding to the receptor depends on the properties of the receptor, which are usually classified as being either ionotropic (binding of the signaling molecule modulates ion flow across the receptor) or metabotropic (binding of the signaling molecule has more complex, usually slower, effects mediated by intracellular signalling cascades).

An example neurotransmitter is, for instance, Glutamate. Glutamate is by far the most abundant excitatory neurotransmitter in the mammalian nervous system, and it is estimated that in humans 80%-90% of synapses in hippocampus and neocortex are glutamatergic. Pyramidal cells, one of the cell types that can release Glutamate into their synapses, can be found in most structures in the brain, from the hippocampus to the cortex, the amygdala, or the corticospinal tracts that sends motor information from the motor cortex to the spinal cord. The cell bodies of pyramidal cells can be found in all of these structures, and each of these neurons fires according to the information it receives through its various inputs. In this sense, glutamatergic pyramidal neurons are sparsely distributed across most of the brain, and their activity can be thought of as tendentially 'local', in the sense that it's

limited to information transmission between the specific inputs of that particular neurons and the neurons that may receive its outputs downstream.

One of the defining characteristics of neuromodulators is that they don't follow this pattern: the cell bodies tend to be located in a reduced number of nuclei, from which axonal projections are sent to broadly distributed postsynaptic targets. In that sense, a reduced number of neurons, densely packed in few specific nuclei, broadcast signals throughout the rest of the brain, thus giving these neuromodulatory systems the ability to simultaneously modulate the activity of big portions of the brain. In that sense, their action tends to be thought of as less local and more 'global'. Still, each neuron's firing is modulated by the overall inputs it's receiving, and will reach mainly its postsynaptic targets, but because of the particular distribution of the neuromodulatory cells which I just described, neuromodulatory systems are ideally suited for the coordination of brain activity at a global scale.

Another feature that is typically assigned to neuromodulators is the tendency to activate metabotropic postsynaptic receptors, that is, receptors which, upon binding of the neuromodulator activate intracellular signaling cascades that can lead to a multitude of complex responses including the regulation of protein synthesis in the cell, gene expression, or widespread effects on membrane dynamics (compared to ionotropic receptors, these tend to lead to slower changes in postsynaptic targets).

Serotonin is considered a neuromodulator, with its anatomy and physiology following the patterns that I just described[42]. Serotonin in the brain is produced by nine small nuclei located in the brain stem called the raphe nuclei, from which broad projections emerge to reach targets

[42] Ligneul, *Serotonin*

broadly distributed all over the brain. Neurons from nuclei B1, B2, and B3 project to the spinal cord and medulla, and seem to regulate functions such as breathing, temperature regulation, and sleep-wake cycle dynamics. B4 and B9 are very small and not very well understood, and their neurons seem to mainly project to other near-by brainstem structures. Most projections to forebrain originate from Medial Raphe Nucleus (MRN = B5 and B8 nuclei) and Dorsal Raphe Nucleus (DRN = B6 and B7 nuclei).

MRN and DRN are estimated to contain around 15.000 neurons in mice, and around 200.000 in humans. Projections from MRN and DRN reach structures everywhere in the brain, including sensory structures like the retina or the cochlea, with the DRN projecting more densely to lateral targets in basal ganglia and cortex, and MRN projecting to more central regions, mainly in Hippocampus. Again, these widespread projections allow the serotonergic system to have broad effects across the brain, as is characteristic of other neuromodulatory systems too. This property of the serotonergic system has prompted some authors to propose that Serotonin may be metaphorically conceptualized as an orchestra conductor, coordinating activity all over the brain[43]. While the orchestra conductor metaphor may be a good way to bring across the ability of the serotonergic system to modulate activity in targets distributed all across the brain, it's also important to highlight its shortcomings[44]. For instance, the 'orchestra conductor' metaphor may inadvertently promote a homuncular view of cognition which might be problematic in multiple ways[45]: while it is tempting to assume a unified role for serotonin, it's important to remember that, while serotonin is a single molecule, the serotonergic system itself is extraordinarily complex

[43] *Ibid.*
[44] Syed, *Languaging*
[45] Fidor, *The fallacy*

(as we will detail now), which may explain why it has historically been difficult to shed light on *the* function of serotonin in the brain[46].

Ascending inputs to these nuclei relay information about pain, temperature, and in general interoceptive and exteroceptive stimuli. Descending inputs, on the other hand, are believed to provide serotonergic neurons with information about context (e.g. cortical and subcortical inputs). Serotonergic neurons also receive inputs from and send projections to other neuromodulatory systems such as the noradrenergic nucleus Locus Coeruleus (LC), or the dopaminergic Ventral Tegmental Area (VTA). This complex interconnection between the serotonergic system, interoceptive and exteroceptive information, contextual information relayed by descending inputs, and other neuromodulatory systems already hints at the sheer complexity of the serotonergic system. The way in which information from these different sources may be manipulated and the ways in which it affects the outputs from the serotonergic system are poorly understood, with one emerging idea being that 5HT neurons seem to form feedback loops with their areas that are connected to, sending axonal projections to the same areas where they receive their inputs from[47].

Apart from the neuroanatomical organization of the serotonergic system, the metabotropic nature of most well-known serotonin receptors also matches the typical properties of neuromodulatory systems. The number of identified 5HT receptors also speaks to the complexity of this system, with 16 types having been characterized in humans. It's important to remember that serotonin is just mostly an inert molecule, and as such, it doesn't itself do that much. While some enzymes do very specific functions that are related to their molecular structure, Serotonin's role is fulfilled mainly by reaching the receptors in the postsynaptic

[46] Okaty, *Embracing*
[47] Ligneul, *Serotonin*

neuron: the fact that there are at least 16 types of receptors, with different molecular and physiological properties means that there are at least 16 somewhat different effects that serotonin can have on the postsynaptic neuron upon binding to those receptors[48].

Organized in 7 different families (Type 1 - 7 families), receptors from families 1 and 2 are metabotropic and are thought to have long-lasting effects on gene expression, plasticity, and neural excitability[49]: while both families are G-protein coupled receptor (GPCRs) families, type 1 receptors have slow inhibitory effects, while type 2 receptors have excitatory effects. Breaking away from the metabotropic neuromodulators trend, type 3 receptors are ionotropic and lead to fast excitatory effects comparable to those of some glutamatergic receptors. Receptors from families 4 to 7 have been identified and are all metabotropic, but are barely understood. While most families are widely expressed in neurons, glia, vessels, centrally, and peripherally, different receptors tend to be expressed in different cell types and regions[50].

A given population of neurons receiving inputs from serotonergic nuclei can express different types of 5HT receptors: this is important because it suggests that serotonergic inputs to a certain population can have complex effects on the population dynamics that may be best understood by modeling at the level of the population geometry and dynamics. For instance, serotonergic neurons often express somatodendritic and axonal 5HT1a and 5HT1b receptors, both inhibitory autoreceptors which likely participate in negative feedback loops to tightly control the activity of these neurons. On the other hand, pyramidal neurons are likely to express both inhibitory 5HT1a receptors and excitatory 5HT2a receptors, which again suggests that the effects of

[48] *Ibid*
[49] *Ibid*
[50] *Ibid*

serotonin signaling on these areas may not be appropriately captured, for instance, by trying to assess whether it increases or decreases firing rates in the overall population, and should rather be conceptualized as a complex, cell-type specific, geometrical transformation of the populations' activity. For instance, serotonin input to olfactory neurons can inhibit spontaneous activity while leaving sensory-driven dimensions of population activity seemingly unaffected.

Serotonin in the CNS is synthesized from tryptophan in two simple enzymatic steps that occur in the cell body of serotonergic neurons in the raphe nuclei. It is unstable at physiological pH levels, and it's thus usually actively packaged into vesicles by the vesicular monoamine transporter 2 (VMAT2). After these vesicles are transported to the axon terminals, they can fuse with the cytoplasmic membrane and release the serotonin onto the synaptic cleft, allowing these 5HT molecules to reach their postsynaptic targets and bind to serotonergic receptors therein. Serotonin is cleared from the synapse mainly by reuptake through the serotonin transporter (SERT) into the pre-synaptic cell, and once in the cytoplasm it can be oxidized by the mono-amine oxidase (MAO) enzymes which are localized in the outer mitochondrial membrane. In non-junctional synapses (e.g. most serotonergic synapses in prefrontal cortex), serotonin can escape reuptake by SERT and diffuse (when the synapse is circled by gap junctions, serotonin cannot leave as easily)[51].

Transport mechanisms that clear serotonin from the synapse are crucial in determining the extent to which serotonin affects the post-synaptic neuron. While classically, this transport has been exclusively associated with reuptake by SERT, a diffusion-like type of transport has also been described since as early as the 1960s. The

[51] Andrews, *All the Brain*

polarity of the serotonin molecule keeps it from crossing the brain-blood barrier (BBB), but it became clear from early studies on peripheral serotonin in platelets that serotonin can cross the membranes of many cell-types in a diffusion-like manner, including cells in the kidney, heart, and endothelium, neuronal synaptosomes, and neurons. This type of transport was determined to be mediated by non-specific carriers, and is probably involved especially when repeated neuronal firing raises the extracellular levels of serotonin to micromolar concentrations[52].

In this sense, after the release of serotonin from axonal buttons, post-synaptic targets can be reached either by point-to-point contacts or through diffusion to other targets, also known as volume transmission. The latter occurs, for instance, in inputs to local inhibitory interneurons in the cortex via 5HT3a (the fast-acting ionotropic receptor), while the former is common in cortical and subcortical areas where serotonin can diffuse and reach excitatory neurons in the vicinity. The slow nature of the diffusive process and its increase with elevated firing rates over sustained periods of time effectively turn volume transmission into a low-pass filter (i.e. it will only transmit information about slow fluctuations in the pre-synaptic activity, and not faster frequency components)[53].

This low-pass filter effect of volume transmission is relevant when considering the firing properties of serotonergic neurons: it was shown early on that DRN neurons have a highly regular, clock-like firing pattern which fluctuates slowly over time, which has been connected to arousal, stress, and sleep/wake cycles. Thanks to modern methods such as calcium imaging and optogenetics, which allow for more control and specificity in measuring and stimulating 5HT neurons, burst, or phasic activity has been identified in serotonergic neurons too: salient external events activate serotonergic neurons in the short term. There is no

[52] *Ibid*
[53] Ligneul, *Serotonin*

unifying framework to explain the responses of serotonin neurons to specific stimuli, with results having shown phasic responses to appetitive, aversive, and salient events, as well as to prediction errors, novelty, or task engagement. Baseline tonic activity, on the other hand, may encode information such as motivational valence or uncertainty[54]. The fact that serotonergic neuron activities seem to have these two different channels in which they carry information (tonic and phasic) may explain why sometimes pharmacological (characterized by slower onset times) and optogenetic (characterized by extremely fast dynamics) manipulation experiments have in some instances come up with contradictory results.

Notwithstanding the incredible complexity that we are starting to glimpse from the physiological properties of the serotonergic system that we have discussed so far, pharmacological interventions targeting different components of this system are ubiquitous and have proved to be highly effective in treating a multitude of ailments, including some psychiatric and neurological disorders. Serotonin receptors, MAO, SERT, and VMAT2 are important pharmacological targets for medications with antiemetic, anticonvulsant, antimigraine, antipsychotic, anxiolytic, and antidepressant properties. Likewise, as we have already mentioned, research about serotonin has been intimately related with research about psychedelic substances since its very beginning, and the interest in these drugs is perhaps at its peak nowadays.

The fact that psychedelics have such profound effects on subjective experience, combined with their therapeutic efficacy has influenced the way we think about our brains since these drugs started to be studied. As we will see, one of the features of the serotonergic system that has caused difficulties in understanding its functioning is the

---

[54] *Ibid*

fact that serotonergic neurons' activity seems to be heavily influenced by context, to the extent that in different contexts, the same manipulation can lead to radically different results. Consistent with this fact, as we mentioned above when discussing Beecher and Leary, the contextual dependency of psychedelics not only was clear from very early on, it also led to important advances in research ethics such as the establishment of double-blind placebo controlled studies as a new standard.

Lastly, because we will later on discuss the physiology of psychedelic drugs, it is important to mention Serotonin's involvement in regulating plasticity in the brain. Metabotropic 5HT receptors can lead to intracellular signaling cascades that will ultimately regulate gene expression and morphological modifications in the cell. As we will discuss later on, 5HT2a receptor agonists have been proposed to produce dendritic arborization and the formation of new spikes. 5HT4 receptors seem to be involved in long-term depression in basal ganglia, and generally speaking 5HT release is crucial for hippocampal neurogenesis and the formation of cortical circuits [55]. Some propose this neuroplasticity as a possible mechanism for the occasional role of 5HT in increasing behavioral flexibility. Now, before taking a closer look at the different existing theories of serotonin function and psychedelics, let's take a quick look at the neurophysiology of one example psychedelic.

DOI and the medial prefrontal cortex

While it would be impossible to give a detailed account of the state of the art in the neurophysiology of psychedelic drugs in general, it will be illustrative to briefly bring our attention to the current state of affairs regarding one particular psychedelic drug.

[55] *Ibid*

2,5-Dimethoxy-4-iodoamphetamine, also known as DOI, is perhaps the most studied psychedelic drug, thanks to one of its properties which has made it both *desirable* and *available* for researchers interested in psychedelics and in the serotonergic system: its affinity for 5-HT2 receptors.

This molecule, a substituted phenethylamine often considered a 'classic' psychedelic, has one of the strongest known affinities for the 5-HT2R family. It binds to these receptors so strongly that two things occur: first, the subjective effects of this drug are so long that it's not a popular recreational substance (which has made it so that it's still not classified as a *Schedule I* substance by the FDA, thus making it easier to obtain for researchers worldwide), and second, it's so effective at occupying these receptors that it's even used as a radioligand in tracing studies (thus making it of general interest outside of the scope of psychedelic research).

A recent systematic review[56] by Hidalgo Jiménez *et al.* provides a great perspective on over three decades of research focused predominantly on this substance. Most of the literature they analyzed focuses specifically on pyramidal neurons on layer 5 (L5p) of medial prefrontal cortex (mPFC), the area with the highest 5-HT2a receptors expression in all of neocortex, specifically on the apical dendrites of these neurons. We will now go through some of the results recounted in this review in order to give a perspective on the intricacies of psychedelic effects when looked at from an electrophysiological perspective. This is but a fraction of the complexity of the physiology of psychedelic drugs: we will only consider some results specific to one substance, in one brain area, in one specific type of neuron.

[56] Hidalgo Jiménez, *Electrophysiological*

First, there are important differences between in vivo and in vitro studies on the subject, as well as between different forms of administration in in vivo studies: this should serve as a cautionary tale to consider when extrapolating results across fields. It is not uncommon to see these kinds of extrapolations suggested in the field (e.g. assuming, for instance, that results in animal studies translate to humans).

In vitro studies show a mild, consistent depolarization of resting membrane potential, a suppression of NMDA-evoked excitatory post-synaptic potentials (EPSPs) and currents (EPSCs), and a dampening of excitatory transmission through AMPAR internalization. Despite this suppression, a late shift in excitatory/inhibitory balance towards excitation appears, leading to so-called ‘up-states’. Firing responses are variable across studies, with some reporting increases, others reporting concentration-dependent suppression, and others reporting no change.

In vivo studies, on the other hand, show strong inhibition of L5p firing when DOI is administered microiontophoretically, but mixed effects when it is administered systemically, with rate- and dose-dependent effects, sometimes leading to excitation and sometimes to inhibition. Net inhibition is often reported across studies. On the LFP band, low frequencies tend to be reduced, while high frequencies sometimes are reported to increase. Some results point towards cross-regional hypersynchrony and altered spike-LFP coupling.

Around 24 hours after the administration, some report increased miniature EPSCs (mEPSCs), spontaneous EPSCs (sEPSCs), and burst firing, possibly attributable to synaptic/dendritic plasticity.

Apart from these differences, stimulation studies show that DOI has different effects on different compartments of L5p dendrites, leading to enhanced EPSPs/EPSCs in the apical compartment, a suppression of activity in the basal compartment, and an increase in excitability and

promotion of up states in the coupling compartment. DOI is quite selective for 5-HT2 receptors, which is likely the reason why other psychedelics, such as LSD (which, contrary to DOI, is also a 5-HT1A agonist), show entirely different patterns. Based on theories of how different dendritic compartments receive different streams of information, the pattern of apical coupling or hyperexcitability combined with basal hypoexcitability (sometimes referred to as ‘apical drive’), has been suggested as support for theories that attribute hallucinations to increased top-down processing.

Furthermore, there are also important variations across and within studies due to concentration and time differences. Initially, eEPSP/eEPSC are enhanced via increased presynaptic glutamate release, but after ~15-20 minutes, postsynaptic processes dominate (5-HT2a receptors can appear both pre- and post-synaptically), leading to AMPAR internalization and the suppression of NMDAR currents. In apical dendrites, eEPSPs can be sustained beyond 20 minutes, contributing to extrasynaptic up-states. The early phase described above is absent in LSD (likely because of its 5-HT1a activity), and abolished at high concentrations of DOB, meaning that both substance and concentration can qualitatively change the time course of the effects.

Lastly, there is also cell-type specificity. Type I L5p neurons are selectively excited by DOI, in a 5-HT2a-mediated manner. Type II L5p neurons, on the other hand (most L5p neurons) are inhibited, also in a 5–HT2a mediated manner, but involving GABAergic signaling.

Summarizing, even when looked at from the perspective of a specific neuron type, in a specific brain area, limiting us to rodent studies, and focusing only on DOI, the effects of psychedelics in neuronal activity show a high degree of heterogeneity and complexity. With results varying according to the administration method, measurement timing, dosage, substance, cell type, and cellular

compartment, it is important to note that even after more than three decades of research, there is still no consensus about some basic properties such as the effects on firing rates. This will serve as background for the results presented in Chapter 2, but it should also serve as a perspective on the theories of psychedelics that we will soon describe.

Theories of serotonin and psychedelic action

Some necessary intuitions

We will now turn to the recent history of the efforts towards conceptualizing serotonin's activity, as well as the effects of psychedelic drugs, from a theoretical standpoint. In order to do so, it will be necessary to lay some fundamental concepts regarding the three main theoretical frameworks that have inspired these theories: bayesian inference, reinforcement learning, and control theory. While it is not essential to understand these theories in depth, I believe it will be necessary to have some basic intuitions about them, which I will do my best to convey now.

The two most widely adopted comprehensive frameworks within the field of statistics are Bayesian statistics and frequentist statistics. At a philosophical level, the two frameworks differ in their definition of the meaning of probability: in frequentist statistics, probabilities are meant to refer to what would happen if you repeated a given experiment many times, while in Bayesian statistics probabilities refer to beliefs about a certain event. Named after Thomas Bayes, who worked on the theory surrounding conditional probabilities (the probabilities of two different events that depend on each other in some way) in the late 1700s, the field of Bayesian statistics has become especially prominent in applied

statistics in the last 50 years. The field of Bayesian statistics is vast, and has been applied in different ways in Neuroscience, both as a theoretical framework and as a specific data analysis toolset. For our case, we only need to understand the basic idea behind the concept of Bayesian inference, which is one of the most influential concepts perhaps in all of theoretical Neuroscience[57].

Bayesian theory is focused on calculating the probabilities of conditional events, i.e. in situations where one of the events happening influences the probability of the other event happening. For instance, when applied to hypothesis testing, the probability of a hypothesis given the current available evidence is calculated: if a certain evidence exists, the hypothesis may be more likely than if a different evidence existed. In other words, given the available data, Bayesian inference can estimate how certain we can be about a certain interpretation being true. This approach is at the core of one of the most popular theories in computational Neuroscience: predictive processing (PP). According to predictive processing, the brain's task is to formulate predictions based on sensory evidence and internal models built from that sensory evidence. Sensory inputs are conceptualized as variables carrying information about a latent, inaccessible generative process. The brain's role is to form models about those latent variables that are good enough to allow accurate predictions. The process by which those models are updated can be modeled as Bayesian inference, where the probability of the model given the current sensory evidence is calculated based on Bayes theorem, first formulated by Laplace in 1825:

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

[57] Van De Shoot, *Bayesian*

P(A|B) is read as ‘the probability of A being true given that B is true’, and is generally used as a form to express conditional probabilities. A and B could be any two events that are not independent. In the specific case of Bayesian inference, based on the fact that we want our models to be built on evidence (and thus *not* independent from it) this term would become P(H|e), the probability of the hypothesis (H) being true, given the evidence that has been observed. The goal in Bayesian inference is to optimize this term, to find the hypothesis that is the most likely given the evidence we have observed. The formula thus becomes:

$$P(H|e) = \frac{P(e|H)P(H)}{P(e)}$$

This formula can be used in the context of statistical analysis to express the process by which evidence accumulation in a scientific experiment updates our beliefs about a certain hypothesis being true. It can also be applied to other contexts, where instead of a hypothesis being tested in an experiment, *H* can represent, for instance, different types of internal models of an agent, and *e* can represent the different types of evidence that may be informing such internal models. The terms *hypothesis, belief, model,* and *priors* are often used interchangeably in this context.

Applied to the sensory inference case described above, Bayes theorem states that the probability of the internal model being true given that the sensory evidence happened (the posterior probability, or posterior for simplicity) can be calculated by multiplying the probability of the sensory evidence happening if the model was true (the likelihood, how likely the evidence is to happen if the model is true) by the probability of the the model being true in general (the marginal probability of the model, independently of other variables, usually referred to as prior probability, because it’s the probability assigned to

the model *before* sensory evidence has been obtained[58]), and dividing the result by the probability of the sensory evidence happening in general (the marginal probability of the evidence). Once the posterior has been calculated, it can become the prior in a future round of inference when new sensory evidence is acquired.

This model of inference is central in PP, and leads to a question that is at the core of the cognitive flexibility theory [59]: how much should new sensory evidence affect our internal models of the world? In other words, how much should the priors and the evidence be weighted relative to one another when calculating the posterior? In this sense, perception can be thought of as a continuous decision making process where the relative weights given to perceptual information and internal models has to be adjusted. Depending on the features of the environment, this relative weights might need to be adjusted in order to be most adaptable: if the environment is very unpredictable, it might be beneficial to be more flexible, needing less sensory evidence in order to substantially modify our internal models; conversely, if the environment is very predictable, it might not be necessary to adapt so quickly, having strong prior beliefs to avoid unnecessarily updating them when faced with a constant stream of confirmatory sensory inputs.

Uncertainty plays an important role in Bayesian statistics, with the 'weighting' of priors and sensory evidence described above being inversely proportional to the uncertainty in their distribution: when we are very certain about our models of the world (very low uncertainty, in the extreme, a probability distribution where the probability for a given value is 1 and it's 0 everywhere else), they will be weighted very heavily, and

[58] This is a crucial part of the equation, especially in the context of statistical inference. In a theoretical sense, it acknowledges the fact that we already have a belief about a certain hypothesis, even before we have performed an experiment.
[59] Uddin, *Cognitive*

conversely, when they are very uncertain (in the extreme, a uniform distribution where all possible values are equally likely), they will barely affect the outcome of the inference (in both cases how much uncertainty is present in our sensory evidence will also equally contribute to the outcome, the important thing is their relative accuracy). Many of the concepts that we just described have been central in different threads of contemporary research into the serotonergic system[60] and psychedelics[61], as we will discuss in the next section.

While Bayesian inference has been an incredibly fruitful theoretical construct in the study of perception, Reinforcement Learning (RL) has surely been the most popular framework in the study of animal behavior in computational Neuroscience, and occupies a very central position in Machine Learning (ML) and Artificial Intelligence (AI) as well. In RL parlance, an agent (be it a human, another animal, a robot, or any other type of agent) is learning and behaving in an environment. The environment can be in different states, and the agent can choose different actions. Different states are usually associated with different reward amounts, and the agent uses these as a learning signal to improve its decision making by optimizing a policy. The framework is flexible enough that it can be used to model almost any scenario where these constructs can be applied, with 'actions' being anything from movements in a physical space to choices in a decision making task, and rewards being anything that provides 'value' to the agent, with respect to a given objective.

RL has been used both to model experimental behaviors and to train agents to perform different kinds of tasks. It has been extremely successful in both realms, leading to important theoretical models in the field of computational Neuroscience, as well as to important

[60] Matias, *Activity.* Clarke, *Cognitive.* Zhu, *Inflexibility.*
[61] Carhart-Harris, *REBUS*

breakthroughs in the field of ML, where agents trained using RL have in multiple instances surpassed human performance. While RL can be model-based, and thus have a world model, it can also be model-free, allowing agents to learn based on trial-and-error interactions with the environment without needing to learn an explicit representation of that environment. In both model-based and model-free RL, Bayesian inference can be incorporated into these algorithms, be it in the process of learning the world model in model-based RL, or in learning the value function in model-free cases (a value function maps from either the space of possible states, or the space of possible states and action pairs to the expected cumulative reward over time, i.e. it tells the agent how valuable it is to be in a specific state or to do a specific action in a given state, and is used to find the optimal policy). One of the advantages of RL models is that they can be deployed in unknown environments, since they are meant to learn through interaction: in that sense they can be used to model behaviors that happen when an agent has only partial access to the properties of its environment (which is why they have become so popular in computational Neuroscience), and in that sense they share the intimate connection with uncertainty computations that is characteristic of Bayesian theory.

Lastly, I want to mention control theory, which has also influenced some recent theoretical work in the field of serotonin research. Control theory is a branch of engineering which is concerned with the control of dynamical systems. As opposed to Reinforcement Learning, in control theory the system is usually fully known, and the tools and techniques that are used to optimally control the system are more analytical in nature and don't usually need the complex learning algorithms that characterize RL models. In control theory, the goal is usually to stabilize, track, or optimize the performance of a system according to a predefined criterion. Imagine for instance the software used by an air conditioning

(AC) system: the objective is to obtain a certain temperature in a room, and based on measurements of ambient temperature in that room, the AC unit needs to spend more or less energy in cooling down the air. There isn't any uncertainty in the system, nor anything to learn. The system can be determined by a differential equation, and the control unit only needs to follow a simple protocol to control the temperature. While there are important differences between control theory and RL, they also have important areas of overlap and more recently of crosspollination, and sometimes the boundary between the two is not very clearly defined.

In RL, the emphasis is usually put on how the agent learns and adapts its policies to the features of the environment. In many instances, the effect of the agent's actions on the environment, beyond the consumption of rewards, can be ignored. In control theory, on the other hand, the control system often has a profound effect on the state of the environment. For instance, in the context of an RL virtual agent learning how to navigate an environment, the actions (e.g. movements in space) may determine where the agent is located, and how quickly a reward location is reached; however, the environment itself will often not be impacted by these actions. On the AC system example, on the other hand, the control unit's actions (increasing or decreasing the power output of the AC unit) will ultimately determine the temperature of the room (provided that the room is within the capacity of the AC unit and the system is working properly).

In more complex scenarios, it becomes clear that the line between these two examples can often be much blurrier. For instance, imagine that you are riding a bike. If, while you are pedaling down the street, your chain breaks loose from the chainrings, you will experience a moment of surprise due to your actions (in this case the pedaling) not having the effect that you expected them to have (propelling the bike

forward). In that sense, it becomes clear that the relationship between an agent and its environment is often circular (this is not always the case, some things in the environment may be amenable to being affected by the agent's actions, while other are not), in that actions are chosen based on environmental properties, but the environment is often also directly affected and changed by the actions of the agent. In that sense, agents (whether virtual, robotic, or biological) often benefit from tracking their own ability to affect the environment. The concept of 'controllability' is also central in some contemporary theories about the functions of the serotonergic system.

In the next section, we will go through an overview of different moments in Serotonin research, explaining how the dialogue between these theories and experimental results has evolved over the last few decades.

The role of serotonin

The early success in ascribing Dopamine responses to a computational role through reinforcement learning[62] prompted researchers to pursue the same goal with serotonin. The dopamine-serotonin opponency theory emerged as one of the earliest computational theories of serotonin functioning, which predicted that serotonin would encode punishment prediction errors and the average rate of rewards, as well as mediate behavioral inhibition when anticipating punishment[63]. Different lines of research showed, however, that serotonergic activity can be triggered by a multitude of events including punishments and reward omissions, but also rewards and reward predicting cues (thus coinciding with dopamine and countering

[62] Schultz, *A neural*
[63] Boureau, *Opponency*

the opponency hypothesis), and that serotonin neurons seem to promote locomotion in aversive contexts[64].

The observations that reducing brain serotonin can lead to an increased amount of premature and impulsive responses across different species led to another influential theory which proposed that serotonin regulates impulsivity by modulating the degree to which predicted rewards over different timescales influence current behavior[65]. While stimulation studies confirmed that DRN activation increases patience in waiting for rewards, and showed that serotonin activity increases during the waiting period, this theory fails to explain other aspects of the serotonergic system, such as the transient serotonergic responses that are often observed in response to different types of salient events[66].

The limitations of these theories prompted the consideration of more complex models outside of the most basic reinforcement learning models. Crucially, some serotonergic responses seem to be heavily modulated by context. Optogenetic stimulation, for instance, can lead to decreased, increased, or unaffected locomotion, in spontaneous exploration, aversive contexts, and goal-directed behaviors, respectively. Reward amounts, environmental controllability, and uncertainty, have also been shown to modulate certain effects of serotonergic stimulation.

The observation that serotonin neurons increase their firing in response to some unpredictable events has led to the theory that serotonin may be generally involved in processing prediction errors or surprise signals, a function which may underlie its involvement in certain learning and plasticity processes.

The broad projections from DRN to the forebrain and the entire neocortex, which has sometimes been proposed as an anatomical

---

[64] Ligneul, *Serotonin*
[65] Miyazaki, *The role*
[66] Ligneul, *Serotonin*

structure concerned with unsupervised learning (the learning of statistical structure in a dataset without a guiding set of labels, instructions, or reward signals), are sometimes used as an anatomical basis for arguing that serotonin is in a privileged position to modulate processes related to such a form of learning. The Bayesian inference framework presented above is one possible way of carrying such an unsupervised learning by continually updating prior predictions based on incoming sensory evidence, and from this perspective serotonin has been theorized to perform different functions such as the tracking of relative confidence or uncertainty.

Alternatively, from the perspective of control theory, serotonin has also been proposed to have important roles in tracking the degree to which the environment is controllable by the animal. Serotonin release is known to participate in adapting behaviors to uncontrollable environmental stressors, such as in learned helplessness paradigms, and the responses of serotonin neurons are stronger when changes in sensory input closely follow actions, suggesting that serotonin neurons may encode the degree to which actions lead to predictable outcomes.

While the fact that a given theory cannot explain the entirety of the complexity of serotonin signaling has led to the development of new theories in an attempt to find a high-level, unified theory that may explain the role of serotonin in the brain, it is important to keep in mind that such a unified theory of serotonin action may not be possible due to the varied nature of the functional roles of serotonin neurons.

All serotonergic neurons express a shared set of genes that lead to the synthesis and release of serotonin, but beyond this, they are extremely diverse in their cellular properties regarding anatomy, morphology, hodology, electrophysiology, gene expression, and co-transmission with other neurotransmitters. This diversity suggests the existence of functionally heterogeneous subtypes of 5-HT neurons, even

though it's been difficult to tie such subsets to different functional roles due to technical limitations. [67] Contemporary genetic, electrophysiological, and imaging approaches which allow population recordings from identified serotonergic neurons will undoubtedly be crucial in further characterizing the complexity of the serotonergic system and its multiple roles in modulating brain activity.

The effects of psychedelics

For more detailed descriptions of the current state of research concerning psychedelic drugs, we recommend consulting one of the many reviews and articles published over the last decade on the topic:[68] for now, we will limit ourselves to giving a quick glimpse at the high-level theories that have been proposed thus far.

Different models have emerged from different subfields of psychedelic research, sometimes aiming to explain different dimensions of their effects. The cortico-striato-thalamocortical (CSTC) and cortico-claustro-cortical (CCC) models focus on explaining the nature of psychedelic action from a neural circuit perspective. The Relaxed BEliefs Under pSychedelics (REBUS) and the Strong Priors (SP) models have emerged from research concerned more specifically with psychiatric symptoms of psychosis in the case of the SP model, and from clinical antidepressant trials in the case of REBUS, both aiming at giving a computational explanation of the effects of these drugs, with differing degrees of explanatory aspirations in other dimensions (the authors behind REBUS have tended towards tying multiple levels of description, from circuit level to psychological, from implementation to computation,

[67] Okaty, *Embracing*
[68] Kwan, *The neural;* Cummins, *5-HT2A;* Doss, *Models;* Gattuso, *Default;* Halberstadt, *Behavioral;* Hatzipantelis, *The effects;* Kelmendi, *Psychedelics;* Kadriu, *Ketamine;* Lladó-Pelfort, *Effects;* Nichols, *Psychedelics;* Smausz, *Neural.*

etc, while SP has so far remained more agnostic regarding implementation and neural hypotheses).[69]

The CSTC model postulates that under the effects of psychedelics, thalamic gating is disrupted, leading to an increase in feedforward information reaching the sensory cortices from thalamic nuclei. Results showing impaired sensorimotor gating in humans, as well as neuroimaging studies showing increased thalamocortical functional connectivity and synchronization of cortical sensory regions are cited to support this model.[70]

The CCC model, on the other hand, emphasizes the role of the claustrum, where 5-HT2AR are densely expressed, in mediating the effects of psychedelics. According to this model, psychedelics disrupt the coupling between claustrum and cortex, leading to the attenuation of canonical cortical networks that is observed under the effect of psychedelics.[71]

The REBUS model suggests that psychedelic drugs exert their effects by diminishing the precision of prior beliefs (in the Bayesian inference/predictive processing sense), thus allowing an increased flow of bottom up sensory information, as proposed by the CSTC model.[72] The authors behind this model then propose that the disintegration of association networks that is sometimes observed in neuroimaging studies with psychedelics and the increase in the entropy of neural dynamics are the mechanisms behind the 'relaxation' of prior beliefs (for more details on this, see their 'entropic brain'[73] and 'anarchic brain'[74] theories). By tying 5-HT2AR agonism with increased entropy and

---

[69] Kwan, *The neural*
[70] *Ibid.*
[71] Doss, *Models*
[72] Carhartt-Harris, *REBUS*
[73] Carhartt-Harris, *The entropic*
[74] Carhartt-Harris, *REBUS*

relaxed prior beliefs, the authors aim at giving a comprehensive explanation of psychedelic effects bridging every level from the receptor agonism of psychedelics, to their neural circuit effects, to their computational and subjective effects.[75]

Some of the papers in this niche have drawn enormous attention in the field, reaching some of the highest citation counts in the history of psychedelic research. However, this model fails to explain some results, such as the fact that sensory deprivation seems to reliably elicit hallucinatory phenomena in some subjects (which contradicts the idea that hallucinations come from an increased flow of bottom-up sensory information), results showing reduced stimulus-evoked spiking activity in the visual cortex under the effects of LSD[76], or the 'apical drive' described above when discussing the DOI literature.[77] Furthermore, this literature has been criticised for methodological reasons[78], the misrepresentation of results,[79] and for being part of a trend portraying psychedelics as a panacea with scarce experimental results to back these statements and problematic economic interests at stake.[80]

Without delving deeper into the socioeconomic context of the emergence of this literature, we will highlight that some of these theoretical proposals are exceedingly reductive, alleging that multiple levels of psychedelic action can be tied together in a simple one-dimensional spectrum (low to high occupation of 5HT2AR at the molecular level, low to high brain entropy at the network level, low to high reports of mystical experiences at the experiential level, low to high improvements in depression at the clinical level, etc…). As suggested by

---

[75] Carhartt-Harris, *REBUS;* Siegel, *Psilocybin*
[76] Kwan, *The neural*
[77] Hidalgo Jiménez, *Electrophysiological*
[78] Drummond, *Navigating*
[79] Devenot, *Dark Side*
[80] Devenot, *TESCREAL*

some critics,[81] these entropy-based accounts of psychedelic action and depression seem to be on their way to becoming an alternative to the once popular 'serotonin hypothesis'[82] of depression, sometimes even transcending the scope of explaining depression and proposing the dimension of 'brain entropy' as critical for a multitude of psychiatric disorders.[83]

Finally, more recently, the SP model[84] has emerged from research in psychiatric hallucinations (considering psychedelic hallucinations as just one type of pharmacologically-induced hallucination), with the potential to make up for some of the shortcomings of other theories. According to the SP model, hallucinations occur due to priors being overly precise or strong in an inference process. This hypothesis emerges from a literature concerned with psychiatric symptoms of psychosis, as well as with the generation of hallucinations through conditioning and suggestion[85], which has also shown how people presenting different symptoms of psychosis seem to be particularly susceptible to these effects. While this theory successfully accounts for some properties of hallucinatory phenomena, the authors themselves point out that there are at least two important instances where it breaks down: the reduced sensibility of schizophrenic patients to some illusions, and the idea that voice hallucinations in schizophrenia have to do with impaired corollary discharge.

As proposed by Kwan *et al.,* SP and REBUS theories may be reconciled if we allow for multiple levels of inference by modeling the brain as a hierarchical structure of interconnected inference processes, where perhaps low-level sensory beliefs may be weakened (following

---

[81] Devenot, *The Dark*
[82] Moncrieff, *The Serotonin;* Möller, *Is the serotonin*
[83] Carhartt-Harris, *The entropic*
[84] Corlett, *Hallucinations*
[85] Schmack, *Striatal;* Ellson, *Hallucinations,* Davies, *An effective,* Kot, *Increased*

the proposal in REBUS), but ultimately culminate in stronger higher-level extraperceptual beliefs. Importantly, the authors also note that more precise definitions of priors and beliefs will be helpful, and suggest that a unified model of psychedelic action will need to integrate knowledge from a growing body of research assessing both implementational and computational possibilities.

Indeed, increasing the complexity of our models may allow us to reconcile different theories. However, it may also be beneficial to question our previous models and to assess which normative assumptions we may be making, in order to guide our modeling efforts in a more theory-driven manner. In Chapter 4, we will come back to this and propose a new conceptual framing motivated by the literature on the effects of psychedelics on suggestibility.

Chapter 2

LSD and population activity

Contributions

This project is part of the International Brain Laboratory. The scientists who have participated in the project so far are Guido Meijer, Joana Catarino, Olivier Winter, Zachary F. Mainen, Daniel McNamee, Davide Crombie, Martín Zúñiga, and myself (Jaime Arlandis).

Interlude

"As the children stared enraptured by these most beautiful heavenly visions, the countless thousands of people were amazed and overpowered by other miracles in the skies. The sun had taken on an extraordinary color. The words of eyewitnesses best describe these stupendous signs. 'We could look at the sun with ease,' Ti Marto testified; 'it did not bother at all. It seemed to be continually fading and glowing in one fashion, then another. It threw shafts of light one way and another, painting everything in different colors, the people, the trees, the earth, even the air. But the greatest proof of the miracle was the fact that the sun did not bother the eyes.' A man like Ti Marto who spent all of his days in the open fields with his locks and tended his garden under the hot sun of the Portuguese hills, marveled at this fact. 'Everybody stood still and quiet, gazing at the sun,' he went on. 'At a certain point, the sun stopped its play of light and then started dancing. It stopped once more and again started dancing until it seemed to loosen itself from the skies and fall upon the people. It was a moment of terrible suspense.'[161]

[161] De Marchi, *The true*

Marian apparitions

In October of 1930, Bishop Dom Jose Alves Correia da Silva announced in a pastoral letter:

> “In virtue of considerations made known, and others which for reason of brevity we omit; humbly invoking the Divine Spirit and placing ourselves under the protection of the most Holy Virgin, and after hearing the opinions of our Rev. Advisors in this diocese, we hereby:
>
> 1. Declare worthy of belief, the visions of the shepherd children in the Cova da Iria, parish of Fatima, in this diocese, from the 13th May to 13th October, 1917.
>
> 2. Permit officially the cult of Our Lady of Fatima.”

Since then, the apparitions of Virgin Mary to these three Portuguese shepherd children in 1917 have been recognized by the catholic church as authentic: every year millions of devotees perform pilgrimages to Fátima to visit the place where they happened, with 2024 alone receiving an estimated 6.2 million visitors. The

case of Fátima is only one of the thousands of marian apparitions that have been reported since the first ones dating back to the 4th century.

Some critics suggest that the Fátima phenomenon was engineered by Portuguese bishops of the time as a way to undermine the secular First Republic that replaced the centuries-old Portuguese monarchy after the 1910 revolution, and it is clear that a multitude of factors exist that could motivate individuals to falsely report such experiences, not only political incentives, but also social, economical, and personal situations. On the other hand, while no systematic study has been done to date to characterize the features of the thousands of apparitions that have been reported in the last few decades, some phenomenological inquiries into the experiences of marian visionaries report vivid, realistic experiences, often shared by multiple individuals[162]:

> "descriptions of Mary as a "real, external person, occupying three-dimensional space", [who] spoke to them in their native language, and the children could hear and touch her. The reality of the vision was also seen in the later actions of the visionaries. Children were willing to forgo the pleasures of youth to become uncharacteristically religious. In Medjugorje, the children withstood interrogation by the police, as well as other social and political threats by people wanting them to recant. The children at Fatima were interrogated by the police and

[162] Horsfall, *The Experience*

threatened with death if they did not reveal the secret they were told by the vision.

While it may very well be the case that the Fátima phenomenon was entirely constructed for political reasons, the thousands of apparitions that have been reported over the years, for which in many cases no political motivations seem to exist, prompt us to at least consider the possibility that the visionaries truly experienced such apparitions, and did not just invent them post-hoc. Now, leaving aside the hypothesis of Virgin Mary having truly appeared on thousands of occasions over the last century, the possibility remains that people may have experienced such apparitions, without the Virgin having actually appeared. Of course, one possible explanation is that all apparitions were staged, and that someone enacted the Virgin in a way that was realistic enough to convince the visionaries. The super-natural features of many of these apparitions, and the fact that visionaries sometimes report having different degrees of control over the apparitions make it unlikely for this to be the only explanation behind this amusing phenomenon.

Assuming that coordinated efforts to theatrically stage such apparitions (whether or not the visionaries are aware) are not the only explanation behind this phenomenon, and leaving aside the possibility of the Virgin truly appearing to people, I suggest another possible mechanism to explain the marian apparition phenomenon: people may unconsciously generate such experiences for themselves, to then experience them with the absolute conviction of their reality. Much like the hallucinations generated by psychedelic drugs, or hallucinatory phenomena characteristic of psychosis, people could be generating convincing

multisensory experiences without being aware of having done so. Importantly, as opposed to schizophrenia, marian apparitions seem to be aimed at a socially-validated goal or intention, and visionaries don't seem to share a history of severe mental illnesses. To illustrate my point about intentions, just consider the following: there are multiple locations in the world now that yearly receive up to millions of pilgrims in order to visit the locations where alleged apparitions happened. On the other hand, it could be argued that the delusions of paranoid schizophrenic patients rarely lead to mass cult situations of the same caliber.

Now, while it is clear that humans are capable of generating multimodal hallucinations and experiencing them as real, the question remains: do we have the capacity to do so in a targeted way? Does this capacity to generate experiences ever align with some kind of logical goal or intention? Or is it always the pathological outcome of an imbalance or dysregulation? Throughout the following chapter I will address this question and, later on, I will use it to shed light on some aspects of research about depression, antidepressant treatments, psychedelic drugs, and, more generally, on some popular theoretical frameworks that aim to explain the computational goals of brains.

Chapter 3

Hypnosis, aesthetics, and sociality: on how images can create experiences

Abstract

In this article, I use Object Oriented Ontology's (OOO) account of metaphor as a perspective on the topic of hypnosis and some related phenomena. This analysis shows the potential of OOO's theory of aesthetics to be informative outside of the usual realm of aesthetics, while simultaneously highlighting some of its shortcomings. Understanding hypnosis from this aesthetic point of view can be illustrative of the ways in which our experience is more generally mediated by factors outside of our conscious awareness. In particular, I will take advantage of this understanding to convey a message of caution regarding how we carry out psychological experiments and scientific research at large. At the same time, the connections drawn in this work highlight the central role played by social dimensions in aesthetic situations, and should serve to highlight the need to bring forth such dimensions when thinking about aesthetics in OOO.

Introduction

In this article, I will use Object Oriented Ontology's (OOO) theory of aesthetics[163, 164] to propose a perspective on hypnosis and related phenomena as a special class of aesthetic experiences. To do so, I will consider a contemporary interpretation of hypnosis called phenomenological control (PC)[165], which proposes that hypnotizability can be interpreted as the ability of a given subject to exert control over their own experience, without being aware of having exerted such control. According to the proponents of PC theory, the terms hypnosis

[163] Harman, 'Guerrilla', 101
[164] Harman, 'Object', 59
[165] Dienes, 'The Role'

and suggestibility are misleading because they evoke ideas about sleep and gullibility, respectively, which are not helpful in conceptualizing the realities they refer to[166]. Instead, they propose PC as a way to highlight that the experiences classically associated with hypnosis are related to a capacity to generate an experience for oneself without being aware of having done so.

I will use Harman's analysis of metaphor to interpret phenomena related to PC as aesthetic experiences, drawing a parallel between the objects that participate in Harman's metaphor and those participating in a hypnotic suggestion, as well as the dynamics between the different parts of those objects. I will argue that a new object is generated in hypnosis in a similar way as it happens in OOO's account of metaphor, and I will generalize this scheme to other scenarios involving phenomenological control. The parallelism between metaphors in OOO and phenomenological control will hinge on what I believe are some shared dynamics between the two, but it will at the same time highlight some important differences between these scenarios: first, that in many PC cases, no one needs to craft the object that the aesthetic beholders will experience, second, that this object doesn't always need to be explicitly presented to the subjects, and third, that in PC, this object often manifests in ways which rarely happen in metaphor. The application of OOO's theory of aesthetics to PC presented here provides a novel perspective on the topic of PC, which can lead to new intuitions about how our experience can be mediated by implicit factors that we may be systematically ignoring. At the same time, this parallel between metaphor and phenomenological control highlights some shortcomings of OOO aesthetics: while analyzing situations involving PC I will draw attention to the importance of social dimensions in these situations,

[166] Dienes, 'Phenomenological'

which will make it easier to appreciate such dimensions in the context of metaphor as well, and point out the need for OOO to account for these dimensions.

The main contributions of the paper will thus be, first, to illustrate how the interpretation of aesthetics proposed by OOO can be applied to understand certain aspects of PC, and second, how such an application of OOO's interpretation puts it to the test, reveals some important departures between the different scenarios, and indicates some shortcomings in OOO's take on aesthetics.

I will start by summarizing OOO's account of metaphor (Sections 1 and 2) and mapping it to a hypnotic example (Section 3). I will then generalize the hypnotic situation through the framework of PC theory, and illustrate this with the example of 'demand characteristics', a phenomenon in which subjects in psychological experiments tend to form an interpretation of what the experiment is about and involuntarily modulate their experience to fit that interpretation (Section 4). I will then consider the similarities and departures between the different scenarios treated here, and close by proposing some ways in which these considerations can inform our understanding of aesthetics, suggestibility, and related issues (Sections 5 and 6).

Real, sensual, objects, qualities

In the Overview section of "Object Oriented Ontology: A New Theory of Everything"[167], Harman summarizes his ideas on aesthetics in the following way:

[167] Harman, 'Object', 260

> Aesthetic experience is crucial to OOO as a form of non-literal access to the object. It occurs when sensual qualities no longer belong to their usual sensual object, but are transferred instead to a real object, which necessarily withdraws from all access. For this reason, the vanished real object is replaced by the aesthetic beholder herself or himself as the new real object that supports the sensual qualities. Thus we can speak of the necessary theatricality of aesthetic experience [...]

Harman condenses here his ideas about metaphor, in which a peculiar dynamic emerges between the three objects involved: the reader and the two objects proposed by the metaphor itself. I will later use this interpretation of aesthetics to analyze the dynamical structure of a successful hypnotic suggestion, which will be the starting point for some more general points regarding PC and related topics. Because it is quite a central part of this article, I will now dedicate some time to unpack the concepts summarized in the quote above, starting with some basics about OOO.

OOO is a flat ontology, centered on de-emphasizing the importance of humans in accounting for what reality is, suggesting that we are in urgent need of considering other objects with the same rigor[168]. In a nutshell, OOO proposes that all existing things are ontologically equal, i.e., they exist and are real in virtue of themselves and not due to any grounding entity such as a human consciousness (as Harman argues is often the case in Modern philosophy). OOO proposes that reality is entirely made up of objects: things that are not colloquially referred to as objects, such as myself, a political party, or a war, are all

[168] This is a crucial part of OOO, but I want to highlight that the ideas about hypnosis and related topics presented in this paper concern humans, and I don't intend to imply that they generalize in any way to non-human entities.

considered objects in OOO. In Harman's theory, the way in which objects are in relation to one another is always different from the way they are outside of any given relation, which constitutes the first of two dichotomies characterizing objects in OOO: the dichotomy between parts of objects labeled 'real' (which remain withdrawn) and those labeled 'sensual' (which are accessible to other objects). The second dichotomy, which highlights that objects are not reducible to a set of qualities, is the one between the object and its qualities. The combination of these two dichotomies gives rise to the four parts of the object in OOO (i.e. the four-fold object).

The Real Object (RO) is withdrawn from all other objects and constitutes the inaccessible inwardness of the thing itself. Every object has qualities, and one of the central arguments of OOO is that there is a deep cleft between an object and its qualities. OOO argues that there is something deep within the object that cannot be exhausted by a summation of all its qualities, something that cannot be reduced downwards (to its constituent parts) or upwards (to its effects or consequences). The fact that we cannot gain any access to the inwardness of the RO doesn't mean that it's not there, it's just a consequence of the RO being always withdrawn. Similarly, the Real Qualities (RQs) are themselves withdrawn too, albeit as real as the RO. On the other hand, every object has a Sensual Object (SO) and Sensual Qualities (SQs), which are the only parts of the object that are accessible to other objects. A consequence of this position is that, because *objects are never just bundles of literal properties*[169], OOO claims that literal language, which describes things in terms of definite literal properties, is always an oversimplification[170]. We will get back to literalism when considering the realm of aesthetics as a non-literal relation to objects. To

[169] Harman, 'Object', 37
[170] Harman, 'Guerrilla', 105

better illustrate the idea of the four-fold object, I will now consider myself as an object in this framework. We will later come back to myself as an example in order to analyze the dynamics of hypnotic suggestions.

To an external observer, I appear as an entity with a certain set of features. A person looking at me will form an idea of me as an object through their senses (they have access to my SO and SQs), and will in most cases understand that I'm a separate entity from the person standing next to me. In the same line of thinking, let's say that this person is able to perceive that I have brown hair. That is one of my features, a SQ which they are accessing through their senses. I could shave my head, but our imagined external observer would still recognize me as myself. In that sense, the SQ of having brown hair is not essential for me to remain the same object. As opposed to shaving my head, however, some changes would make me stop being me. For instance, if I died and decomposed into organic matter, most would agree that I would have ceased being me at some point in the process. The qualities that cannot change without me being changed as well are what Harman refers to as Real Qualities (RQ), and in this case they would have changed at some point in the process of my disappearance as an object. As inaccessible as the RO, RQs are only known by indirect allusion or innuendo.

The difference between my SO and my SQs is important too: the external observer in our example can recognize me as being the same entity somewhat independently of SQ changes, and across situations, because they have access to my SO (e.g. they understand that I'm me independently of my hairstyle, my behavior, my clothing, my location… and many other changes that don't fundamentally change what I am). In that sense, for Harman, I have an identity as an object that cannot be exhausted by the sum of my perceivable qualities, and which remains implicit in all of my varying instances (an external observer can see my

SQs change while still perceiving me as the same entity because they have access to my SO as well). At the same time, as much as they may perceive me as a single entity, external observers will never have access to *all* that it means to be me, because my RO, akin to Kant's thing in itself (the noumenon, the object as it exists independently of the mind or human perception), is always withdrawn from external access.

With this fourfold structure in mind, Harman argues that literalism, understood as a way to approach objects in terms of their definite literal properties, is a superficial way to embrace objects. The accumulation of factual information about the SQs of objects, he argues, doesn't come any closer to the real core of the object of study. According to him, this is the way that science is usually carried out, and it doesn't actually bring us any closer to the RO and RQs of objects. On the other hand, he proposes that '*indirect allusion, hint or innuendo are more powerful than direct access to the truth'* [171]. In his philosophy, aesthetic experiences (exemplified by metaphor) have a privileged position because they allow us a peculiar type of indirect relation with other objects. Harman analyzes in depth Ortega's 'An Essay in Esthetics by Way of a Preface' [172] (which heavily influenced his views on aesthetics), and draws on Ortega's analysis of metaphor to illustrate his own ideas about aesthetics. Still withdrawn and inaccessible, the real parts of the objects remain forever out of reach, but through aesthetics, in Ortega's words, it '*seems'* that we are granted access to them[173]:

> Ortega is effectively saying that Kant's noumenal realm *is not* inaccessible, but that art consists precisely in giving us this noumenal realm in person. Yet he adds an important

[171] Harman, 'Object', 63
[172] Ortega, 'Ensayo'
[173] Harman, 'Object', 71

> qualification: ‘Notice I am not saying that a work of art reveals the secret of life and being to us; what I do say is that a work of art affords the peculiar pleasure we call esthetic by making it *seem* that the inwardness of things, their executant reality, is opened to us’. He goes on to compare scientific discourse unfavorably to this aesthetic contact with inward, executant realities, though his real target is not so much science as what we have called *literalism*.

Later on, Harman points out that the tension between real and sensual poles of an object becomes explicit not only in art but in a limited number of other cases[174]. The analysis of metaphor that follows will be instrumental to later illustrate my argument about the case of phenomenological control being a very special instance of these other cases. I will start with Ortega’s take on metaphor, highlighting some important points that we will later come back to, and then move on to Harman’s interpretation.

És com l’espectre d’una flama morta

As pointed out by Harman, Ortega’s essay makes an important contribution before going into the section about metaphor: he extends Kant’s idea of the *noumenon* to things other than humans.

> There is the same difference between a pain that someone tells me about and a pain that I feel as there is between the red that I see and the being red of this red leather box. Being red is for it what hurting is for me. Just as there is an I- John Doe, there is

[174] Harman, ‘Object’, 85

also an I- red, an I- water, and an I- star. Everything, from a point of view within itself, is an I. [175]

Ortega talks about *images* when referring to things as they are perceived or used, and about their *executant reality* when referring to them apart from how they are seen or used. This can be mapped to *sensual* and *real* parts of objects when thinking in OOO's terms. However, in Harman's view, as we will see later when discussing symmetry in metaphor, Ortega misses the opportunity to establish the other dichotomy central to OOO: the one between an object and its qualities.

A central example to Ortega's analysis is a metaphor by López-Picó from his poem 'of a cypress'[176], in which he writes that it 'is like the specter of a dead flame': leaving out the 'specter' and 'dead' metaphors, and focusing on the metaphor '(the cypress) is like a flame', this example is used by Ortega to present his views about metaphor, which I will briefly summarize now, before going into Harman's take.

In Ortega's view, even though every metaphor includes a resemblance, it's a mistake to consider metaphors to just be assimilations between distant things: instead, by taking objects that are far from each other, and thus difficult to assimilate, metaphor satisfies us by using the pretext of their surface similarity to give us a coincidence that is *'deeper and more decisive'* than any possible resemblance. In

[175] Ortega, 'Ensayo', 157. In 'Guerrilla', 104, Harman labels these last two sentences as 'one of the most radical sentences of twentieth-century philosophy'

[176] Zimmermann, '*Actes', 201.* The original poem, '*D'un Xiprer'* reads as follows (translation mine): "Ta vida és un desig d'agilitat; | voldria ser gentil i és massa forta. | Ta vida és un desig llarg i callat; | és com l'espectre d'una flama morta."("Your life is a desire for agility; | it would like to be gentle and it is too strong. | Your life is a long and silent desire; | it is like the specter of a dead flame.")

that sense, the *'real similarity'* [177] which is suggested by the metaphor is just an '*insignificant geometrical observation'* (in the case of the cypress and the flame), a pretext to bring these two distant objects together.

> The mechanism, then, may be as follows: it is about creating a new object that we will call the "beautiful cypress" in opposition to the real cypress. To achieve this, it is necessary to subject the real cypress to two operations: the first one involves freeing ourselves from the cypress as a visual and physical reality, annihilating the real cypress; the second one involves endowing it with that new, extremely delicate quality that gives it the character of beauty.[178]

The role of the assimilation discussed so far is to achieve the first operation: *'united by a coincidence, in something insignificant, the remnants of both images resist integration, repelling each other'*. The clash between the two things as '*real images'* causes their annihilation[179]. Importantly, in this last quote he clearly states that the goal is to create (this creative outcome of metaphor is central for Harman too, as well as it will be for my analysis of hypnosis) the 'beautiful cypress', in *opposition* to the real cypress. While earlier in the essay he states that metaphor gives us the peculiar pleasure we call aesthetic *'by making it seem that the inwardness of things, their executant reality, is opened to us'* [180], here, he clearly states that the outcome of the metaphor, the new object that is created, is not only

[177] Ortega, 'Ensayo', 165
[178] Ortega, 'Ensayo', 166
[179] Ortega, 'Ensayo', 167
[180] Ortega, 'Ensayo', 163

different, but *opposed* to the real cypress[181]. Referring to the cypress and the flame, he goes on to say:

> When they collide, their rigid carapaces break, and the internal matter, in a molten state, acquires a plasma softness, suitable for receiving a new form and structure. The cypress thing and the flame thing begin to flow and turn into ideal cypress tendency and ideal flame tendency. Outside of the metaphor, in non-poetic thinking, each of these things is a destination, a point of arrival for our consciousness, they are its objects. Because of that, moving towards one of them excludes moving towards the other. However, when the metaphor makes the declaration of their radical identity, with the same strength as their radical non-identity, it leads us not to seek that identity in what both things are as real images, as objective terms; hence, to make them a mere starting point, a material, a sign beyond which we must find identity in a new object, the cypress to whom, without absurdity, we can treat as a flame.[182]

After having asserted that the identity between the cypress and the flame is not in their real images, the metaphor insists in proposing this identity and, in what Ortega considers the second operation, pushes us into another world where it is possible. For this, *'it will be necessary to find a way for the word "cypress" to erupt, become active, and acquire a verbal value[183].* In that sense, Ortega explains that every image has two faces: '*one is the image of a certain thing; the other is, as an image,*

[181] In Harman's words, 'Ortega's claim for metaphor, of course, is only that it presents the inner execution of the things in *simulated* form'. Harman, 'Guerrilla', 107
[182] Ortega, 'Ensayo', 168
[183] Ortega, 'Ensayo', 169

something of mine[...], with respect to the cypress, [the image of the cypress] *is only an image, but with respect to me, it is a real state of mine, it is a moment of my self, of my being' [184].* While I'm executing the act of perceiving the image of the cypress, thus, the object that exists for me is the cypress: in order to turn my perception towards my state while perceiving the cypress, *'it is necessary that I position myself, so to speak, with my back to the cypress thing, and from there, in the opposite direction to before, look towards my inside and see the cypress de-realizing itself, transforming into my activity, into me' [185].* Ortega calls this face of the image, my executant state, my action, a '*sentimiento',* usually translated as 'feeling'. He explains that whenever an *'objective image'* enters or exits our consciousness, it produces a subjective reaction, a feeling, which '*is nothing but the very act of perception' [186].* Because this subjective reaction is the very act of perception, and in order to attend it we would have to stop attending the object that was generating that subjective reaction (thus concluding the act of perception), we can never have our own subjective reaction as the object of our perception: '*our intimacy cannot be a direct object for us'.* He then recapitulates his interpretation of the metaphor dynamics in the following way:

> We are first invited to think of a cypress; then the cypress is removed from our sight, and we are asked to place the specter of a flame in the same ideal place the cypress occupied. In other words, we are to see the image of a cypress through the image of a flame, we see it as a flame, and vice versa. However, if they are mutually opaque, they exclude each other. Yet, it is a fact that

[184] Ortega, 'Ensayo', 168
[185] Ortega, 'Ensayo', 169
[186] Ortega, 'Ensayo', 169

> when reading this verse, we realize the possible perfect integration between them - that one, without ceasing to be what it is, can be in the very place where the other is; thus, we have a case of transparency that occurs in the sentimental place of both. The feeling-cypress and the feeling-flame are identical. Why? Ah, we do not know why: it is the always irrational fact of art, the absolute empiricism of poetry. Each metaphor is the discovery of a law of the universe. Even after a metaphor is created, we still ignore its why. We simply feel an identity, we live executively the being cypress-flame[187].

In a footnote, Ortega explains that metaphor, etymologically, refers to the positioning of one thing in the place of another. This transference, according to him, is always mutual in metaphor[188], which, for him, suggests that the place where each of the two things is placed is not the place of the other, but rather a sentimental place that they both share: *'The metaphor, then, consists of the transposition of a thing from its real place to its sentimental place' [189].* As explained above, he thinks of my executant reality while perceiving the cypress as a *sentimiento*, and thus when he explains that the metaphor consists of the '*transposition of a thing from its real place to its sentimental place',* he is referring to the transposition of the thing into my executant reality while

---

[187] Ortega, 'Ensayo', 170

[188] This is one of the points that Harman disagrees with. In his view, this is a missed opportunity to highlight the tension between an object and its qualities. Even though 'the flame is the ghost of a dead cypress' would be as poetic as the original form of the metaphor, they are clearly different: Harman highlights that metaphors are always asymmetrical, because one is always contributing its object, while the other one is contributing only qualities. In Harman's view, this *deep divide or tension between an object and its own qualities is something that comes to the forefront in many situations, but especially in art and philosophy.* Harman, 'Object', 75

[189] Ortega, 'Ensayo', 170

perceiving it: *'We simply feel an identity, we live executively the being cypress-flame'.*

> We have found an object consisting of three elements or dimensions: the cypress thing, the flame thing - which now become mere properties of a third person - the sentimental place or the 'me' form of both. The two images endow the new marvelous body with an objective character; their sentimental value gives it a sense of depth, of intimacy. Being careful to equally accentuate both words, we could call the new object '*sentimental cypress*'.
> This is the new conquered thing - for some, symbol of the supreme reality[190].

This quote concludes Ortega's analysis of metaphor by stating that there is a new object, which Ortega calls the *sentimental cypress*, which is formed by three elements or dimensions: the images of the cypress and the flame, and their shared sentimental place or 'me' form. While earlier in the essay he explains that my act of perceiving an object cannot be the object of my perception, his conclusion of this section points to this perception becoming available, in some way, through metaphor. The new object is composed of the cypress and the flame images, along with their respective sentimental places or 'me' forms, my executant state when perceiving them: that which I would perceive if I turned around while perceiving them and looked towards my inner reality. The metaphor thus *'leads us not to seek that identity [of the cypress and the flame] in what both things are as real images, as objective terms; hence, to make them a mere starting point, a material, a*

[190] Ortega, 'Ensayo', 171

sign beyond which we must find identity in a new object, the cypress to whom, without absurdity, we can treat as a flame.' According to Ortega, the metaphor asks us to use the images of the cypress and the flame as starting points, and to look towards ourselves to find the *sentimental cypress* that we can treat naturally as a flame. *'The feeling-cypress and the feeling-flame are identical. Why? Ah, we do not know why: it is the always irrational fact of art, the absolute empiricism of poetry.'* In a sense, while metaphor may *seem* to give us access to the executant reality of things, it is instead pointing towards our own executant reality in perceiving them. We will now see how Harman adds emphasis on the proactive nature of our role as aesthetic beholders with his concept of *theatricality: 'It would be more accurate, however, to say that in art the part of the image which looks towards the object is subordinated to our efforts, as basically thespian beings, to become the new object generated by the metaphor.'* [191]

Let's now go into the perspective proposed by Harman[192] to illustrate the dynamics of metaphors in OOO. Usually, mentioning the cypress object would elicit the corresponding SO and its SQs in the reader. However, by adding to the picture the, in Harman's words, '*improbable, but not impossible*'[193] qualities of the flame, the SO-SQ relation of the cypress is disrupted.

> By assigning improbable but not impossible new sensual qualities to the sensual object – such as the metaphorical

[191] Harman, 'Object', 85
[192] Harman, 'Object', 72. I hesitate to correct either Ortega or Harman in their interpretation of this poem, but I believe that in the original 'is like the specter of a dead flame' doesn't refer directly to the cypress, but rather to the *life* of the cypress ("Ta vida [...] és com l'espectre d'una flama morta"). Furthermore, the word used by the López-Picó is *specter* and not *ghost*. For the purpose of this analysis these corrections don't really matter, so I will just refer to their interpretation of the metaphor 'the cypress is like a flame'.
[193] Harman, 'Object', 84.

> "wine-dark sea" rather than the literal "dark blue sea"– the sensual object "sea" is canceled [...], being unable to uphold such unusual qualities. A mysterious real object is needed to do the job. But since sea as real object withdraws inaccessibly from the scene [...], the sensual qualities of the metaphor are supported instead by the only RO that is not withdrawn from the situation: I myself, a real experiencer of the metaphor.

The terminology here is somewhat ambiguous: on the one hand the qualities are *improbable but not impossible,* on the other hand, the SO of the "sea" gets canceled because it is *unable to uphold such unusual qualities.* My interpretation is that *improbable* and *unusual* here is meant to highlight that the two objects in the metaphor are, on their own, incompatible in a literal sense (except for the assimilation that Ortega refers to as *pretext)*, but can become (thus the '*not impossible')* a compound object through the involvement of the reader, as we will see soon. I will keep using these expressions in that sense: some objects seem a priori incompatible, but can be combined in metaphor through the active involvement of an engaged subject.

Because the SO of the cypress cannot really support the SQs of the flame, it is immediately canceled out from the scene. The RO of the cypress is still always inaccessibly withdrawn from the situation, and the only RO left in the scene that could support the SQs of the flame is *my* RO, as the experiencer of the metaphor. Thus, because of the tension between the cypress and the flame, a void is left where the cypress's SO used to be, and my RO ends up entering the scene. This pulling of the reader's RO into the metaphor is a key point, which will also play an important role in understanding hypnosis later on. Similar to Ortega's point about the sentimental cypress and flame identifying with each other in the executant reality of myself perceiving them, Harman here argues

that my RO, my inaccessible inwardness, is pulled into the scene by the metaphor. Harman uses the idea of theatricality to explain this relation of the reader to the objects involved in the metaphor:

> All we are saying is that the real object at stake in metaphor is neither the absent cypress-object to which we never gain direct access, nor the human being who takes note of it, but rather the new amalgamated reality formed from the reader (who poses as a cypress-object) and the qualities of the flame. These are the two components of the cypress-flame.[194]

Importantly, this interpretation doesn't consider metaphors as a way of accumulating knowledge about a given object, it rather emphasizes the generative nature of metaphors, their ability to create a new object. Again, this is in agreement with Ortega's essay. When I engage with the metaphor (or in any other aesthetic experience), a new amalgamated object (compound) is created through what Harman refers to as 'theatricality'. One of Harman's contributions, as I understand it, consists in emphasizing the proactivity of the RO of the reader in 'posing' as the new object. While Ortega talks about the inner executant reality of the reader when perceiving the images in the metaphor, Harman turns this inner executant reality into a RO *acting, posing, theatrically* enacting the new cypress-flame object.

In the following section, I will translate the dynamics of the three four-fold objects (cypress, flame, reader) described here to the context of hypnotic suggestions, and argue that a similar theatricality underlies the fulfillment of suggestions, connecting it to examples outside of hypnosis. Before I move on, I believe it is important to note that the experience of

[194] Harman, 'Object', 88

reading a metaphor is not actually that similar to that of playing a role in a theater play. My interpretation of the term ‘theatricality’ used here by Harman is not that the reader of a metaphor is voluntarily ‘acting’ out the metaphor, but rather that the mere act of reading a metaphor while being engaged in the reading and trying to understand it requires a particular form of implicit theatricality. In other words, the experience of reading ‘the cypress is like a flame’ is related but different from that of following a request to act as a cypress flame (this will become more clear in the hypnotic example).

Soon you will feel that your hand is starting to raise

Moving on to the example of hypnosis, I will now give a small introduction to this vast field of research dating back to the origins of psychological research itself in the eighteen-hundreds. I will then use the ideas about aesthetics explained above to analyze the dynamics of a hypnotic suggestion. The definition of hypnosis is a highly controversial topic on which no consensus exists. For instance, in the American Psychological Association’s (APA) online Dictionary of Psychology, hypnosis is defined as follows:

> The procedure, or the state induced by that procedure, in which suggestion is used to evoke changes in sensation, perception, cognition, emotion, or control over motor behavior. Subjects appear to be receptive, to varying degrees, to suggestions to act, feel, and behave differently than in an ordinary waking state. The

> exact nature of hypnotic suggestibility, and its possible therapeutic uses, are still being studied and debated. [...] [195]

This definition considers hypnosis to be both a procedure (usually referred to as *induction*), as well as the state induced by that procedure[196]. It doesn't specify any properties of such a state, apart from the fact that suggestions are given to the person in the state, and that subjects appear to some degree receptive to those suggestions, which compel them to behave or feel differently from how they ordinarily would. The definition of hypnosis as a procedure or a state, the idea that hypnotic inductions increase suggestibility, and the possibility of specifying what is an 'ordinary waking state' are all controversial topics, and the main reason why I'm bringing up this definition here is precisely to show that even after almost two hundred years of history, the field of hypnosis research is still struggling to define its scope, which I think is symptomatic of the complexity of the topic.

In the nineteenth century, hypnotism was used predominantly by surgeons as a way of inducing anesthesia during surgery[197]. By the 1880s, hypnosis started to attract the attention of doctors treating mental health disorders[198]. If we fast forward to the 1950s, Milton Erickson

---

[195] https://dictionary.apa.org/hypnosis, April 2024

[196] In an amusing coincidence, Ortega writes in the essay here analyzed: "Above all, we should note that the term 'metaphor' refers both to a process and a result, a form of mental activity as well as the object obtained through that activity"[21]

[197] Pintar, 'Hypnosis', 41

[198] Pintar, 'Hypnosis', 77. The relationship between hypnosis, hysteria, and the origins of psychoanalysis in the late nineteenth century is a fascinating topic on its own, but as much as I believe it to be extremely relevant for the current work, I cannot afford to delve deeper into it here. For some interesting references on the topic check Marshall, 'Performing', where the relationship between performance, hysteria and hypnosis is analyzed in the case of Charcot and his studies on hysteria patients at the Salpêtrière hospital, or Breuer, 'Studies', 215, one of the foundational works in the field of psychoanalysis, where the first instance of 'the talking cure' (the famous Anna O. case) is discussed, and

popularized a style of hypnosis where, among other techniques, suggestions were discreetly interspersed throughout psychotherapy sessions in order to influence the long term behavior of the patients[199]. It's beyond the scope of this paper to analyze the history of hypnosis in depth, or the controversies over its definition, but I think it's relevant to point out that the term has been used to describe both a procedure used to get a patient into an unconscious state in which pain-free major surgeries are possible, as well as a set of techniques that can help in a years-long psychotherapeutic process where unconscious states are not desirable. These two examples merely hint at the varied nature of hypnotic phenomena: hypnosis has been studied in relation to the induction of 'involuntary' movements, hallucinations, amnesia or catalepsy, as well as for pain management, anesthesia, or psychotherapy, just to name a few[200]. Sometimes the concept of 'state' is emphasized, where in order for something to be hypnotic someone has to be in 'trance'[201], while other times the only thing needed for a context to be hypnotic is for the word 'hypnosis' to be included into the induction preceding a set of suggestions[202]. One of the most robust results in the hypnosis literature is that the degree to which subjects respond to hypnotic suggestions, often referred to as 'hypnotizability', seems to be a very stable trait for any given individual (over spans of many years), and to be roughly normally distributed in the adult population[203]. These

---

where Breuer dedicated a section to his theory of 'hypnoid states', stating that "We [Breuer and Freud] should like to balance the familiar thesis that hypnosis is an artificial hysteria by another - the basis and sine qua non of hysteria is the existence of hypnoid states." The theory of 'hypnoid states' being the basis of hysteria would later on be abandoned by Freud in favor of his theory of repression, but I think it's worth mentioning here to give a sense of the relevance of hypnosis in the history of psychoanalysis.

[199] Erickson, 'Hypnotherapy'
[200] Oakley, 'Hypnotic'
[201] Pintar, 'Hypnosis', 120
[202] Gandhi, 'Does hypnosis'
[203] Elkins, 'Hypnotizability'

features of hypnotizability can lead to some interesting considerations once we establish the link between aesthetics and hypnosis in the following paragraphs.

Given the complexity associated with the idea of hypnosis, I will now focus on the concept of suggestion, for which it seems more feasible to have an operational definition, and which is enough to illustrate the main ideas that I want to convey in this section[204]. In a recent review on the topic of hypnotic suggestibility[205], Acunzo and Terhune give the following definition of suggestion:

> A suggestion refers to an invitation to perform an action or experience a cognition or percept in such a way that it is experienced in an involuntary manner and evokes conviction as to the reality of the experience. Suggestions are typically structured as happenings (e.g., "when X happens, you will find that Y"), that is, events that happen to a person rather than doings (e.g., "when X happens, you will do Y") – actions that one performs. The experience that one's response to a suggestion is outside one's control (i.e., a distortion in the sense of agency[206]) is the hallmark phenomenological feature of response to suggestion and widely referred to as the classic suggestion effect.

Using their example structure, a typical suggestion could be phrased as follows: "when you are as relaxed as you can possibly be,

---

[204] I will still refer to the example as a hypnotic suggestion, because most research regarding direct verbal suggestions comes from the hypnosis literature, but as mentioned in the introduction, I'll also later explore some recent views that propose moving away from the term hypnosis altogether.
[205] Acunzo, 'A Critical'
[206] Sense of agency refers here to the feeling of control over one's own actions [20]

you will find that your hand starts to feel very light, as it slowly floats away from the table where it's resting now", or, to simplify: "soon you will feel that your hand is starting to raise". This is a classic example of suggestion, which in the taxonomy of their paper would be classified as a *facilitative motor suggestion*, since it facilitates an involuntary arm movement. If the suggestion had its intended effect, the subject would then raise their hand, and experience it *as if* the hand was rising on its own, or was being raised by some other entity. This altered sense of agency, the perception that the suggestion is having an effect outside of one's control, is often central to the experience of hypnotic suggestions[207].

I argue that by describing hypnosis in terms of OOO's aesthetics, it becomes apparent that it constitutes a very special case of indirect experience of the tension between the real and sensual poles of objects. In this case, the amalgamated object resulting from the hypnotic process manifests in a way that presents some fundamental differences with respect to a successful metaphor in literature. Let's first go through what I mean by 'describing hypnosis in terms of OOO's aesthetics', and we will come back to these points later.

To recapitulate, in his analysis of López-Picó's metaphor 'the cypress is like a flame', Harman explains that the flame qualities '*are improbable but not impossible'* for the cypress to support. This makes it

---

[207] I would argue that it's not the only *hallmark phenomenological feature of response to suggestion,* as this wouldn't apply, for instance, for most hypnotically-induced visual hallucinations, where an altered sense of agency is not salient during the suggestion: in such a case the suggestion could be considered successful when the subject reports perceiving the suggested hallucination. Later on, when we consider the active role of the hypnotic subject, we can reconsider the hallucination example as also implying an altered sense of agency in the sense that the subject is generating the experience of the hallucination without realizing that they are doing so. However, this altered agency is transparent to the subject in the case of the visual hallucination, while it becomes visible in the case of the motor suggestion.

so that the SO of the cypress can't remain as the substrate for these qualities, being thus forced to abandon the scene. Because the cypress' RO is always withdrawn, the only RO that can possibly then fill in that void is the RO of the reader of the metaphor. The real object at stake in the metaphor is then, according to Harman, '*the new amalgamated reality formed from the reader (who poses as a cypress-object) and the qualities of the flame. These are the two components of the cypress-flame*' [208].

Our example suggestion "soon you will feel that your hand is starting to raise" can be explained in very similar terms. In the metaphor analyzed by Harman the objects involved are the reader, the cypress, and the flame (the real parts of the cypress and the flame are, as always, withdrawn and inaccessible, and the only parts that participate in the metaphor are their sensual parts, or in Ortega's terms, their images). In the case of the suggestion, those correspond to the subject receiving the suggestion, their image of themselves in the future, and their image of themselves in the future proposed by the suggestion, respectively. For clarity, I'll once again use myself as an example subject.

When hearing the hand levitation suggestion, I'm compelled to imagine a certain future (in the case of this suggestion, an immediate future, but it could be delayed for an arbitrary amount of time) in which my hand raises. Because, as far as I'm aware, I don't have any intention to raise my hand, the idea that my hand will soon rise on its own is somewhat disconcerting, it doesn't match my tacit expectations. In that sense, insofar as the improbable suggestion conflicts with my expectations for the future, the suggestion is also evoking the counterpart to its own contents: this default expectation that my hand will *not* rise on its own. This is my 'non-hypnotic' image of myself in the near

[208] Harman, 'Object', 88

future: if I was asked about my near future instead of having received a suggestion, this is the image of myself that would be evoked[209]. I propose that this is the equivalent of the image of the cypress, and in the same way as in metaphor, this is the image which will initially contribute its sensual object to the scene. I will call this my Default Image, DI. On the other hand, the image that is elicited by the hypnotist, I propose, is the equivalent of the flame, which will contribute its sensual qualities to the scene. I will refer to this as my Suggested Image, SI. Finally, as the hypnotic subject, I'm the equivalent of the reader of the metaphor: Current Me, or CM, myself at the time of hearing the suggestion.

When giving me the suggestion, the hypnotist is taking an SQ (a spontaneously rising hand) from the SI (which they invented), and suggesting to me that it will happen to DI, my current expectation of myself in the future[210]. This SQ is improbable but not impossible for the SO of DI to support, as much as flame qualities are improbable but not impossible for the SO of the cypress. And much in the same way as in the metaphor, because the SO of DI is not suitable to support the SQ of SI, and because all other ROs in the scene are inevitably withdrawn, my RO is left as the only possible object in the scene to support the SQs of SI, and thus the suggestion takes effect.

---

[209] I'm emphasizing here that it's non-hypnotic because it is elicited by negating the hypnotic suggestion. Of course, multiple images of myself in the future can coexist and they could be elicited, for instance, by asking me about my future in different ways. However, I believe that the suggestion elicits one specific such image, characterized by the suggestion *not* happening.

[210] Similarly to another metaphor used by Harman in his work, Homer's 'wine-dark sea', in the case of this suggestion, it's also a simplification to consider that the only SQ that is evoked is the one mentioned explicitly: apart from the hand rising spontaneously, I may infer other SQs when receiving the suggestion. For instance, I could interpret that for my hand to rise independently from my will, I would have to be in a very peculiar state of mind. I decided not to get into the intricacies of the reality of trance states by focusing on the concept of suggestion instead, but I do want to highlight that this can be an interesting perspective on the idea of trance.

Now, an immediate objection to this view could be that as opposed to a cypress and a flame, DI and SI are both images of future versions of me, of the same object, and thus the SO of DI can easily support the SQs of SI. This is indeed the case here, but I propose that even though there is sometimes this fundamental difference with the case of literary metaphor in the degree to which the images involved are compatible (in the case of metaphor the images evoked correspond to different objects while in this suggestion example they do not[211]), there is always some kind of conflict in the case of suggestions too, where the SQs proposed are still *improbable but not impossible* for the SO involved in the scene. In this case, we are being told that our hand will rise on its own, in a situation in which we didn't have any intention of raising our hand. In that sense, the contradiction appears between our expectation and the future suggested by the hypnotist. If the suggestion was instead driven towards obtaining analgesia, for instance, the conflict would appear between the sensation of pain (if the suggestion was intended to curb an already existing pain), or my expectation to experience such sensation in the future (if the suggestion was phrased, for instance, as 'you will feel a tingling sensation when I poke you with this needle'), and the suggested absence of such sensation. In reality, this point directly emanates from even the most intuitive definition of suggestion: if there is no such conflict, there is no suggestion. If I told you, on a sunny day, 'you will feel the sun on your skin once you exit the building', the fulfillment of my prediction wouldn't usually be considered very hypnotic.

[211] It could be, however, that the evoked images corresponded to different objects in the case of the suggestion too, if the suggestion was phrased in a more poetic way, for instance, as 'your hand is like a hot air balloon'. Because of the same reason why metaphors cannot be translated literally, this suggestion could perhaps lead to an even wider array of possible outcomes: perhaps on top of the hand levitation, I could also experience a sensation of warming of the hand. Sometimes suggestions are phrased in such intentionally open ways, often in order to constrain less the range of outcomes that would be perceived as successful by the receiver (see Yapko, 'Trancework', 268).

Same as if I said ‘soon you will feel that your hand is starting to raise’ the moment you are about to raise your hand to ring a doorbell.

Apart from these particularities about the objects involved and the nature of the conflict that arises, there is another important difference with the metaphor example: the outcome. Again, in Harman’s words: *“the real object at stake in metaphor is [...] the new amalgamated reality formed from the reader (who poses as a cypress-object) and the qualities of the flame”*[212]*.* The equivalent new amalgamated reality that emerges from the hypnotic situation consists of myself (posing as a DI-object), and the qualities of SI. The clash between DI and SI occurs in the same way as it occurs between the cypress and the flame, but the fact that the suggestion is successful and my hand actually rises indicates that in some way, the amalgamated compound resulting from the suggestion is possible and in this case, as opposed to the cypress-flame, it can transcend the private experience of the aesthetic beholder (anyone witnessing the scene can see the hand raising, while the cypress-flame is only experienced by the reader). Discussing the nature of the aesthetic object, Ortega explains that *“ ‘Don Quijote’ is neither my feeling, nor a real person or the image of a real person: it’s a new object that lives in the ambit of the aesthetic world, which is distinct from the physical world and from the psychological world”* [213]. I could argue that, as opposed to the aesthetic object, which stays in the aesthetic world, the hypnotic object escapes this aesthetic world and happens in the physical world. However, I’m not particularly enthusiastic about Ortega’s categorization of the world into a physical, a psychological, and an aesthetic world, and I don’t think it would be easy to fit that statement into a OOO framework, either. From the perspective of OOO, the way in which my hand actually raises in the physical world

[212] Harman, ‘Object’, 88
[213] Ortega, ‘Ensayo’, 171

doesn't make the new amalgamated compound any more real than the one generated in metaphor, so stating that the compound object is somehow more real in the hypnotic case is also not an option here. However, I will still argue that in many cases[214] the way in which this compound object happens in hypnosis constitutes a crucial difference between the metaphor and hypnotic contexts. Instead of just allowing me to, as in literature, *experience a new entity*[215] in a private fashion, in the hypnotic case I get to directly become this new entity, in a way which is often perceivable from the outside, and which can thus also elicit a similar aesthetic experience in other people[216]. While a metaphor may sporadically lead to a change in the behavior or attitude of the reader, a successful hypnotic suggestion will in most cases lead to such an outcome. This will be crucial when discussing social dimensions in the next sections.

According to Harman, in order for the metaphor to occur, the reader has to step in and attempt the electrifying work of becoming the cypress-substance for the flame-qualities, otherwise no metaphor occurs. When the metaphor occurs, *'we are method actors playing a cypress playing a flame'* [217]. Again, a central point in this interpretation is that the metaphor bringing together cypress and flame is thus not a form of knowledge about a pre-existing object, but rather the production of a new object. These properties are central to the hypnotic context, too: if

---

[214] It's not the case, for instance, when the suggestion aims to generate visual hallucinations: the object in hypnosis also tends to remain as a private experience there.
[215] Harman, 'Object, 73
[216] One example of this is the case of 'modeling trance behavior', an induction technique mentioned several times in Erickson, 'Hypnotherapy', for example, in page 109: *Erickson is using one of his favorite approaches to trance training. He simply has the new subject watch another more experienced subject go into trance.* Another more subtle example (which will become clearer after discussing placebo effects in the next sections) is the case of the socially transmitted placebo effects discussed in Chen, 'Socially'.
[217] Harman, 'Object', 87

the subject is not engaged with the suggestions, these have no magical powers to influence their experience. Importantly, by 'playing the role' of the hypnotized subject, we are creating a new object, which in our example, as highlighted above, has the potential to immediately influence our social surroundings.

I want to emphasize here that through this process, the decision of the hypnotist to imagine a certain future situation has become a generative process, where the situation actually ends up realizing itself. By imagining this hypnotic version of my future, and skillfully suggesting it to me, the hypnotist has turned this imagined scenario into a reality. At the same time, I want to reiterate that even though the terms 'method actor', 'posing', and 'theatricality' have been thrown around, they are not meant to imply that there is a conscious process of compliance or a conscious decision neither to become an actor posing as a cypress-flame, nor to become an actor posing as an amalgamated DI and SI. In both cases, these terms are used to conceptualize processes that would not necessarily be reported in this way by neither the reader nor the hypnotic subject.

In the next section, I will contextualize the example of the hypnotic suggestion by exploring the contemporary idea of PC, focusing on the example of demand characteristics to illustrate some properties of PC that may not be illustrated by the hypnosis example.

Generating experiences to meet expectancies

One recent account on the topic of hypnotic suggestibility explains it as a special case of a more general human ability referred to as PC. Dienes *et al* [218] describe the concept as follows:

[218] Dienes, 'Phenomenological', 102

> Phenomenological control is the ability to control subjective experience so that a constructed counterfactual state of affairs appears real. It is not a new concept. We as a community have been calling it hypnotizability (in the context of hypnotic inductions) or suggestibility. But “hypnosis” refers to sleep, which is unrelated to phenomenological control; and “suggestibility” implies being manipulated contrary to one’s real intentions, a gullibility that is little related to hypnotic response.

Without recurring to supernatural powers such as telekinesis, the only possible explanation for why my hand would move in the hypnotic suggestion example we described is that I’m the one moving it. At the same time though, I feel like I’m not the one executing the movement, but rather it was the hypnotist through their hypnotic powers, or some other entity that is influencing me. One way to explain this is that I’m controlling my subjective experience so that it feels like my hand is being raised, while I’m actually the one raising it. As emphasized by the above explanation, instead of attributing my responsiveness to suggestion to a certain ease in being manipulated against my will, the idea of PC suggests that we can instead attribute it to my ability to control my own subjective experience to match a “*constructed counterfactual state of affairs”*, without being aware of having done so. Going back to the potential objection that because the suggestion contains two images which refer to the same object, a clash like the cypress-flame conflict would never happen, I want to emphasize this idea of the *‘counterfactual state of affairs’*: as discussed above in the case of hypnosis, a contradiction is always present when phenomenological control takes place, otherwise such a mechanism would not be necessary. The authors use the word counterfactual here to point to the fact that the

content of the suggestion often goes against what would be reasonable to believe in a certain situation, it goes 'against the facts'. For example, if someone saw a video of my hand raising without knowing the hypnotic context, convincing them that I was not just raising my hand in an ordinary way would require some effort, given that I would have to go against their first impression given the facts (in that case, the video). However, I still get to experience the hand levitation suggestion as if my hand was rising on its own.

One possible explanation of PC is given by the 'cold control theory' proposed by Dienes *et al.*[219] According to it, in the hand levitation example I would have the intention of raising my hand, and the only difference with a situation where I had simply decided to raise it would be that in the hypnotic example I'd be unaware of having such an intention. The fact that I have the intention to raise my hand but I'm not aware of it is understood as part of a mechanism that allows me to reach a goal, in this case having the experience of my hand rising on its own, which is expected in the hypnotic situation. In that sense, cold control theory is a metacognitive interpretation of hypnosis which postulates that there are different cognitive processes going on at the same time, with both an intention and a plan to fulfill it happening in the background, while at the same time our conscious awareness is strategically not being brought on to those processes, *despite sustained reflection*[220].

Cold control theory is limited to hypothesizing this relationship between intentions and awareness, and doesn't go into the reasons why we could have such intentions. In the hypnotic context it's not hard to imagine some possible reasons: wanting to conform to the expectation associated to a hypnotic interaction, politeness towards the hypnotist, not wanting to ridicule the hypnotist in front of others, being a good

[219] Dienes, 'Phenomenological'
[220] Dienes, 'Phenomenological', 105

subject in the context of stage or experimental hypnosis, wanting to be cured in the case of clinical hypnosis, etc. Other cases of PC may have different kinds of expectations and goals playing in the background, while maintaining the same combination of intentions and lack of awareness.

One such other case, analyzed by Dienes *et al.*[221], is the example of 'demand characteristics'. Proposed by Orne in 1962[222], the term posits that in many psychological experiments, participants can form an interpretation of the experiment's purpose (the demand characteristics) and subconsciously change their behavior to fit that interpretation. Dienes and colleagues[223] report results from their laboratory experiments for the cases of vicarious pain (experiencing someone else's pain as oneself's), mirror touch synaesthesia (reporting a tactile sensation when seeing someone else being touched'), and the rubber hand illusion (RHI, the sight of a rubber hand being brushed at the same time as brushing is being felt in one's own hand results in reports of a change in location of one's hand toward the rubber hand and altered reports of ownership [224]). In all cases, they reported a correlation between hypnotizability scores and the reports of each subject. Interviews with the participants revealed that expectations about the specific illusion before the experiment also highly correlated with the reports. The authors argue that PC may be a pervasive way in which demand characteristics are turned into subjective

---

[221] Dienes, 'Phenomenological'
[222] Orne, 'On the social'
[223] Dienes, 'Phenomenological'
[224] In RHI experiments, a rubber hand is usually placed on top of a table while the subject is sitting and has their hand positioned below the table, outside of their view. Both the rubber hand and the subject's hand are synchronously stroked (or asynchronously in one possible control condition), and subjects are then asked to report on their sense of where the hand is located, as well as on their perceived relationship to the rubber hand. The illusion is rated based on reports of the subjects about the location of their hand, which can shift towards the rubber hand, as well as on their report of their sense of ownership: some subjects report feeling the rubber hand as their own, to varying degrees.

experiences. In some cases, such as in the rubber hand illusion (a very well established experiment with hundreds of papers published in its more than 25 years long history), they argue that the possibility remains open for the exercise of PC to be a complete explanation of the extent to which people experience the illusion, as opposed to the illusion being a consequence of some underlying neural mechanism connecting visual and somatosensory cues to influence proprioceptive percepts. It is concerning to consider the extent to which demand characteristics may constitute a confounding factor in many well established psychological paradigms, and perhaps even more concerning to think that this more than 60 years old construct seems to be routinely ignored in the field.

In the words of the authors, *"phenomenological control may be a pervasive way in which demand characteristics are turned into subjective experience, convincing both experimenter and participant of the reality of a phenomenon that may in fact be perhaps wholly constructed by the way the paradigm is presented"* [225]. We will later delve deeper into the point about the experimenter, which should serve as a cautionary tale for psychology researchers and scientists at large about assuming the exhaustive nature of literal observations without considering the possibility for this kind of aesthetic mediation being involved in the scientific process.

Taking the example of the rubber hand illusion, we can see how the OOO reading of hypnotic suggestions can also be applied to other instances of PC: the main difference being in this case that the hypnotic suggestion is substituted by the demand characteristics. Let's focus on how, as a participant, I may be involved in an aesthetic process during the psychological experiment: in the setting of an experiment, where I go to a Psychology Faculty and have the experiment explained to me by the

[225] Dienes, 'Phenomenological', 104

researchers, I could easily end up forming the implicit assumption that the experiment is aimed towards testing some hypothesis regarding the relationship between the rubber hand and my hand. The fact that the goal of the experiment is to measure the effects of the experience on my perception could also be easily inferred, for instance, from the fact that the only outcome measures collected by the experimenters are questions about my experience and perception. These implicit understandings are the so-called demand characteristic, and perhaps through PC, they can materialize in me experiencing the expected experimental outcome.

The dynamic between the objects involved here is almost identical to the one in the hypnotic scenario: the demand characteristics are the equivalent of SI, my expectations of what would happen outside a situation which presents such demand characteristics are the equivalent of DI, and current me is still current me, just placed in a different situation. We can think of the demand characteristics as an inferred image of what a 'good subject' would experience. The idea behind demand characteristics is that by participating in the experiment, a subject gets a set of informative cues that allows them to infer such an image. This image is the equivalent of the flame, the object contributing SQs (in this case an altered perception of my hand's location as well as an altered sense of ownership over the rubber hand) to the scene. At the same time, this image contradicts what would be my usual projection into the future in a similar situation where the same cues were not present (for instance if I was interacting with a rubber hand outside of an experimental context), which is the image (the cypress equivalent, or DI equivalent) that will contribute the SO onto which the SQs of the 'good subject' image are meant to be attached in this context. Finally, the amalgamated new object that is created in this context is constituted by

me posing as myself in the future with the qualities suggested by the demand characteristics.

Placebo effects, spirit possessions, esoteric martial arts, and ASMR (Autonomous Sensory Meridian Response, an internet phenomenon where people report feeling certain sensations in response to particular types of videos) are considered by the same authors[226] as possible instances where PC could be taking place outside of a laboratory setting or a hypnotic context:

> Why would people have the capacity to distort their experiences? Should we not have experiences that reflect reality as accurately as possible? Dienes and Perner (2007) proposed that as spirit-possession experiences were ubiquitous across continents and throughout history, often helping the person possessed to speak with the authority of a powerful spirit, the function of phenomenological control may have been to convince the person themselves of their specific cultural beliefs, especially of the spirit world, so that they could convince others of their contact with that world, bonding them to their group and enhancing their status. Indeed, Pekala et al. (1995)[227] found that out-of-body experiences and experiences of contact with the spirit world correlated with hypnotizability. Because phenomenological control is guided by goals and intentions, it can fit whatever beliefs a given culture has; and in our time and culture, that is a peculiar mixture of the powers of hypnotism, the healing power of pills, tingles produced by folding sheets—and surely much else yet to be shown. [228]

[226] Dienes, 'The Role'
[227] Pekala, 'Anomalous/paranormal'
[228] I assume that the choice of examples (placebo effects, demand characteristics, hypnosis, ASMR…) is biased towards experimentally

The authors pose some interesting questions here, and suggest that phenomenological control may have the role of convincing individuals of their cultural beliefs. We will get back to this point in the next section. To make sure we are all on the same page, I will now go through a brief summary of the key points considered so far.

In the metaphor example, we saw that the objects combined by the author when writing the metaphor (cypress and flame) clash in a specific way that pulls in the reader, allowing for a peculiar experience we called aesthetic. In Harman's terms, this doesn't overcome the withdrawal of the objects, but it does grant an experience that is as close as it gets to contacting their ROs. In that sense, once the reader engages with the metaphor, a new compound object is generated, the '*new amalgamated reality formed from the reader (who poses as a cypress-object) and the qualities of the flame*'[229]. In this case, the cypress that is like a flame was a new object created voluntarily by the writer when writing the metaphor (we can think of the writer as the first reader generating the compound object for the first time), which was explicitly presented to the reader who read it, and intended to cause such an aesthetic experience. According to Ortega, this new object *lives in the ambit of the aesthetic world, which is distinct from the physical world and from the psychological world*[230]. In Harman's reading, because the cypress does not ordinarily support the qualities of the flame, a conflict emerges which pulls in the real object of the reader who, through a form of theatricality, gives rise to the new compound object.

---

controllable, measurable situations; I don't see any reason why PC shouldn't also be involved in other situations where the individually-driven construction of experiences is guided by cultural beliefs around things like, for instance, gender roles, political ideologies, religious beliefs, etc

[229] Harman, 'Object', 88

[230] Ortega, 'Ensayo', 171

We saw a similar dynamic in the hypnotic example, too. Instead of the author putting together the cypress and the flame in a way that pulls in the reader, we considered a hypnotist who would be putting together my expectations of my future (the equivalent of the cypress, the object which contributes its SO to the metaphor) and a different, somewhat incompatible, hypnotic description of my future (the equivalent of the flame, which contributes the SQs in the metaphor). I argued that this generates the same type of peculiar clash, which similarly to the case of the metaphor, also pulls the engaged subject to become part of the scene. Contrary to Harman's example of metaphor, in the hypnotic context the new amalgamated object formed by the experience is actually possible, and thus the suggestion takes effect: this is a fundamental difference that applies to all phenomenological control examples. In the hypnotic example I proposed, instead of a cypress-flame, the image at play in our scene is the version of me in the near future whose hand raises involuntarily. This image combines the sensual object of my default projection into the future with a version of my future in which I have the atypical sensual qualities suggested by the hypnotist. Much in the same way as in the metaphor case, here too, the new compound object generated by the suggestion was voluntarily designed by the hypnotist when they thought of the suggestion, and it was explicitly made available to me, with the intention of giving me a 'hypnotic' experience. This is perhaps the main contribution of this paper: the proposal that a hypnotic experience can be seen as a special case of aesthetic experience, with the peculiarity that the compound object that is generated often manifests directly in the physical world in a way that can be perceived by others.

When talking about PC to explain hypnosis, we showed how, according to this interpretation, the phenomenon of the hypnotic suggestion is just an instance in a class of situations where humans can

craft specific experiences for themselves without being aware of doing so, in order to meet certain goals[231]. According to the proponents of the

[231] When thinking about our ability to generate an experience for ourselves without being aware of having done so, one of the first examples that comes to mind is perhaps the case of dreams. While dreams are different in some fundamental ways from all the cases of PC described here, they also share some similar properties, and while it would be beyond the scope of this paper to provide a psychoanalytic account of all the arguments proposed, I think Freud's theory of dreams [Freud, 'The interpretation'] brilliantly shows some of these similarities, and deserves at the very least a brief mention in the context of this work.
Not only did he consider the manifest content of dreams to be generated by a process of censorship and deformation of the latent 'dream-thoughts' (in that sense, he considered dreams as a metaphor for these 'dream-thoughts') [pp.295], he also emphasized that the most favored type of logical relation that is translated from its original form in these 'dream-thoughts' to a metaphorical representation in the dream content is precisely the relation of *similarity, consonance, or approximation–the relation of 'just as'* [335]. In other words, in the process that converts 'dream-thoughts' into the contents of the dream, something akin to a literary metaphor (as described in OOO) is the most common transformation, where things that are in some way assimilated in the 'dream-thoughts' are often unified into a compound object, which Freud refers to as a 'composite structure'. In that sense, the relationship between generativity and metaphor proposed by Ortega and OOO is maintained, and same as in my proposal to apply it to phenomenological control, Freud, too, sees it as a core component of dreams: *The possibility of creating composite structures stands foremost among the characteristics which so often lend dreams a fantastic appearance, for it introduces into the content of dreams elements which could never have been objects of actual perception* [339]. In another striking coincidence, Freud specifies that these structures can be formed in a great variety of ways, *the most naïve of [*which*] merely represents the attributes of one thing to the accompaniment of a knowledge that they also belong to something else* [340](I say coincidence here because the statement is written almost in OOO terms, and clearly reminiscent of OOO's asymmetric interpretation of metaphors: one object is contributing sensual qualities, while the other is contributing the sensual object).
In a sense, the writer and the reader of the metaphor coincide here in the dreamer, only that while the 'reading' (the experience of the dream) happens in a conscious way (or at least in a way that can be recalled later as having been a conscious experience), the 'writing' (the process that creates the dream starting from the 'dream-thoughts') is out of reach for the dreamer. Similarly to the case of literary metaphors, the writer communicates with the reader by proposing a new object, only that in the case of metaphors the writer only provides the elements that need to be turned into the new compound object by the reader, while in the case of dreams, the compound object is given to the reader already in its composite form.

PC theory, this class of situations includes other cases such as placebo effects, ASMR, or spirit possessions. The case of demand characteristics was briefly explored to illustrate how PC can play out in a scenario other than hypnosis. In the case of the rubber hand illusion, I drew again a parallel with the three elements involved in the metaphor case. The object contributing the SQs to the scene in this case is the 'good subject' image, which any subject in the experiment could infer, and which conflicts with the equivalent of the cypress: the expectations I would have in a similar situation if the same suggestive cues were not present to make me infer such a 'good subject' image. Same as in the metaphor and the hypnotic cases, the RO of the subject of the experiment then gets pulled into the scene by this conflict, and theatrically poses as the new compound object. Same as in the hypnotic example, this new compound object can and does happen, in this case manifesting as the experience of the subjects of having an altered perception of their hand, which according to the authors could be entirely caused by PC[232]. In the next section, I will explore some consequences of this OOO interpretation of phenomenological control.

Expectations, missing writers, inferred metaphors, and sociality

All the instances of phenomenological control bring to the fore an element that is not considered by Harman, even though it is implicit in his account of metaphors: the expectations of the subject. If I read that *the cypress is like a flame* in a botanical description of a specific species of cypress, I would probably interpret the sentence as, in Ortega's words,

[232] Dienes, 'Phenomenological', 104

"*a mute, insignificant geometrical observation*"[233], and no metaphor would happen. Only when encountered in the appropriate situation, the metaphor will elicit the dynamics described by Harman. This property is easier to miss in the case of metaphor than it is in the phenomenological control cases considered here, where it is more immediately apparent: beliefs about hypnosis, scientific experiments, and the medical establishment play crucial roles in the hypnosis, demand characteristics, and placebo effect scenarios, respectively. If instead of the hypnotist, the hand levitation suggestion was delivered by my friend's 6 year old kid during lunch, it would probably be less effective. This is of course an extreme example, but much subtler differences have been studied, for instance, with regards to placebo effects, where it is now well established that features of the medical provider such as their attitude, facial features, perceived similarity, and perceived empathy influence the degree to which placebo treatments induce, for instance, analgesia[234]. Studies on placebo effects show that the expectations of the provider also affect the outcomes in patients[235], which points to the fact that, also in relation to the expectations, "*the author is also a reader*" [236].

This idea of socially transmitted placebo effects, as well as *Dienes et al.*'s proposal that PC may have the role to *convince the person themselves of their specific cultural beliefs*, point to the fundamentally social nature of these phenomena. I believe this is an important piece missing in Harman's analysis of aesthetic encounters: the expectations or beliefs of the aesthetic beholder, which can determine whether such an encounter even happens at all. While *Dienes et al.* discuss cultural beliefs as pertaining to the subject exerting phenomenological control, I would argue that, given their fundamental

[233] Ortega, 'Ensayo', 166
[234] Atlas, 'A Social', 997
[235] Chen, 'Socially'
[236] Harman, 'The Graham'

role in mediating the relationship between individuals and social context[237], it may be more informative here to even consider these expectations and beliefs to be an object of their own, which deserves recognition independently of the aesthetic beholder.

As you may have already noticed, an important difference between the case of demand characteristics and the previous examples (hypnosis and metaphor) is that no one had voluntarily crafted the "metaphorical image" that leads to the formation of a compound object in the scene to induce a certain experience. On the contrary, well-intentioned researchers were just trying to study a certain putative phenomenon, and the effects of demand characteristics go strongly against their interests. Nevertheless, the amalgamated object is created just the same, and as in the hypnosis example, it is a plausible object, which, perhaps through the same mechanisms as in hypnosis, can become a reality outside of the world of aesthetics posited by Ortega and the private experience which would characterize the reading of a literary metaphor (e.g. in this case, for instance, being measurable by the researchers).

Another important peculiarity of this example is that, contrary to the metaphor and hypnosis cases, the images which are having an effect in the context of demand characteristics were never explicitly available to the subjects: they were instead inadvertently inferred by the subjects from contextual information. The situation is still structured in the same ways, with an improbable but not impossible combination of objects

[237] For an interesting take on the relationship between aesthetics, individuals, and society, see Bottici, 'Imaginal'. Even though her analysis in that book is centered on pictorial images, it still constitutes a great example of the complex relations that connect aesthetic objects and their social surroundings. Regarding the idea of treating expectations and beliefs as an object of their own, it's interesting to consider her genealogy of the words imagination, imaginary, and imaginal: this genealogy elegantly captures the crucial role of images (and I would argue, more generally, of aesthetics) in mediating between individuals and the collective.

generating a tension that leads to a new amalgamated object, but all of this happens without anyone in the situation consciously deciding to generate such an experience for the subjects, and without the subjects ever being explicitly told about the images that will clash and generate the compound object.

Finally, the fact that in phenomenological control the new amalgamated objects that are created often manifest in the physical world, points to one last departure between phenomenological control (including hypnosis in this case) and metaphor: the new compound object can now be directly perceived by others, influencing their expectations and potentially acting itself as a suggestive image. So far, we have three important differences between the cases of PC and metaphor: the compound object that emerges in the PC situation was not voluntarily crafted by anyone, it was never explicitly presented to the subjects, and, by often having consequences outside of the private experience of the subject, it has the potential to contribute to the aesthetic experiences of other subjects[238].

The previous point regarding beliefs and expectations, together with the differences discussed now, illustrate how phenomenological control has the potential to be a mechanism that allows for collective

[238] Again, this last difference is relevant but not universal to all PC cases: there are cases of phenomenological control where the new compound object is not necessarily perceivable by others (as in the example of a suggested visual hallucination). Likewise, it is not impossible for the same to be applicable to cases in the realm of art and aesthetics. The way in which someone in the public experiences a certain moment in an artistic performance can influence the aesthetic experience of those around them: however, I'd argue that in that case the compound object is not actually perceivable by others, except for a very rare hypothetical case where the compound object would coincide with the reaction of the person. In the case of the hypnotic suggestion the compound object and my externally perceivable reaction are the same: I raise a hand. This is perceivable from the outside and can contribute to the same experience in someone else. In the case of an artistic performance it seems harder to think of a similar situation: it would have to be something like a comedy based on using laughter itself as the aesthetic object to generate laughter, for instance.

coherence to emerge without the need for any single individual's conscious awareness of it: without needing anyone to craft a specific image, nor to explicitly present it to the subject, phenomenological control allows beliefs and expectations to materialize into the experience of individuals, thereby creating compound objects that conform to those beliefs and expectations in a potentially self-perpetuating process. According to the views presented here, central to the reality of phenomenological control would be what Harman calls 'theatricality'. In his essay 'Materialism is not the solution: on matter, form and mimesis'[239], Harman closes by posing a question which he answers in a way I believe is closely connected with the interpretation of phenomenological control that I'm considering here:

> What if it were the case that all good art is sincere, in the sense that it provokes our investment by placing us inside the scene, letting us step in as understudies for the real object, forcing us to play the part of the cypress enslaving the qualities of the flame? If this were the case, then all art would be a branch of the performing arts. Form defeats content, not because content must refer to its background medium, but because aesthetic participants themselves provide the aesthetic medium, by standing in for the cypress and stone that cannot attend in person.

In the case of phenomenological control, the aesthetic participants (including the equivalents of the author of the metaphor, i.e., the hypnotist, the experimenter, the doctor, etc) also provide the aesthetic medium where these processes occur; however, contrary to

[239] Harman, 'The Graham'

the ontological performativity that Harman proposes, in many PC cases the equivalents of the reader actually perform the new object in a literal sense, bringing it from a private space of aesthetical objects to that of externally perceivable realities. Both the idea that *art would be a branch of the performing arts,* and the idea that the *participants themselves provide the aesthetic medium* are more literally manifest in the case of PC. In PC, the subjects are often actually performing their aesthetic objects, and they constitute the medium for these objects in a way that can be perceived by others. A social component is present in Harman's analysis of metaphor, but like in Ortega's, it remains limited mainly to the individuals directly involved in the situation.

In Ortega's essay, while describing his emotional reactions to the appearance of new poets, he writes that such an event is '*the promise that the world is gonna be augmented for us'.* In that sense, the social interaction in metaphor can be seen mainly as a one-directional one: an author augments our world by generating new objects that we can theatrically enact. However, as highlighted by the examples of demand characteristics and placebo effects, both the participants' and the experimenters/providers' beliefs come into play in those contexts, creating the possibility that in some cases, no one directly involved in the situation has any indication that phenomenological control may be playing a role therein[240]. Because of this, I think the case of

[240]An interesting case is that of placebo effects in studies of antidepressant medications. The literature on the topic is vast, with some authors pointing that there seems to be a steady historical increase in placebo effects in antidepressant studies overall (See Walsh, 'Placebo', or Holper, 'Raising'), as well as a tendency for these treatments to become less effective over time for any given patient, which could be related to a reduction in placebo effects (See Fornaro, 'The emergence'). Given that all antidepressant medications have some adverse effects, and given the small improvements that they provide over the effects seen in the placebo controls, some authors (see Kirsch, 'The Emperor') even propose that they could act as 'active placebos', i.e. their effect could be explained by a stronger placebo effect caused by their active nature, which allows both patients and providers to 'unblind' (discern the treatment from

phenomenological control elicits a more complex interpretation of aesthetics: while aesthetic experiences can indeed have the role of opening our world by suggesting new objects creatively invented by an artist, the same mechanisms underlying our experience of art can also serve to perpetuate existing systems of meaning and to constrain the range of possible experiences an individual can have by conforming them to shared beliefs. Of course in the specific case of art, the involvement of our beliefs and expectations in the aesthetic experience can also put them to question and help make them visible: my point here is just to highlight that similar dynamics can lead to the realization of such beliefs.

Lastly, I want to propose an interpretation as to why hypnosis seems to be halfway between phenomenological control and metaphors in some ways, which I believe could be the reason why PC theory emerged in the field of hypnosis and not in others. In hypnosis, like in metaphor, the compound object needs to be carefully crafted by someone (in this case, the hypnotist) before it can be presented to the subject, and this presentation often happens explicitly[241]. On the other hand, like in other instances of phenomenological control, the role played by beliefs and expectations in the context of hypnosis is central, and the resulting compound objects can in many cases be directly perceived by others too. Having proposed that phenomenological control

---

the placebo). In that regard, Kirsch notes that *the patients who show at least a little improvement during the run-in period* [most antidepressant trials include such initial periods in which all participants receive only placebo] *are the ones most likely to respond to the real drug*.

[241]Implicit suggestions are one of the most important contributions of Ericksonian hypnosis, and to this day their effectiveness in comparison to explicit ones remains somewhat controversial. There are definitely cases where suggestions are presented indirectly/implicitly, and the debate is about how effective they are compared to direct ones. In that sense, there are many instances of hypnosis, like there are of other cases of phenomenological control, where the new object to be created in the experience is not explicitly presented to the subjects.

may be a self-perpetuating mechanism which promotes cultural coherence across a collective without the need for any of the individuals therein to be aware of it, I think one possible interpretation is that hypnosis constitutes somewhat of a glitch, a hack of the PC mechanisms: it is an instance where phenomenological control is playing a role, but at the same time it loses its transparency, becoming visible, as a mechanism, for the individuals involved in the situation. Because at least the hypnotist needs to be somewhat aware of the aesthetic experience that is being created, the mechanism that would usually act silently (PC) is brought to awareness, and thus can be questioned.

The metaphor is like the ghost of a dead hypnosis

In this article, I applied OOO's theory of aesthetics, as exemplified by metaphor, to the concept of phenomenological control. I started by considering the case of hypnosis, and then I generalized the same structure to other cases where phenomenological control is believed to be playing a role. Common to all these cases are the three main objects: a flame equivalent, contributing SQs, a cypress equivalent, whose SO cannot support such SQs, and a reader equivalent, whose RO enters in the scene and fills in the void left by the cypress's SO, theatrically posing as the cypress posing as the flame, resulting in an amalgamated compound object. While this structure remains constant across all the cases considered here, I also highlighted some differences between the different cases: in the cases of phenomenological control, the compound object that results frequently appears in the physical world, while in metaphor this object remains in the world of aesthetics (in Ortega's view), or at least is not usually perceivable outside of the reader of the metaphor. Except for hypnosis, in all phenomenological control

cases PC can be mobilized without requiring neither someone who consciously crafts the equivalent of the cypress-flame object, nor an explicit presentation of such object to the equivalent of the reader. One observation emerging from the analysis of PC is that the beliefs and expectations of the subjects play a crucial role in these experiences, a role which I believe is not addressed in OOO's account of metaphors (where beliefs and expectations, as noted before, likewise play a crucial role). Together, these considerations about PC point to it being a mechanism that can allow for cultural beliefs to manifest through the experience of individuals, which can potentially reinforce such beliefs in a self-perpetuating process. The application of OOO's ideas about metaphor to hypnosis and PC scenarios brings us an interesting new perspective of such scenarios as aesthetic experiences, but also highlights a fundamental gap that requires further attention in OOO: what exactly is the role of social beliefs and expectations in aesthetic experiences and in the metaphorical formation of compound objects?

The observations made here can also function as a reminder of the message of caution given by OOO: we should stay alert about the possible metaphorical dimensions of our experiences. As exemplified by the case of demand characteristics, this warning is especially important in science, where careless mistakes can easily lead to the fabrication of scientific conclusions that ignore the influence of aesthetic processes on their conception. While the effects of PC on the experiences of subjects involved in psychological experiments should serve to illustrate some concerns specific to psychological research, the role played by PC in experimenters, as well as the way in which the provider's attitude and beliefs influence the outcomes in placebo studies should serve to also extend this concerns to all areas of scientific research: we need to stay aware of the mediated nature of our interactions with the world independently of the flavor of our experiments. Moreover, the views

proposed here highlight the presence in aesthetics of the same beliefs and expectations which shape PC experiences and which in my view are overlooked in OOO. This analysis thus opens some interesting possibilities to understand the complex relationship between the realms of aesthetics and social theory as well, and proposes PC as a mechanism that could mediate the mutual constitution of individuals and the collective.

While I started this paper by explaining that I would consider hypnosis and related phenomena as a special class of aesthetic experiences, given the considerations made so far, I will close now by proposing that we should also entertain the opposite possibility: perhaps aesthetic experiences are part of a wider class of situations where humans exert control over their own experience without being aware of doing so.

Chapter 4
The 'what', 'how', and 'why' of psychedelic extrapharmacological effects: psychedelic research meets phenomenological control

Contributions

In this perspective piece I will synthesize my views on the question "in which ways may phenomenological control be related to the effects of psychedelic substances and our understanding of their properties?". After having worked with psychedelic substances in the experimental setting described in chapter 2, and having done theoretical research on the topic of hypnosis and related concepts for the work presented in chapter 3, I have developed some high-level views about ways in which these two extensive fields of research interact (or don't), and I will now present a synthesis of those views, focusing on providing a high-level description of said interactions in a way that I believe should be understandable for people coming from either of these (in my view, overly independent from each other) fields, while also highlighting some important consequences of the interactions described here, and ways in which we may want them to inform our future scientific inquiries about either of them. For the basic definitions of some of the concepts dealt with here, such as PC, hypnosis or demand characteristics, feel free to go back to the beginning of the previous chapter, where you will find them discussed in detail. Importantly, it will not be necessary to understand the philosophical contribution made in the previous chapter. Some of the conclusions from that work have served as inspiration for the ideas presented here, but it will not be necessary to go beyond what's mentioned here in order to understand the core ideas.

Abstract

In this narrative review, we apply the ‘phenomenological control’ construct to elucidate the relationship between different threads in the research concerned with psychedelics and classic antidepressants. Ideas regarding suggestibility, placebo effects, and meaning enhancement will be contextualized using the framework of phenomenological control, and the literature considering these ideas in the fields of psychedelic and antidepressant research will be reconsidered accordingly. Furthermore, the concept of alignment will be proposed as a normative framework with the potential to circumvent some of the difficulties that have been encountered when modeling phenomenological control and psychedelic effects from a predictive processing perspective. This framing of the current landscape will allow us to propose future directions both experimentally and clinically, highlight some key questions that need to be addressed at an ethical level, and criticize some current trends in the field.

Introduction

Psychedelics are often defined as a class of molecules that produce psychoactive effects in humans through their affinity for the 2a subtype of the serotonin receptor (depending on the author, sometimes drugs which don’t have strong affinities for this receptor, such as cannabis, ketamine, or MDMA, are also classed as psychedelics). Some of these molecules have been consumed by human populations for thousands of years [1], and they have been under scientific scrutiny since at least the 1930s. After a period of strict legal restrictions on these substances starting in the 1970s, there has been a resurgence of

interest in the last couple of decades. Due to their potential in treating a variety of psychiatric conditions such as addiction, post-traumatic stress disorder (PTSD), and depression, psychedelics have elicited widespread interest, not only in scientific, medical, and pharmacological settings, but also in the general public.

According to the World Health Organization's (WHO) depression fact sheet,[242] around 4% of the global population (around 332 million people) suffers from depression, a number that rises to 5.7% in the adult population. Researchers estimate that 12 billion productive work days are lost every year to depression and anxiety alone, at a cost of nearly US$ 1 trillion. These numbers are often leveraged to argue for the urgent need for new pharmacological agents in the treatment of depression. While it is undoubtedly beneficial to develop effective treatments for mental health conditions, it is important to consider the socioeconomic context in which the medicalization of psychedelic drugs is occurring.

Right-wing politics have repeatedly been shown to go hand in hand with increases in inequality,[243] which have in turn been associated with worsening health statistics[244], especially regarding mental health and depression.[245] With the international rise of far-right ideology, and the accompanying quick deterioration of social protection programs and of social welfare more generally, it is paramount to remember that pharmacological treatments for mental health disorders, especially within the neoliberal model of individualized, for-profit healthcare, have the potential to shift responsibility to individuals while creating market

[242] https://www.who.int/news-room/fact-sheets/detail/depression Numbers presented here correspond to their August 29th, 2025 update.
[243] Román-Aso, *When government*
[244] March, *Potential*
[245] Belle, *Poverty;* Paskov, *Social;* Pabayo, *Income;* Patel, *Income*

opportunities that further extract wealth from the masses and worsen inequality.[246]

The global antidepressants market was estimated to be valued at close to 19 billion US dollars in 2024, and the medicalization of psychedelics has quickly attracted investors to what promises to be the new boom in the pharmacological treatment of mental disorders.[247] In some cases, such as in the US, the exact same individuals who are attacking social healthcare policies that have demonstrated to be effective in decreasing the incidence of depression and suicidality[248] are the ones pushing for expedited approval of new psychedelic treatments while investing millionaire sums in the field.[249] This context highlights the utmost urgency of maintaining strict methodological rigor in scientific inquiries on the topic of psychedelic treatments, and the need for attentive scrutiny of existing results.

It's no surprise that the promise of psychedelics as a potentially revolutionary antidepressant treatment has been key in elevating them to a central position in public discourse and in research, in what has been termed the 'psychedelic renaissance'. Immediate action, long-term effects from single doses, and a safe risk profile are amongst the alleged features of psychedelic treatments that would demarcate them from other available antidepressant treatments and give them a privileged status in the current research landscape.

This resurgence of psychedelics has brought to the forth issues with blinding and placebo controls that were already apparent in antidepressant medications, and one of the main goals of this article is to showcase the complexity of these issues and to accentuate the need for

[246] Devenot, *TESCREAL*
[247] Devenot, *The Psychedelic*
[248] Oliphant, *The evolving*
[249] Chapter 11 in Devenot, *The psychedelic*

them to be conceptualized more carefully[250]. We feel that the understanding of these issues is concerningly limited in the current literature, and hampered by many social and situational factors. In particular, the economic interests mentioned above go hand in hand with a need to tie the therapeutic effects of psychedelics to a chemical process, disconnecting them from any social or cultural dynamics that may be involved in psychedelic healing, which would be hard to patent and commercialize. In that sense, the possibility that the therapeutic effects of psychedelics may be related to their ability to modulate suggestibility or expectations is inconvenient for the pharmacological industry and likely to be played down as a consequence. This is part of a more general tendency for pharmacological research to consider extrapharmacological effects as a nuisance to be controlled for, as attested by the central role played by the double-blind, placebo-controlled, randomized clinical trial, in modern medicine.

In this article, we will analyze the relationship between psychedelic drugs and a series of extrapharmacological effects in humans which are often clumped into the categories of 'suggestibility' or 'expectancy' effects (a relationship which is inseparable from that between other antidepressants and these same categories[251]). More specifically, we will focus on this relationship in so far as it affects clinical research with psychedelic drugs (as opposed to, for example, analyzing the history of psychedelic drugs used to modulate interrogative suggestibility, or the phenomenological overlap between hypnotic trance states and the psychedelic state). To do so, we will utilize the

[250] Placebo controls are a fundamental component in most clinical research involving human subjects, but recent work has shown that Major Depressive Disorder (MDD) is perhaps the psychiatric disorder where placebo effects have the strongest influence in outcomes, granting special attention to the matter in the context of depression research. Bschor, *Differential.*

[251] See Moncrieff, *What Does,* for a more general discussion about these and other issues in antidepressant research.

contemporary theory of ‘Phenomenological control’ (PC), derived from the field of hypnosis research.

In the first section (the ‘What?’ section), we will begin by giving a rough map of some of the interactions between psychedelics and PC, which motivated the present analysis, as well as giving a brief overview of how other authors have also called attention to such interactions. In the second section (the ‘How?’ section), we will provide an overview of some possible mechanisms through which we believe psychedelics may be modulating PC in clinical trials. Lastly, the third section (the ‘Why?’ section) will be dedicated to considering how these observations could inform existing models of both hallucinatory phenomena and hypnosis, by proposing the concept of ‘alignment’ (as used in machine learning and artificial intelligence research) as a key theoretical missing piece.

What?

Extrapharmacological modulation of psychedelic effects

Psychedelic research is undergoing a resurgence in the last decade, with scientific and economic interest in these substances reaching unprecedented levels. One of the most promising research avenues in the current psychedelic ‘renaissance’ is the one dedicated to elucidating their effects as antidepressant medications: due to their fast-acting nature, their long-term effects, and their relatively safe risk profile, psychedelic drugs have the potential to become the new gold standard in antidepressant treatment. Multiple threads exist in the literature concerned with the possible mechanisms of action that may underlie these antidepressant effects, with theories of brain synchrony[252],

[252] Siegel, *Psilocybin*

neuronal plasticity[253], or meaning enhancement[254] being amongst the most popular contemporary takes on the subject. In this narrative review, we will consider the theory of phenomenological control as a candidate framework to tie together certain threads in the existing literature about psychedelics and other antidepressants.

In this chapter I will thus bring together the fields of phenomenological control and psychedelics research to show how a dialogue between the two can be informative for both fields, as well as transcend them to give important new perspectives for Neuroscience at large. In particular, I will suggest that applying the phenomenological control theory to some dimensions of psychedelics research can highlight the necessity to move from individual to social interpretations of psychedelics, a movement which is formally reminiscent of the transition from single-unit to population-based models in contemporary Neuroscience.

The relationship between expectancy effects and psychedelics is complex and remains understudied and poorly understood[255]: since the beginning of scientific research into psychedelic drugs, different theories have emerged highlighting the fact that their effects seem to be very heavily modulated by context and by the state of the subject. While it will of course be impossible to exhaustively review all such theories, we will now briefly go through some authors who have formalized this property of psychedelic drugs in slightly different ways.

Henry K. Beecher was amongst the first to draw attention to the danger of overseeing extrapharmacological effects in psychedelic research[256]. He pointed out how early research with LSD may have been attributing to the substance itself some such extrapharmacological

[253] Du, *Psilocybin;* Zhao, *Psilocybin;* Bredenberg, *The Oneirogen*
[254] Hartogsohn, *The meaning*
[255] Oliver, *Suggestibility;* Lemercier, *Psychedelics*
[256] Mashour, *From LSD*

properties. Later on he also laid some foundational work in advocating for the importance of the double-blind placebo-controlled trial in medical research, an innovation of his time which has become the very basis of contemporary clinical research.

His observation that pain seemed to be processed in very different ways depending on context led to his groundbreaking work on the topic of placebo in the fifties, which constitutes perhaps the first use of the term placebo with its modern biochemical meaning. While he was serving as a military anesthesiologist in World War II, he realized that soldiers in the battlefield needed lower doses of morphine compared to the ones that civilians in a hospital would normally require. This observation led him to postulate that the experience of pain seemed to have two components, one being the actual damage caused to a given tissue, and the other being the *meaning* that the subject would attribute to the situation. While he didn't coin the term 'placebo', he was the first to use it in its modern biomedical sense, and played a crucial role in popularizing the double-blind placebo-controlled randomized trial (RCT).[257]

Here, the word 'meaning' was used to refer to how a sensory experience is interpreted by the subject, and it was meant to emphasize the fact that different interpretations (a wound which may seem worrying for a civilian may be completely inconspicuous during battle) could lead to profoundly different experiences.

During his service in WWII, Beecher became aware of the mescaline experiments carried out by Nazis in the concentration camp at Dachau, and later on he got involved in experiments with LSD in the US. He was likely also aware of the CIA's LSD experiments in the 1950s[258]. Beecher soon transposed his ideas about the influence of meaning on

[257] Kaptchuk, *Powerful*
[258] Mashour, *From LSD*

experience to the budding field of psychedelic research, prompting him to show concern about how these effects were routinely overlooked in psychedelic trials:

> The results recounted are based entirely on the subjective responses and symptoms, and conclusions are drawn without the use of mandatory controls. In a meaningful evaluation of LSD, it must be known whether it is the LSD or the strong suggestion, which precedes the drug that is operant in this situation; the powerful action of the placebo has been unequivocally demonstrated.[259]

Ultimately, these early experiences with psychedelics and placebo effects were crucial in shaping his views about clinical ethics and RCTs. Soon after, and inspired by, Beecher's observations about placebo effects in LSD research, Timothy Leary popularized the 'set and setting' catchphrase which is still prevalent today[260]. According to this perspective, the experiences elicited by psychedelic drugs are determined to a significant extent by both the mental state of the subject undertaking them (set), as well as by the context where they are happening (setting). This catchphrase is still extremely common and is often used to refer to the effects of other psychoactive substances, even though some authors argue that set and setting play a particularly important role in the effect of psychedelic drugs[261].

In a similar line, Czech psychiatrist Stanislav Grof argued in his 1975 book[262] that LSD '*is an unspecific amplifier of mental processes that brings to the surface various elements from the depth of the unconscious*', reinforcing the belief that 'set' is a fundamental determinator of the psychedelic experience. In Grof's case, the proposal

---

[259] Mashour, *From LSD*
[260] Moreno, *Acid*
[261] Hartogsohn, *Set*
[262] Grof, *Realms*

was explicitly intertwined with psychoanalytic theory, and his focus on *set* was aimed at emphasizing that the hallucinatory phenomena caused by psychedelics are not generated from scratch, but instead amplify pre-existing elements that were hidden in the unconscious. Both the 'set and setting' and the 'unspecific amplifier' proposals emphasize the fact that psychedelic drugs seem to be better understood as modulators of pre-existing psychological and contextual factors.

Moving on to the current 'psychedelic renaissance' decade, some authors have directed their attention again to the issue of extrapharmacological effects in psychedelic research. Having re-traced the history of 'set and setting' in his 2016 work[263], Ido Hartogsohn proposed the 'meaning-enhancement' theory in 2018[264]. Unifying work on placebo coming from medical anthropology[265] which suggested the use of the expression 'meaning response' as a substitute for 'placebo effect' (arguing that the expression 'placebo effect' suggests that it is an effect caused by the placebo pill itself, while 'meaning response' is more accurate because it emphasizes how it is the way in which the person interprets the situation that actually leads to the effect, and not the pill in itself), with evidence that psychedelics enhance the attribution of meaning (referring to the fact that a certain percentage of participants reporting their psychedelic experience in a trial being amongst the most meaningful experiences of their life), Hartogsohn argues for an equivalence whereby if psychedelics enhance the perception of meaning, and placebo can be thought of as a 'meaning response', then *'the amplification of meaning by psychedelics therefore automatically entails amplification of placebo, and can offer help in explaining psychedelics' extraordinarily versatile uses and applicability in a wide*

[263] Hartogsohn, *Set*
[264] Hartogsohn, *The Meaning*
[265] Moerman, *Meaning*

variety of medical conditions'[266]*.* A similar proposal can be traced back to Kirsch, who suggested that classic antidepressants may in fact be just 'active placebos', substances which, because of their often noticeable adverse effects, lead to unblinding and thus potentiate the extrapharmacological effects observed in the placebo group[267].

While the meaning-enhancement theory doesn't seem to provide a very precise definition of the word 'meaning' (an absence that seems problematic and can lead to some ambiguities[268]), Hartogsohn's work has played an important role in synthetizing different threads concerned with the extrapharmacological effects of psychedelics, in bringing attention to this issues in the contemporary research boom, in introducing important anthropological considerations into the conversation, and in arguing for the need to shift away from the term 'placebo', and to focus instead on the fact that these effects are mediated by the meaning attribution of the subjects involved in these studies.

Importantly, Hartogsohn highlighted some differences between placebo and 'set and setting': while the 'set and setting' literature is wider in scope and considered how these factors could impact different dimensions of the psychedelic experience, the concept of placebo is mostly unidimensional, whereby only the desired clinical outcome is used as a measure of both pharmacological and extrapharmacological effects. On the other hand, he argues that the literature on placebos is

---

[266] Hartogsohn, *The Meaning*

[267] Kirsch, *The Emperor.* For a recent review of active vs. standard placebo differences check Laursen, *Impact.*

[268] Note how the equivalence quoted above conflates two different interpretations of the word 'meaning' which could arguably be completely independent: a patient can have a 'meaning response' in the sense that they interpret the situation as being a medical one, which *means* they will get cured, while not ranking it amongst the top *most meaningful* experiences of their life, and conversely, an experience which is ranked amongst the *most meaningful* of one's life could easily not be interpreted as a curative one.

mostly descriptive, aiming to characterize a portion of the response that would ideally be separated from the portion attributable to direct pharmacological activity, while the set and setting catchphrase is often used more prescriptively, accentuating the possibility for these factors to be controlled in order to enhance the effects of psychedelic drugs.

Another popular contemporary author writing about these issues is David Dupuis, who has also introduced anthropological perspectives into the mainstream conversation about psychedelic extrapharmacological effects[269], proposing the idea of the 'socialization of hallucinations' as a way to emphasize the importance of the social dimension that was classically absorbed in the 'setting' component of set and setting, clumped together with other contextual factors[270]. His ideas about belief transmission under psychedelics, and the conceptualization of psychedelic hallucinations as cultural projections are very much in line with the conceptual framing of this paper, which will offer a new perspective on these ideas, making use of the phenomenological control framework, and proposing a different computational and normative interpretation (Dupuis usually aligns with the 'strong priors' hypothesis of hallucinations which we will challenge here).

Surprisingly, except for some studies which assessed the extent to which psychedelic drugs can enhance hypnotic suggestibility, the hypnosis literature seems to have stayed mostly isolated from the psychedelic literature since the sixties, even though there are multiple points of contact that demand attention. In that regard, recent reviews[271] have analyzed the multifaceted nature of the interactions between suggestibility and psychedelics, and proposed ways in which, for instance, hypnosis could be used in conjunction with psychedelic

[269] Dupuis, *Culture*
[270] Dupuis, *Psychedelics*
[271] Oliver, *Suggestibility;* Lemercier, *Psychedelics*

research. However, to date, we are not aware of any work providing a unifying framework to conceptualize these interactions and situate them in the wider context of psychedelic research.

We believe that such a framework could allow us to improve our understanding of certain issues that have been at the core of research with psychedelics since its inception. With that purpose, we will utilize the Phenomenological Control (PC) framework to analyze the different scenarios in which the ability of humans to generate experiences for themselves without being aware of having done so may be playing a crucial role in our attempts to understand psychedelics. Importantly, this theory emphasizes the active role of the subject in these processes, it highlights the social nature of these phenomena, and it will allow us to tie different threads in the research (placebo, meaning, suggestibility…) into a single framework[272].

We will now analyze different mechanisms through which psychedelic drugs may affect PC, and tease apart the different predictions that emerge from each. For a brief introduction to the concepts of hypnosis and PC, feel free to refer back to the sections titled ‘Soon you will feel that your hand is starting to raise’ and ‘Generating experiences to meet expectancies’, respectively, in Chapter 3. After the mechanistic considerations of the following section, we will conclude in the last section by introducing the concept of *alignment* as used in multi-agent systems as a possible normative framework to situate PC and psychedelic drugs in a wider context.

[272] Dienes, *Phenomenological*; Arlandis, *Hypnosis*

How?

Labels, pendulums, and neural circuits

Psychedelics have repeatedly been reported to increase hypnotic suggestibility, in studies from as early as the 1960s[273], as well as in more recent (and generally more methodologically rigorous) works.[274] As discussed in Chapter 3, PC theory emerged from the field of hypnosis research, but is abstract enough to include other phenomena like demand characteristics and placebo effects, which are also mediated by expectations and which share some similar dynamics with hypnosis[275]. If we accept the grouping of these phenomena into a common category (of situations where subjects seem to exert an ability to generate certain experiences for themselves without being aware of having done so), we should expect a concomitant increase in placebo effects in the context of psychedelic clinical trials. Indeed, as we have discussed in the previous section, the idea that psychedelics potentiate placebo effects is not new in the literature, and has been proposed for other antidepressants as well. We will now consider PC as a putative mechanism that may mediate both of these effects.

Before we go through some possible ways in which psychedelics may influence PC, let's consider the following question: why would hypnotists ever sway a pendulum in front of their hypnotees in order to induce trance? Answering this question will shed some light on the ways in which psychedelics may influence PC, but first it will require a quick run-through over the recent history of research about hypnotic inductions.

---

[273] Sjoberg, *The effects;* Levine, *Alterations;* Solursh, *LSD;* Middlefell, *The effects;* Kelly, *Effects;* Van Nuys, *Drug use*

[274] Whalley, *Enhancement;* Patterson, *Ketamine;* Carhartt-Harris, *LSD*

[275] Arlandis, *Hypnosis*

If we look, for instance, at the now classic 'Elman induction', based on techniques popularized by the very charismatic hypnotist during the 1950s and 1960s[276] (and still used today[277]), we can see that the hypnotic trance is induced here through a complex procedure involving multiple techniques (e.g. instructions to open and close the eyes multiple times, raising the hand of the subject and then dropping it while suggesting a deepening of the trance, etc).

If we go even further into the past and look at Esdaile's descriptions of his use of Jhar Phoonk to induce anaesthesia in his patients in Calcutta in the 1840s and 1850s[278], we find an even more complex procedure, often spanning multiple hours, over which, among other things, the hands of the surgeon were repeatedly passed over the abdomen, the thorax, and the head of the patient.

Conversely, if we come back to the early 2000s we can already find much more reduced induction procedures. In 2005[279], for instance, Gandhi *et al.* found that the only thing which is necessary for a hypnotic induction to be effective at increasing suggestibility is the presence of the word 'hypnosis' in it. Things that were considered central for the effectiveness of the induction, such as suggestions related to sleep or depth interspersed throughout the procedure, turned out to be mostly irrelevant.[280]

Even more recently, if we look at the phenomenological control literature[281], it's important to consider that imaginative suggestions delivered without a hypnotic context (which is considered as a potential

---

[276] Elman, *Hypnotherapy*
[277] Barth, *Effectiveness*
[278] Esdaile, *Natural*
[279] Gandhi, *Does*
[280] Woody, *What*
[281] Dienes, *Phenomenological*

confound by the proponents of the PC theory), lead to similar outcomes as hypnotic suggestions[282].

These brief considerations will now allow us to identify three different levels at which psychedelic drugs may be modulating phenomenological control.

The meaning response

On the first level, the fact that Gandhi et al found that mentioning the word 'hypnosis' was crucial, points to the fact that invoking a network of symbolic associations, a conceptual framing for the interaction that is about to happen, has a significant effect on the responses of subjects. In other words, there is no need to attribute any supernatural properties to the word hypnosis here:

> [...] a simple explanation is that it drives particular demand characteristics (aspects of an experimental situation which, sometimes contrary to experimenter's intentions, communicate experimental expectations to participants; Orne, 1962; cf. Sharpe & Whelton, 2016) in participants who arrive with a culturally acquired knowledge of the hypnotic context. Again, we emphasise that response to imaginative suggestion predates the introduction of the term "hypnosis" (most famously in mesmerism but also other contexts, Hammond, 2013).

In the hypnotic scenario, such a symbolic space can be invoked by simply including the word 'hypnosis' into the induction, allowing the subject to identify the situation as a hypnotic one, and thus mobilizing their beliefs about hypnosis. The same applies to the placebo and demand characteristics contexts: in those cases the beliefs that are being mobilized can be triggered for instance by implicit contextual cues

[282] Lush, *The Phenomenological*

such as the doctors' outfit and location (e.g. a lab coat, an office in a hospital, etc[283]) or the experimental study setting (e.g. a psychology faculty in university, the experimenters, etc).

Of the three levels, this first one is the most abstract one: the presence or absence of the word 'hypnosis' in an induction leads to changes in the effectiveness of the induction, highlighting the fact that the subject's interpretation of the situation has a direct effect on PC. We could call this level the 'meaning response' following the definition of meaning used in Moerman, 2002[284] (i.e. the way in which subjects conceptualize a situation impacts their experience).

In a psychedelic context, the mere fact that the situation is labeled as 'psychedelic' (which is of course an ethical necessity), may be mobilizing our beliefs about psychedelics. Both increased suggestibility and antidepressant effects may very well be part of such beliefs in most modern clinical trial participants, and both could affect PC and study outcomes. Even if a given participant wouldn't have well defined beliefs about these properties of psychedelic drugs, induction procedures in psychedelic clinical trials (it would be unethical to give these substances to people without first educating them about their possible effects) will often provide plenty of beliefs about these drugs[285].

In that sense, the collective imaginary surrounding psychedelics would be playing a role equivalent to that played by our cultural beliefs about the medical establishment in the case of placebo effects, or the one played by scientific praxis in the context of demand characteristics. There are multiple lines of evidence that could (or have) shed light on the issue of how beliefs shape psychedelic therapeutic effects and placebo effects in general.

---

[283] Belcher, *Role;* Chen, *Socially*
[284] Moerman, *Meaning*
[285] The induction procedure of some studies could in fact be conceptualized as a hypnotic induction with interspersed suggestions.

In a study by Olson *et al.* from 2020[286], such an induction process, accompanied by trained confederates acting out psychedelic effects, led some participants (who have been given a placebo but were misled to believe they had ingested a psilocybin analog) to experience psilocybin effects comparable to those usually described after consumption of moderate to high doses of actual psilocybin. No studies to date have, to the best of our knowledge, assessed the impact of such a procedure on clinical outcomes such as depression, but the fact that some participants reported psychedelic effects in this study is a good indicator that the 'meaning response' alone may be enough to deeply impact phenomenological control mechanisms.

Participants in Olson *et al.* 2020 were led to believe that there was no placebo control group and that everybody was ingesting the same active substance, and the study was carried out "in a naturalistic environment resembling a typical psychedelic party". These factors differentiate their study from most psychedelic studies. In most psychedelic clinical trials, it is usually very difficult to design proper placebo control groups, because participants can easily tell whether they ingested the active principle or not. The subjective effects of a high dose of psychedelics are so salient that it is virtually impossible to blind the subjects: this is likely among the reasons why outcomes in the placebo group of psychedelic studies are often worse than those in the placebo group of classic antidepressant trials.[287]

---

[286] Olson, *Tripping*

[287] Hieronymus, *Control;* Hsu, *Comparative:* "In a randomised controlled trial, treatment response was defined as the response observed in the active arm; placebo response was defined as the response observed in the control (placebo) arm. Treatment response consists of non-specific effects, placebo effect, and true treatment effect; placebo response consists of non-specific effects and placebo effect. Therefore, when the placebo effect is not the same for the active and control arms within a randomised controlled trial, the estimation of the true treatment effect is biased. For example, in a psychedelic trial, unsuccessful blinding may occur due to the profound subjective effects of

Another possible source of information about the meaning response in psychedelic research is to study their consumption in different contexts. For instance, while in no way conclusive, the increased rate of depression among recreational ketamine users in some studies[288] might be interpreted as an indication of this 'meaning response' level playing an important role in clinical outcomes: to which extent does labeling these substances as antidepressants determine their antidepressant effects?

Finally, there are two hypotheses that have been proposed in the field of antidepressant research which may also be informative regarding the extent to which beliefs affect extrapharmacological effects in antidepressant trials and in pharmacological clinical trials in general. First, it has been proposed that placebo effects may have become bigger throughout the history of antidepressant research,[289] or in general of pharmacological and neurostimulation clinical trials.[290] While these results are suggestive of such an overall increase in placebo responses, this topic has been quite controversial, with other authors reporting an absence of such an effect.[291] Second, it has also been proposed that for any given antidepressant, therapeutic effects seem to be strongest in the earlier trials, which could point to a positive influence of novelty on clinical outcomes. However, this last effect may also be attributable to publication biases and small study effects.[292]

---

psychedelics. This unblinding may lead to high placebo effect in the active arm and low placebo effect in the control arms, and the true treatment effect is overestimated."

[288] Palamar, *Ketamine*; Krystal, *Ketamine*

[289] Holper, *Raising*

[290] Huneke, *Placebo*

[291] Furukawa, *Is placebo*

[292] Turner, *Selective*

The experience

On the second level, the fact that a wide array of seemingly completely unrelated practices have traditionally been used as hypnotic inductions, and the fact that in some studies inductions seem to have small but significant effects on increasing suggestibility,[293] suggests that the mobilization of the beliefs, the 'meaning response' discussed above, may be potentiated by having some kind of 'experiential substrate' that signals to the subject that something is indeed happening. Initially this distinction may seem superfluous, because there is no clear boundary between what constitutes such an 'experiential substrate' and the dimensions of 'setting' that can lead to a 'meaning response'. However, we believe that this distinction may be informative, especially when applied to the context of psychedelics.

We initially described the previous level as 'invoking a network of symbolic associations, a conceptual framing for the interaction that is about to happen'. Of course, in a sense, such a conceptual framing is closely intertwined with the experience of the subject, and in some cases these two levels may indeed be functionally indistinguishable.

For instance, we may establish a distinction between the situational cues that trigger the meaning response in a hypnotic scenario (e.g. the office of the hypnotherapist, our beliefs about hypnosis, the reputation of the hypnotherapist, etc)[294] and the experience of the

---

[293] Weitzenhoffer, *Suggestibility*

[294] Lush, *The Sussex-Waterloo* highlights how it is unclear if the small increases in suggestibility observed after a hypnotic induction can be attributed exclusively to what we are referring here as the 'meaning response': *"There is evidence that the increase in response to suggestion attributable to hypnotic induction is small (Braffman and Kirsch 1999; see Connors et al. 2012, for an exception), and that any increase in responding over non-hypnotic suggestibility may be attributable to the use of the word 'hypnosis' (Gandhi and Oakley 2005). Thus, a minimal condition for an induction to enhance response may be simply defining the context as one appropriate for hypnotic response."*

induction itself (e.g. eye fixation, arm drops, relaxation exercises, etc). However, the office of the hypnotherapist might be a crucial part of our experience, and, conversely, the eye fixation procedure may be seen as a component of the context that is activating our meaning response.

Contrary to the case of hypnosis, a distinction is easier to make in the case of psychedelics, or perhaps, more generally, in the case of pharmacology: arguably, there will be some components of the psychedelic experience that remain constant across contexts, while different contexts may carry entirely different situational cues that would convey entirely different meanings (e.g. a clinical trial of psychedelics, a Mayan ritual involving psilocybin and human sacrifices in 500CE, or a non-consensual interrogation scenario involving LSD such as those which occurred during the CIA's MK-ULTRA project).[295]

According to the 'active placebos' interpretation of antidepressant effects[296], for instance, the small differences in outcomes observed between antidepressants and placebos in clinical trials[297] may be entirely attributable to the fact that antidepressants have adverse effects[298] which are experienced by participants and thus potentiate the extrapharmacological effects. In a sense, this second level may be a component of the 'meaning response' level, in that the experience of these adverse effects may improve clinical outcomes only by 'unblinding', by confirming to the subjects that they are in the active arm of the study and thus potentiating their beliefs about outcomes. Understanding the extent to which this is the case may prove informative

---

[295] Carod-Artal, *Hallucinogenic;* US Senate, *Project*
[296] Kirsch, *The Emperor*
[297] See Fig. 2 in Stone, *Response*
[298] A fact which highlights the need to consider carefully when they are superior to other options such as psychotherapy which seems to have similar efficacy in some cases: Leichsenring, *The efficacy*

in assessing future treatment guidelines and pharmacological developments.

The risk of patients unblinding due to the adverse effects in the drug group had already been raised before, and in fact some studies with antidepressants have used active placebo controls since as early as the 1960s. However, the use of active placebos seems to be extremely infrequent in clinical trials in general[299], which is particularly concerning for antidepressant research: Jensen *et al.* "[...] suggest that active placebos are used more often in trials of drugs with noticeable side effects, especially in situations where the expected therapeutic effects are modest and the risk of bias due to unblinding is high" (all of these clearly apply to antidepressants). Some factors limiting the adoption of active placebos include the risk of the active placebos themselves influencing the outcome (thus introducing an underestimation bias for the drug effect), exposing participants to harm, and the difficulty in choosing agents that will closely mimic the adverse effects profile of the treatment compound without also having some therapeutic effects.[300]

Following the hypothesis that the subjective experience of adverse effect and the concomitant unblinding in antidepressant trials may be the reason why they seem to be slightly more effective than placebos at improving outcomes[301], it follows that the the slight superiority of psychedelics when compared to classic antidepressant in some trials[302] may be attributable to the profound alterations in subjective experience that they lead to[303]. If this is the case, and the

[299] Jensen, *Active*
[300] Moncrieff, *Active*
[301] Hieronymus, *Control*
[302] Hsu, *Comparative.* This superiority is only apparent in some studies of psilocybin. Metaxa, *Efficacy*
[303] This effect may be due to the overall experience, but it may also be specific to some component of it (for instance, it may be specifically related to the increased frequency of 'Eureka moments' as described in McGovern, *An Integrated*)

psychedelic experience has a causal role in leading to antidepressant effects (independently of whether it is through unblinding or through some other mechanism), the current interest in developing non-psychedelic psychedelics may never lead to drugs with similar therapeutic value[304]. Likewise, other ways of providing experiential substrates such as different drugs, hypnotic procedures, or even an elaborate VR experience may be able to provide antidepressant effects if the antidepressant effects of psychedelics are mainly related to their subjective effects. Of course, it may also be that the psychedelic experience has some specificities to it that are not present in other types of experiences.

The ability to control experience

Let's now consider the third and last level. From a PC perspective, both the activation of a specific symbolic network and the presence of an identifiable effect on experience are only modulators of an underlying ability to generate experiences for oneself (PC), which could also be recruited in the absence of these elements: what if psychedelic drugs are directly affecting PC by modulating the underlying neural circuits? In PC studies, subjects are told about PC and invited to experience different 'imaginative suggestions' which are equivalent to classic hypnotic suggestions except for the fact that they are not labeled as hypnotic in the first place:[305] this can be seen as an indication that PC can indeed be recruited without the aforementioned elements.[306]

---

[304] Wallach, *Identification*

[305] Sheldrake, *The Experience*

[306] The relationship between hypnotic inductions and PC studies, as well as that between classic placebo studies and 'open-label' placebo studies (were subjects are explicitly told that they are getting an inactive substance, which strikingly still leads to clinical effects), are formally reminiscent of a certain inversion performed by Slavoj Žižek while discussing the concept of ideology in his 1989 work '*The sublime object of ideology'*. There, he explains that "The

According to the 'cold control' theory of PC,[307] PC can be thought of as the ability to strategically act on intentions while being unaware of those intentions. In the case of placebo effects in an antidepressant trial, for instance, if we think of the improvements observed by the placebo group as the result of PC, the subjects experiencing those improvements would be strategically acting towards improving their symptoms because of their intention to cure themselves, while staying unaware of this intention and ascribing the effects to the treatment.

Depending on the context, this mechanism may require different moving parts to be coordinated. There has to be an intention to obtain a certain goal, which the subject remains unaware of throughout the experience. Any resources that may be needed in order to generate the desired experience also need to be recruited: this may vary widely, from 'antidepressant resources' (whatever those may be), to perceptual, cognitive, or motor ones that may be needed to fulfill hypnotic suggestions for hallucinations, amnesia, or involuntary movements. In some cases, sensory evidence may need to be actively ignored or manipulated (for example, in the case of a visual hallucination suggestion, some part of the visual scene will need to be modified or

---

most elementary definition of ideology is probably the well-known phrase from Marx's *Capital: [..] 'they do not know it, but they are doing it'.* The very concept of ideology implies a kind of basic, constitutive *naiveté*: [...] a divergence between so-called social reality and our distorted representation, our false consciousness of it.' Then, he poses the question of whether this definition of ideology as 'false consciousness' is still applicable today, and uses Sloterdijk's thesis that ideology today predominantly functions cynically to invert it: "The formula, as proposed by Sloterdijk, would then be: 'they know very well what they are doing, but still, they are doing it'. Cynical reason is no longer naive, but is a paradox of an enlightened false consciousness: one knows the falsehood very well, one is well aware of a particular interest hidden behind an ideological universality, but still one does not renounce it". Recent developments such as the development of the phenomenological control questionnaire, or the introduction of open-label placebo studies, highlight how, in this context as much as in the context of ideology, the *naivité* that was considered at some point constitutive might turn out to be dispensable after all.

[307] Dienes, *Phenomenological*

ignored for the hallucination to occur). These different parts likely need to be coordinated for PC to achieve the goal of generating a given experience. Naturally, there must be different neural circuits involved in such a process, probably with complex dynamics that we are far from understanding.

In this third level then, we are considering the possibility that the chemical properties of psychedelic substances may confer them the ability to directly modulate these neural circuits in a way that impacts PC independently of their subjective phenomenology and our beliefs about them. It is not unreasonable to think that agonism for serotonin receptors (which is shared by most psychedelic substances and seems to be crucial in generating their subjective and therapeutic effects) may confer them such an ability: serotonin is a neuromodulator that projects to most forebrain areas, and thus is in a privileged position to coordinate activity in a brain-wide manner, and has access to all the neural circuits that may intuitively be expected to participate in PC.

If psychedelics are directly modulating PC at a neural level, and if their therapeutic efficacy is attributable to this effect independently of their phenomenology and our beliefs about them, the possibility remains that their effects on subjective experience and their therapeutic effects may be separable. On the one hand, we might be able to design new drugs that allow for the therapeutic targeting of PC mechanisms without the impractical phenomenological consequences, and on the other hand, we might design yet other drugs (perhaps a new 5HT-5a receptor antagonist[308]) that would allow subjects to have a psychedelic experience without the concomitant increase in suggestibility.

The aim of this section was to dissect the different ways in which psychedelics may have an effect on phenomenological control. Of

[308] Sagi, *Emergence*

course, the three levels proposed here are not intended to be exhaustive nor independent, and it is likely that they may interact in different ways. For instance, as mentioned above, the first two levels may often be hard to separate. Still, we believe that having these levels in mind might help analyze certain situations: for instance, the fact that psilocybin induced, on average, an increase in nature relatedness and a decrease in authoritarian political views in one clinical study should be interpreted with caution[309]. While it is tempting to ascribe such effect to the substance itself, such an effect could be due to the amplification of pre-existing beliefs by a substance which doesn't actually inherently target those beliefs or directions of change, implying that the same substance may amplify entirely different beliefs[310].

Why?

The current status of research in both psychedelics and phenomenological control is symptomatic of some broader realities in the field of Neuroscience as a whole: theoretical accounts tend to focus on individuals[311]. Even when social dynamics are brought into the picture, they tend to be seen from the perspective of individuals, in a sense always prioritizing the individual before the group[312]. However, evolutionary biology has taught us that evolution often acts at the level of the population rather than staying at that of the individual. Here, I will use the concept of alignment as it is used in the context of multi-agent

[309] Lyons, *Increased*
[310] Pace, *Right-Wing*
[311] This is arguably the case more generally, including other areas of science and contemporary thought at large. A shift of focus towards group dynamics is urged by many contemporary philosophical frameworks, with some emphasizing that the relationship between individuals and the collective can only be understood as one of mutual constitution.Balibar, *Sobre;* Bottici, *Anarchafeminism*
[312] Pokorny, *Effects;* Corlett, *Hallucinations;* Lush, *Expectancies*

systems in order to propose a new perspective on both psychedelic effects and phenomenological control.

Alignment and current theories of hypnosis and psychedelics

As we have discussed in previous chapters, some of the most popular theories of psychedelics in the current literature include REBUS[313] and the strong priors theory of hallucinations, which respectively suggest that psychedelic experiences (and hallucinatory phenomena more generally in the case of the strong priors theory) result from having overly relaxed or overly strict priors in a Bayesian inference framework. Such a conceptualization of perception through an inference framework is extremely common in modern neuroscience[314], and has proven to be a very productive perspective on the intricacies of sensory processing. Likewise, similar Bayesian approaches have been successfully applied to cognitive and motor functions, showing the extreme flexibility and generalizability of the framework. However, in both hypnosis[315] and psychedelics[316] research, attempts to offer a unifying model based on Predictive Processing (PP) or similar inference-based frameworks have encountered important limitations in recent years. Here, I want to propose that precisely through the idea of PC, and its application to the field of psychedelic research, we can overcome some of the limitations of priors-based theories and suggest future directions.

Prior-based models like REBUS or the strong priors hypothesis of psychosis can be thought of as 'why' models. They aim to answer a normative question, why is it that these phenomena occur? And they

[313] Zeifman, *Relaxed*
[314] Charlton, *Perceptual*
[315] Lush, *Expectancies*
[316] Corlett, *Hallucinations*

both find their answers in one of the most popular normative models in contemporary neuroscience: Bayesian inference, or, as it is often referred to when applied to Neuroscience in particular, Predictive Processing (PP). According to PP accounts of brain function, the main role of the brain is that of constructing accurate representations of the world in order to allow for adaptive decision making and behavior. These representations are used to predict incoming sensory evidence, and in turn the incoming sensory information is used to update the representations when needed. Following a Bayesian approach, these models can be thought of as priors, internal models that estimate the latent, hidden variables generating sensory evidence.

This model can be applied to many different situations, and offers a remarkable amount of flexibility in allowing us to conceptualize different scales of phenomena without needing to adjust the underlying assumptions of the model. In general, this is the process that is performed when a researcher or statistician applies Bayesian statistics to any numerical problem: a prior belief is assumed to exist, and through a study of the information available in the data, this belief is updated and optimized to fit reality. For instance, imagine a study trying to assess the distribution of body weights in my workplace. Of course, if we had enough funding, we could just weight everyone and know the exact distribution of weights, but because our funding is very limited, or perhaps because only a few people are willing to jump on the scale for us, we are limited to measuring a subset of the data and make our best guess from there.

If we wanted to study the average body weight in that workplace, we would already have a certain prior belief about the value, even if we are not aware of it. For instance, if I was told that the average weight in my workplace is 100kg, or 20kg, I would be perplexed. The fact that I would be surprised indicates that I have some beliefs about the

distribution of body weights, otherwise no single piece of data would seem surprising. If needed, we could estimate my prior belief by asking me questions about how likely I think different values are to be the average value that we are looking for, or by asking me how frequent I think a certain value is in the population. Regardless of whether or not we estimate my actual prior belief (or just 'prior', for simplicity), we can start doing a study by weighting people who work here. After we have weighted enough people, we could then form a new estimate of the true distribution of body weights in this population. Independently of whether or not this distribution fits our priors, it would now be the best estimate that we could make given the data, which is called the 'posterior'.

Now, if we were to repeat the same study a few years down the line in order to assess the evolution of body weights in this population over time, that value, our posterior from the original study, would become the prior for the new study. We would start accumulating data, and we would then form a new posterior probability distribution, a distribution of probabilities corresponding to different weights based on the observed data. This iterative process is the same that can be applied in many different scales to many different processes.

For instance, we could think of vision in the retina as a low level example. There is a constant flow of photons arriving to a certain photoreceptor in the retina, which is trying to constantly estimate the true value of the generative process behind that flow of photons[317] (e.g. what is the intensity of that source of light?). Based on the distribution of incoming photons, retinal photoreceptors are continually inferring statistical properties of the sources of those photons, a set of latent variables that are not directly observable, but which can be inferred by

[317] Korenbrot, *Speed*

accumulating a certain amount of sensory samples and building internal models to estimate those hidden variables accordingly.

Likewise, we can go to a more abstract level to apply the same models in a different context: there is ample evidence that humans spontaneously infer many different types of traits from behavioral information[318]. For instance, upon observing or reading about a person who carries an old woman's groceries across the street, people tend to infer that this person is helpful[319]. It's easy to imagine more complex social scenarios where inference is necessary: someone looking at us on the street can be a sign of aggression, of sexual interest, of criminal intent, or a trigger for a paranoid schizophrenic episode centered on the idea that we are being followed.

This brings us to the idea of cognitive flexibility. If we think of inference as a moment where our internal models are updated based on new information, it becomes clear that such an update may be done in different ways[320]: the amount to which a single piece of evidence influences our internal models can change, and some argue it *should* change in order to be optimally adaptable to changing environments. If we are in an environment which is highly predictable, we might benefit from having stable internal models of the environment that don't change too readily when we receive the odd dissonant piece of evidence: this might be more efficient in that less updates would be required, and it would confer a certain robustness to our understanding of the world, which would be unaffected by outlier events that may otherwise throw our internal models off. On the other hand, if we are in a highly unpredictable environment, it may be more beneficial to have more flexible internal models, making sure that we update our beliefs at the

[318] Bott, *Spontaneous*
[319] Winter, *When*
[320] Daunizeau, *Observing*

slightest sign of change in the environment. While it would perhaps be more costly from an energy perspective to constantly and radically change our views on the world, it would allow us to have the best models at any given point in time, adapting quickly to the changing environment.

According to the REBUS model of psychedelics, one of the main effects of psychedelics is that they *relax* prior beliefs, allowing these to be reconfigured more flexibly during and after a psychedelic experience. By relaxing prior beliefs originating internally, psychedelic substances would then be enabling an enhanced bottom-up flow of information coming from the senses. In their 'entropic brain' theory, these authors suggest that an increase in entropy in brain activity may be the underlying neural mechanism leading to this relaxation of prior beliefs during the psychedelic experience. According to some of their work, the brain can be thought of as lying on a spectrum regarding entropy levels and prior belief flexibility. On one end of the spectrum, where entropy is minimal, there is coma, and on the opposite end of the spectrum, with maximum entropy, there is the phenomenon of epileptic seizures. In a more physiological range, without reaching such extremes, lay different disorders. On the low entropy side of the spectrum we can find disorders such as depression, obsessive-compulsive disorder, or addiction, while higher entropy states correspond to pathological states such as early psychosis or the dreamy state associated with temporal lobe epilepsy, and other states such as infant consciousness, REM sleep/dreaming, near-death experiences, or the psychedelic state.

These models are based mainly on the observations that neural signals can become more complex in EEG and magnetoencephalography studies, and the neuroimaging studies that show disintegration of association networks such as the default mode

network under the effects of psychedelics[321]. However, studies have repeatedly shown reduced stimulus-evoked spiking activity in visual areas in animals, and it is well established that sensory hallucinations don't tend to occur in response to very strong sensory stimuli, on the contrary, they occur more easily in sensory deprived conditions. These failures of the REBUS model suggest that a different theory might be needed to explain the effect of psychedelic drugs, and one of the most popular candidates in that sense is the strong prior (SP) model[322], which suggests that psychedelics may instead be *reinforcing* prior beliefs and reducing the flow of bottom-up information.

Strikingly, this model can be thought of as an inversion of REBUS, the main difference apart from this inversion being that the authors proposing the SP model are not so committed to any particular implementation or neural substrate that may be underlying these effects[323]. As opposed to the REBUS model, which to the best of our knowledge emerged primarily from research with psychedelics, the SP model comes from a more comprehensive background, focusing less on psychedelics and considering instead the occurrence of hallucinations in general, both in psychotic and schizophrenic patients, as well as in the general population. According to the authors of the SP model, the main challenges that escape conceptualization by their model are the fact that schizophrenic patients seem to be particularly insensitive to certain illusions (indicating that they seem to be relying *less* on their prior beliefs instead of more as would be predicted by their model), and the fact that corollary discharge seems to be prone to failure in people with schizophrenia in a way that correlates with the severity of their symptoms (a failure of corollary discharge is interpreted to be caused by

[321] Kwan, *Neural*
[322] Corlett, *Hallucinations*
[323] *Ibid.*

having less precise priors in place, and thus is also difficult to accommodate into their model as it represents an instance where weak priors seem to lead to psychotic symptoms).

Now let's go back to the theoretical explanation about inference and let's consider what happens in a context where multiple agents are involved, such as a multi-LLM pipeline, a swarm intelligence algorithm, a multi-classifier machine learning solution, or a human tribe. In all of those cases, single agents may perform inferences that lead to different solutions to a given problem, or different internal models of a given environment. Thus, since now multiple agents with different solutions might need to coexist or even collaborate, a new problem emerges: how to create cohesion in the group at the level of internal representations. Let's again illustrate this with a practical example.

In the example mentioned before about behavioral inference in humans, we could imagine a scenario where a group of people agree on their inference: everyone seeing the person helping the old lady with her grocery might agree that this person is helpful. However, some scenarios have more uncertainty and may pose more challenges in inferring a given latent variable.

Let's imagine, for example, the case of a human tribe inferring the causes behind the phenomenon of rain[324]. With no access to modern science, it would be impossible for any given agent to perform an optimal inference and give an accurate explanation of why it rains. While the more rational and mature decision at that point might be to just accept one's failure to understand the situation and live with the discomfort of an 'I don't know', we know that's usually not how it goes. Provided that people would still perform inference and accept their best guess as reality, we would then be facing a group of people with likely independent

[324] van Leeuwen, *Chimpanzees*

solutions to their inference problem (let's say that they all had the opportunity to perform their inference independently of one another). Perhaps one might reach the conclusion that rain happens when the clouds are sad and they cry, while another one might decide that rain is punishment from the gods who are unhappy about the behaviors of the tribe, while yet another individual might decide that rain is just water from the ocean that leaks from the sky in a never-ending flow of water movement.

With as many solutions as individuals in a group, any group behavior based on a given inference would be difficult to coordinate[325], and even without such a behavioral pressure, disagreement may lead to tension and violence in social situations. This exact problem of multiple agents finding multiple solutions has been central in other fields like the ones mentioned above, ranging from classic ML solutions[326] and applications of Bayesian inference to group scenarios[327] to modern multi-LLM algorithms[328]. In ML, it's been known for a long time that sometimes training multiple algorithms and then finding a way to unify the solutions can provide significantly better results than training any single algorithm[329]. In general, it seems like such situations can lead to more robust conclusions and be less sensitive to noise in a given dataset[330]. Conversely, allowing individual solutions to weigh more in the final solution found by a group may provide improved sensibility to changes in the environment, allowing the solutions to adapt more rapidly and flexibly.

---

[325] Bhatt, *When*
[326] Freund, *Decision-theoretic*
[327] Eguíluz, *Bayesian*
[328] Tillman, *Literature*
[329] Freund, *Decision-theoretic*
[330] Angluin, *Learning*

The observation that multi-agent systems prove superior to single large language models (LLMs) has brought a great deal of attention to the problem of alignment in contemporary research on artificial intelligence and machine learning[331]. The balance between aggregating different inferences and exploiting the advantages of having diverse predictions has proven to be a significant challenge[332], and apart from opening possibilities for more advanced algorithms, has also brought attention to the importance of our understanding of alignment when trying to reduce bias in generative models and to keep them from learning problematic inferences and behaviors[333].

Both hypnosis[334] and phenomenological control[335] at large have repeatedly been conceptualized as social phenomena, and proven particularly difficult to model at an individual level[336]. With this in mind, the main proposal of this perspective piece is to suggest that phenomenological control might best be understood as a group-level phenomenon, which may be impossible to conceptualize at the level of individuals. Not only has group-level cohesion proven to be a fundamental piece for different types of computational multi-agent scenarios, it is also perfectly plausible as a normative framework to explain certain deviations from canonical inference and predictive accounts, which are observed in human behavior. Phenomenological control should then be thought of as a mechanism that evolved to solve the problem of aggregating discordant inferential conclusions from different individuals by allowing individuals to generate experiences for themselves that fit into a shared symbolic space.

---

[331] Ueno, *Multi-agent*
[332] *Ibid.*
[333] Varshney, *Decolonial*
[334] See 'Part IV: The Sociocognitive Perspective' in Lynn, *Theories* for multiple examples.
[335] Arlandis, *Hypnosis*
[336] Lush, *Expectancies*

While it might be tempting to absorb this phenomenon back into a Bayesian inference model (by just framing it as social transmission of priors), I think it's important to resist this temptation, because the idea of phenomenological control in itself highlights some divergences from a pure inference scenario: in certain situations, humans seem to be able to selectively ignore highly precise sensory information and to instead experience reality according to a socially constituted state of affairs[337]. While justifying this by arguing that socially validated priors may simply carry a higher precision or weight in order to influence individual inference processes might be a good explanation of this phenomenon, it's important to highlight that this can constitute a departure from an optimal inference framework.

Oftentimes, the solution that gets implemented at a group level might be objectively inferior to some specific individual solution found in the group, as can be exemplified by considering any of the mythical and religious explanations for natural phenomena such as rain, or by any of the incredibly popular conspiracy theories[338] that in some cases coexist with robust and conclusive scientific evidence that negates them[339]. Likewise, understanding the extent to which symbolic spaces validated at a group level can directly influence the generation of individual experience[340], and the degree to which this can deviate from optimal inference, seems to be particularly relevant to situate many contemporary political developments, including the growing tendency towards devalueing scientific evidence[341] and the increasing ease with which fabricated facts and narratives are absorbed by the public[342].

---

[337] Arlandis, *Hypnosis*
[338] Fernbach, *Conspiracy*
[339] Brazil, *Fighting*
[340] Sherif, *Experimental*
[341] See 'Contestation of Science, Post-truth Regimes and Emotions: A Review', in Fage-Butler, *Science*
[342] Nabers, *Discourse;* Bellamy, *Trump*; Tourish, *It is time*

This proposal of PC as a mechanism to generate group cohesion in situations of dissonant individual inferences might seem counterintuitive from a normative point of view, because we are used to think of optimal inference (and this mechanism could often go against optimality from an individual perspective), and because we are biased to think about evolution in individual terms (and this mechanism would require a group level evolutionary pressure). However, the idea that animals or humans in particular are optimizing statistical inference as their sole objective goal is an assumption, and the fact that this might sometimes be the case in perceptual, cognitive, or motor tasks doesn't preclude the possibility that a different dimension may have been optimized by natural selection (a dimension, for instance, like the one of group cohesion proposed here). Likewise, it is a widely accepted fact in evolutionary biology that evolution often acts at the level of populations instead of at the individual level[343], which can sometimes generate situations that are hard to make sense of at an individual level[344] but gain meaning when looked at from a collective perspective.

Psychedelics and phenomenological control through the lens of alignment

Having outlined this proposal, we can now consider the possibility that psychedelic drugs may be able to modulate such a capacity to generate experiences to fit a certain counterfactual state of affairs[345] in accordance with a socially established model. As discussed above, there are different ways in which psychedelics may be influencing phenomenological control, namely, by directly affecting the neural circuits involved in PC (in which case these effects might be dissociable

[343] Losos, *Princeton*; Rensch, *Evolution*
[344] Lush, *Expectancies*
[345] Dienes, *Phenomenological*

from the effects that lead to the psychedelic experience and thus there may be non-psychedelic psychedelics with antidepressant properties, or psychedelic psychedelics without), by providing an experience that can convince people that something is happening, thus potentiating expectancy effects (in which case non-psychedelic psychedelics would prove to have no therapeutic value), or by simply mobilizing a set of cultural beliefs about psychedelics which don't depend on either of the previous options (in which case the effectiveness of non-psychedelic psychedelics would depend upon the degree to which a cultural belief about their therapeutic efficacy can be developed).

Of course, independently of the mechanism of action, if psychedelics were in some way influencing PC, given the boom in their popularity and the amount of research dedicated to elucidating their properties and mechanisms of actions, we would by now have indications to believe this is the case. Indeed, there are multiple dimensions of psychedelic research that may be explained by PC modulation, as well as many theoretical accounts of psychedelic action which support the possibility that this may be one of the effects of psychedelic drugs, especially when conceptualizing PC as a mechanism to promote social cohesion, as proposed here.

One of the most robust results from the hypnosis literature is the fact that, when measured in an experimental context, the ability to respond to hypnotic suggestions seems to be a very stable individual trait that remains unchanged over long spans of time, while widely varying across individuals following a roughly normal distribution, with a small percentage of individuals being very high respondents, a similar amount being very low responders, and most people lying somewhere in between. There is an extensive literature on the topic of hypnotizability modulation, and a myriad techniques have been evaluated in order to assess their ability to increase or decrease hypnotic suggestibility.

Interestingly, one of the few techniques that has been tested multiple times, sometimes showing statistically significant increases in suggestibility, has been the administration of classic and atypical psychedelics before the hypnotic procedure[346].

This is perhaps the most direct evidence for an interaction between these drugs and PC: the fact that psychedelics seem to directly increase hypnotic suggestibility[347]. Furthermore, the history of psychedelic research is intimately intertwined with the history of the concept of placebo, with the first proposals for double-blind placebo effects originating (as already mentioned when discussing Henry K. Beecher) precisely from the study of hallucinogenic drugs. Both classic antidepressants[348] and psychedelics[349] have been riddled with uncertainties and criticisms about their validity because of their only small increases in therapeutic efficacy over placebos, which, since very early on, raised the question about whether they have any effects that are not mediated by a potentiation of placebo or 'extrapharmacological' effects.

Combinations of hypnosis and psychedelics were studied since very early in the history of psychedelic research, sometimes only at a conceptual level[350], other times through actual combination as a therapeutic strategy[351], and yet other times for purely explorative reasons, as in the report by Fogel and Hoffer in 1962, where hypnosis was used to interrupt and later reproduce a psychedelic experience, concluding that "It was possible to make one subject normal at the height

---

[346] Sjoberg, *The effects;* Levine, *Alterations;* Solursh, *LSD;* Middlefell, *The effects;* Kelly, *Effects;* Van Nuys, *Drug use;* Whalley, *Enhancement;* Patterson, *Ketamine;* Carhartt-Harris, *LSD*
[347] Sjoberg, *Effects*; Carhartt-Harris, *LSD*
[348] Kirsch, *Emperor*
[349] Dupuis, *Culture*
[350] Krippner, *Hypnotic*
[351] Levine, *Alterations*; Levine, *Hypnodelic*; Levine, *Controlled*; Arnold, *Controlled*

of her LSD-25 experience. Three weeks later, it was possible to reproduce an LSD psychedelic experience by hypnosis alone"[352]. While early studies suffer from multiple severe methodological flaws, contemporary authors still highlight the commonalities between hypnotic and psychedelic states, point at the multiple ways in which they can be combined to obtain greater therapeutic benefits[353], and highlight the urgency of dedicating greater attention to suggestibility in the expanding field of psychedelic research[354].

Given the relevance of active placebo theories in both psychedelics and classic antidepressants research, the question emerges: what if the way in which psychedelics provide therapeutic benefits in depression is simply through phenomenological control? Behind the super-placebo theory[355] lies the small differences observed between the effect sizes of placebos and drugs in most antidepressant trials. These small differences are not due to the drugs not being very effective, on the contrary, they are attributable instead to the surprisingly large placebo effects found in this context. This suggests that indeed phenomenological control can have therapeutic effects, a notion that is further reinforced by research showing that hypnosis may also have antidepressant effects[356] (the jury is still out on determining the efficacy of such treatments[357]).

As discussed above, there are multiple mechanisms through which psychedelics might be modulating phenomenological control, and we don't have enough evidence to conclude which of these may be playing an active role, or in which ways they may be interacting with one

---

[352] Fogel, *Use*
[353] Lemercier, *Psychedelics*
[354] Olivier, *Suggestibility*
[355] Kirsch, *Emperor*
[356] Milling, *Meta-analysis*; Pang, *Hypnotherapy*; Shih, *Meta-analysis*
[357] Souza, *Hypnosis*

another. While it might be tempting to conclude that this effect is surely mediated by the serotonergic system (given that most psychedelics have affinity for serotonin receptors, and given the serotonergic nature of many antidepressants), the serotonin hypothesis of depression has recently been called into question[358], and further doubts are cast on this idea by the multitude of drugs that show antidepressant effects without having a modulation of the serotonergic system as their main pharmacological effect (the amount of drug classes that have demonstrated to have some antidepressant effects is strikingly varied, including NMDA antagonists[359], stimulants[360], hormones/neurosteroids[361], anti-inflammatories[362], antihistamines[363], GABAergic drugs[364], antipsychotic medications[365], anticonvulsants[366], and opioids[367]).

Putting together these different commonalities, and considering the possibility that a certain proportion of the effects of psychedelic drugs might be attributable to a modulation of PC mechanisms, let's now consider how this could inform our efforts to develop high-level theories of the effects of psychedelic drugs.

Psychedelics and alignment

Both REBUS and the strong priors theory aim at explaining some part of the phenomenology of psychedelics by interpreting them through the lens of statistical inference. They both do so by modeling the effects on the brain as being explainable in the context of the updating of prior

---

[358] Moncrieff, *Serotonin*
[359] Berman, *Antidepressant*
[360] Candy, *Psychostimulants*
[361] Cooper-Kazaz, *Combined*; Nagpurkar, *Neurosteroids*
[362] Köhler, *Effects*
[363] Lamberti, *Antidepressant-like*
[364] Meltzer-Brody, *Brexanolone*
[365] Nelson, *Atypical*
[366] Vigo, *Anticonvulsants*
[367] Yovell, *Ultra-Low-Dose*

beliefs from an individual perspective. In the case of REBUS, prior beliefs are proposed to be relaxed under the effects of psychedelics, or in other terms, to become less precise. This leads to sensory evidence having a stronger effect in the inference process, leading to an altered weighing of priors versus sensory inputs, and enhancing bottom-up signaling. On the opposite side, the SP theory proposes that hallucinations (in general, not specifically in the context of psychedelic drugs) may best be understood as the consequence of overly strong priors, which overpower the incoming sensory prediction errors and lead to illusory, hallucinatory, or delusional percepts and experiences, leading to psychotic symptomatology.

Both theories, among the most popular contemporary theories of psychedelic action, encounter important limitations in trying to explain all the proposed phenomena. Notably, going against the predictions of the REBUS framework, very early work showed that LSD can actually reduce stimulus-evoked spiking activity in the visual cortex[368], with similar results having been reported in recent systematic studies on the topic[369]. Similarly incompatible with the REBUS framework is, as mentioned before, the well established fact that hallucinations are more likely to occur in situations with diminished sensory stimulation[370] and not in those with excessive stimuli, a phenomenon that can be reliably utilized to induce hallucinations in healthy subjects[371]. On the other hand, the SP theory fails to explain some of the nuance in the symptomatology of schizophrenic patients: namely, schizophrenic patients seem to be less susceptible to certain visual illusions (which is taken to indicate that they actually have *less* precise sensory priors), and there is some evidence that different types of hallucinations in schizophrenic patients

[368] Evarts, *Some*
[369] Michaiel, *Hallucinogenic*
[370] Vernon, *Sensory*; Mason*, Psychotomimetic*.
[371] Powers, *Pavlovian*

may be related to a dysfunction in corollary discharge (again, suggesting that their sensory priors may be less precise), in a way that relates to symptom severity[372].

The authors behind the SP model propose that these discrepancies between reality and their model may be explained by considering different hierarchical levels of inference, such that priors may be less precise in lower levels of the hierarchy, but still lead to overly precise priors higher-up[373]. Other authors have suggested, similarly, that REBUS and SP models may be reconciled if we consider the possibility that perhaps 'weakened low-level beliefs eventually culminate in stronger extraperceptual beliefs'[374].

Indeed, it seems like both theoretical proposals fail to explain different aspects of the physiology and phenomenology of psychedelics and psychosis, and this is understandably met with the solution of increasing the complexity of the models. Perhaps a multi-level inference model is truly necessary to explain these complex phenomena, but the failure of these models might also be a good opportunity to question their underlying assumptions and their validity as normative models instead of simply increasing their complexity.

In our opinion, the underlying assumption of both models is that the objective function that was evolutionarily optimized and inscribed in our brains is that of optimal inference at an individual level. While this is undoubtedly a valuable property for an evolutionarily adaptive organism, there is no reason to believe that it is the only 'loss function' being optimized by natural selection. As argued here, the reality of social animals is that on many occasions, individual inferences can contradict each other and lead to problematic dynamics: perhaps populations with

---

[372] Corlett, *Hallucinations*
[373] *Ibid.*
[374] Kwan, *Neural*

certain group-level adaptations had an evolutionary advantage that fixed such adaptations in place. While this may apply to any species, intuitively it seems like the central role of symbolic abstractions in humans may make such group-level cohesion particularly important.

Coinciding with the proposed need for multi-level inference mechanisms in REBUS and SP[375], the authors proposing PC as a framework argue for metacognitive processes as being central in phenomenological control[376]. In order to generate an experience that feels real, one needs to have a certain intention, while also remaining strategically unaware of having such an intention, in order for the fulfillment of such intention to not feel like a simple intentional action.

The subject who has a visionary experience of an encounter with Virgin Mary clearly has the capacity to generate a hallucination of such reality, and according to PC they do so precisely because they have the intention to have such an experience, but simultaneously they can also remain unaware of having had such an intention, and thus experience the hallucination as real. What is considered a hidden 'intention' according to such theories, could perhaps be seen as part of the alignment mechanism proposed here: the christian beliefs behind marian apparitions are a shared collective belief system which benefits from single individuals having such experiences that locally depart from optimal inference, which in turn contribute to the maintenance of such a symbolic system and to the alignment of the beliefs of a multitude of individuals.

While models like REBUS and SP seem to imply that hallucinations and psychosis are departures from the evolutionary goal of optimal inference, an account of hallucinations based on PC can highlight the possibility that these phenomena may be conceptualized as

[375] Corlett, *Hallucinations;* Kwan, *Neural*
[376] Dienes, *Phenomenological*

modulations of an adaptive mechanism within functional ranges, as opposed to being understood as pathological deviations from an optimal balance. Psychosis may have had a functional role in its effects at the group level, and understanding psychedelic drugs as modulating group-level dynamics may explain the pervasive role that they have been documented to play in human groups for thousands of years.

Having established the failure of simple inference frameworks, it is interesting to consider the ways in which a PC account may help unify the different levels that are seemingly required to explain the complex phenomenology of psychedelic drugs or hallucinations. Let's consider an example. In the classic hand levitation hypnotic suggestion, multiple things need to align in order for the hypnotee to have a hypnotic suggestion with the altered sense of agency that is sometimes considered as the 'hallmark phenomenological feature of response to suggestion'[377].

First, the subject needs to ignore any sensory evidence that would inform them of the fact that they just raised their hand. In inference terms, this would equate to having overly precise (and wrong) sensory priors that would overwhelm the incoming sensory information. Simultaneously, they should also have flexible enough high-level priors so that when the hypnotist issued the suggestion 'you will feel your hand raising on its own', the pre-existing prior of their hand *not* raising on its own could be overpowered by this newly proposed prior. As discussed in the previous chapter, such a hypnotic suggestion received from a hypnotist in a hypnotic context carries a certain weight and authority which may not be there if it was delivered in a different context or by a different person. This highlights the fact that the effect depends on socially validated dimensions that traverse the experience.

[377] Acunzo, *'A Critical'*

Thus, in this scenario, a combination of strong low-level priors and relaxed high-level priors would be needed in order for the suggestion to take effect, in a similar fashion to that proposed to reconcile REBUS and SP. However, if we move from the implementation level to a more conceptual understanding of this phenomenon, a more complex picture starts to emerge. The hand levitation suggestion requires a complex orchestration of factors. Triggered by a verbal utterance from a conspecific, a series of events needs to happen for a motor action to take place, while simultaneously all sensory evidence that would usually relay information about such an intentional movement needs to be suppressed so that agency can be attributed to an atypical agency.

While it is temptingly simple to explain this as a multi-level readjustment of prior vs. sensory prediction errors weighting, this explanation may be missing a crucial point. This complex orchestration of different parallel mechanisms leads to the generation of a realistic experience based on a verbal command, in accordance with the cultural image that we have about hypnosis. Instead of inference, it might then be more informative to conceptualize this process as one of generation. It is not about an inference system being accidentally thrown out of balance, this is an instance of a complex mechanism that allows human beings to generate experiences from thin air, even in the presence of sustained contradictory sensory evidence.

While the hand levitation example is an excellent illustration of this phenomenon, it might be useful here to consider the ample possibilities that hypnotic suggestions afford: from visual hallucinations to deep anaesthesia, hypnosis has been used (and studied in a controlled laboratory environment) to induce very varied types of experiences, most of them requiring the orchestration of different

systems such as those involved in sensory perception, nociception, motor coordination, or memory retrieval.

In a situation where a group is faced with a simple inference, one where the optimal solution is within reach, alignment may be possible through minor modifications in the beliefs of single individuals. However, in the case of inferences in the face of extreme uncertainty or in situations where the solution is far from being obtainable, like the rain example proposed above, alignment might require the creation and sharing of a convincing symbolic placeholder that can explain some of the experienced realities. While the first case may be easier to model through modifications in prior weighing, we believe that the second case might require the mobilization of a more nuanced mechanism which may not be explainable by a single dimension of prior strength.

Conclusions

The two main contributions of this chapter have been, first, the proposal of the phenomenological control framework as a new lens to look at certain dimensions of the psychedelic experience and of hallucinations, and second, the suggestion that alignment of beliefs at the group level might constitute an important evolutionary pressure and an informative framework to clarify some of the conceptual difficulties of theorizing about psychedelics and hallucinations. Different mechanisms have been suggested for how psychedelics may be influencing phenomenological control, and some considerations were made about the potential for PC theories to help clarify the relationship between different contemporary models of psychedelic action.

These contributions have the potential to bridge between current computational theories of psychedelic action and more abstract interpretations of their subjective effects such as the super-placebos and

meaning-enhancement ones mentioned above. The conceptualization of PC as alignment has the potential to give more quantitative tools to understand psychedelic effects that have been studied from anthropological and philosophical perspectives, while simultaneously helping neuroscientists bridge computational accounts with high-level conceptual interpretations in a way that may inform the development of new computational theories.

Chapter 5
Conclusions and Discussion

The truth is the whole.[378]

[378] Hegel, *Phenomenology,* p.11

In this thesis I have done my best to recount an important portion of the work that I have developed during my PhD, especially the one concerned with research involving psychedelic drugs. While the field of scientific research with psychedelics is a promising avenue for the development of new therapeutic treatments, I believe that it is currently facing some important limitations that need to be addressed. With no unified theory of psychedelic action being able to account for the complexity of their effects, and given our similarly limited understanding of the serotonergic system that is believed to be responsible for many of their effects, it is safe to say that psychedelic research is still in its infancy. And yet, the rate of publication and the varied nature of the research avenues concerned with psychedelics highlight the immense complexity of the interactions between these substances and our brains.

An important goal in developing this work has been to obtain a panoramic perspective of the field, spanning everything from the history of scientific research into these substances, to their effects in the computations carried out by populations of neurons, to the intricacies of their relationship with expectancies and meaning attribution. As stated by the opening quote of this last section, ‘The truth is the whole’. I believe that one of the main pitfalls to be weary of in the current landscape in psychedelic research is that of the difficulty in obtaining a nuanced comprehensive vision of the field.

Researchers carrying out neural recordings in animals may not need to be aware of cutting edge anthropological studies about the effects of these molecules, those focused on human clinical studies might not benefit from being up to date with the latest molecular studies about receptor interactions in animal models, and scientists and authors writing books about psychedelic drugs from therapeutic, spiritual, or philosophical perspectives might not need to become experts in the physico-chemical properties of the different classes of molecules usually

classed as psychedelics. However, a failure to promote crosstalk among different disciplines can lead to catastrophic consequences in some instances.

Psychedelic substances have posed a challenge for scientific inquiry for multiple reasons, including the profound alterations of subjective experience that they can elicit, the impossibility to perform adequately placebo-controlled studies, and their interactions with a serotonergic system that we are also still grappling with at some fundamental conceptual levels. Since the very beginning of research into these substances, concerns have been raised about the way in which ignoring the poorly understood mechanisms through which they may be potentiating meaning-related responses could lead to erroneous conclusions regarding their pharmacological effects.[379]

From Beecher's idea of how they may influence meaning responses, to today's theories of meaning-enhancement and superplacebos, the idea that the effects of psychedelic drugs are heavily modulated by contextual factors such as the beliefs of the subject about these substances has survived since the origin of this field of research. By going back to the origin of psychedelic research, it is possible to observe how, in a strikingly similar way, some other beliefs have also stayed with us since the beginning, sometimes with dubious evidence to support them.

Coming back to the quotes which opened the introduction to this thesis, from the communications between Osmond and Huxley, we can see some example beliefs about psychedelics that have survived from the 1950s: that they "must play [a role] in changing our outlook on the world", that they "can help us to extend our experience far beyond our

[379] Mashour, *From LSD*

present ability", or that they can assist us in achieving a higher level of wisdom, understanding, and compassion.

These are just a few examples out of an entire set of ideas that have surrounded psychedelic substances since early on, but they will serve the purpose of illustration here: they can all be seen influencing contemporary psychedelic research. The idea that psychedelics will change our views on the world was central to the counterculture movement of the 60s, and can still be inferred today in research concerned with neural plasticity, cognitive flexibility, and belief change. The ideas about them being able to help us extend our experience, or to increase our wisdom, understanding and compassion can be seen in contemporary research claiming, for instance, that psychedelics improve bottom-up signaling, change political views towards less authoritarian ones, increase environmental awareness, or increase empathy.

While some of these may indeed be intrinsic properties of psychedelic drugs, it is important to stay vigilant to the fact that these ideas are part of a collective imaginary that is shared by virtually every subject that has ever participated in a psychedelic study[380], and the fact that these substances are suspected to cause effects that are heavily influenced by factors such as the beliefs of the subject taking them. For example, the fact that psychedelics have become extremely popular within neonazi culture, where they are often used as part of initiation rites, calls into question some of the assumptions presented above. Perhaps their effects in potentiating meaning responses might lead to increased connectedness to nature and empathy when given to someone with a certain cultural background, while when given in the

[380] Especially given that the majority of participants have historically always been white, highly educated, middle class with previous interest or experience with psychedelic drugs, and that most studies have taken place in the United States and Europe.

context of a white supremacist retreat they may potentiate entirely different things, such as racial hatred and other violent ideologies.

The fact that psychedelics have such a big presence in our culture, and the fact that it's impossible to find subjects who are naive to these ideas, combined with the fact that their effects seem to predominantly match the expectations of the user, make them a very difficult target for scientific scrutiny. To make things worse, an induction process is usually necessary for ethical reasons, which can often act as a hypnotic suggestion by creating expectations about the effects of a drug. On the one hand, this can homogenize the responses across individuals, and on the other, it can direct such responses towards previously established beliefs about their effects. Furthermore, these suggestive effects can be cyclical, in the sense that not only the beliefs of the experimenters can influence the subjects, but also the experiences of the subjects (and thus the results of the study) can conversely influence the beliefs of the experimenters, thus creating a feedback loop.

The mystical experience literature is a good example of this problem: after the initial results[381] suggesting that individuals could experience mystical experiences under the effects of psychedelics, many studies added to their induction protocols a description of mystical experiences as a possible outcome of the pharmacological intervention. The Mystical Experience Questionnaire (MEQ)[382] has become one of the most popular outcome measures in the field of psychedelic research, meaning that there are myriads of studies in which participants were first briefed about the possibility that they would experience a mystical experience, then they were given substances that have been shown to

[381] Griffiths, *Psilocybin*
[382] Barrett, *Validation*

increase suggestibility, and then they were given a multiple choice questionnaire asking if they had a mystical experience.[383]

In a sense, some psychedelic studies can be seen as the perfect suggestibility machine. Participants are briefed about what they should expect, then given substances that may potentiate their expectancies, and then given questionnaires that may be suggestive in themselves by asking questions specifically about the concepts presented in the induction. If this danger is not perceived by the experimenters designing the studies, they may interpret the results as indicating some inherent property of the psychedelic molecule under study, and thus be tricked themselves by their own suggestive machinery. When taking into consideration the situational 'hype' surrounding the topic, it may also be the case that papers that emerge from such studies are then increasingly absorbed into the popular culture surrounding psychedelics, such that as time goes by, they can easily inform the beliefs about psychedelics that subjects have when joining new studies. In such a complex context, it should be clear why it is the impossibility to properly blind these studies is particularly concerning here: both subjects and experimenters are often perfectly aware of who is in which arm of the study, thus making placebo controls virtually uninformative.

Some of these problematic dimensions of the psychedelic literature may affect animal studies as well, since these are often intimately intertwined with the narratives that dominate in the human research field. For instance, the entropic brain hypothesis, has generated a narrative according to which psychedelics increase entropy in the neural activity of the subjects, which then translates into increased cognitive flexibility and opens an opportunity to re-establish certain problematic beliefs, which then leads to long-term therapeutic outcomes

[383] Siegel, *Psilocybin*

thanks to the newly acquired behavioral and cognitive flexibility, all of which is perhaps mediated by increases in neural plasticity elicited at a molecular level by psychedelics.

This narrative has been incredibly popular, and some of its papers are amongst the most cited in the literature. However, as we have discussed earlier, it suffers from multiple limitations. On the one hand, it emerged mainly from neuroimaging studies, which suffer from the neurovascular coupling artifacts that we already discussed. Also, it assumes a link between entropy at a neuronal level and flexibility at a behavioral and cognitive level, which has not been demonstrated. Sometimes neuroplasticity is added to this narrative, but it's important to remember that the animal literature on the complex, substance-specific, timing- and dose-dependent, long-term neuroplasticity effects, is still, along with its alleged translatability to humans, a source of debate.[384] Some recent studies have also argued that it is actually very hard to identify any depression- or anxiety-related long-term effects after the administration of psychedelics in rodent models.[385] Furthermore, the entropy/relaxed beliefs narrative suffered, at least initially, from serious conceptual limitations: the proposal of a single dimension of criticality or entropy explaining a wide variety of physiological and pathological states of the human brain seems untenable in light of current neuroscientific and psychiatric knowledge.

However, because it has occupied such a dominant role in the scientific and public narratives about psychedelics, and because it is such a simple and accessible theory, researchers carrying out animal experiments may be tempted to conform their findings to such theories, or to doubt them when they don't fit into such narrative, or when they point to the need for more complex accounts of the effects of

[384] Calder, *Effects;* Lima, *Effects;*
[385] Odilia, *A multi-institutional*

psychedelic drugs. This speaks to a more general concern which doesn't only affect psychedelic research, which is that of our tendency to seek simple unifying explanations that sometimes risk falling into a counterproductive reductionism.

In the study reported in Chapter 2, we decided to assess such entropy measures to form our own opinion about the topic based on data acquired in a process over which we had full control. While we remain open to the idea that there may be interesting avenues to pursue regarding local modulations of entropy in specific brain areas, we did not find a significant effect at a global level that could be robustly attributed to LSD.

During the trajectory of my PhD I realized that my confusion regarding the idea of concepts such as priors, beliefs, or meaning in psychedelic research was not only due to my ignorance but also in part due to ambiguities and conceptual contradictions that arise when facing this literature. My aim in this work has been to clarify some of those both towards myself and hopefully for others as well. The theoretical work in Chapter 3 helped me clarify some nuances about the different moving parts involved in hypnotic and related scenarios, which in turn allowed me to develop the conceptual bridges to the psychedelic literature and the computational theories therein that I presented in Chapter 4. I believe that some of those ideas may become relevant in the field as components of more naturalistic theories about psychedelics that are less constrained by the few existing umbrella frameworks that dominate the neuroscience field at large.

I think that in order for the psychedelic field to progress, we will need to dedicate a considerable amount of effort to better understand exactly the extent to which our beliefs about these substances have shaped and continue to shape our research and conclusions. Because there are some indications to believe that these drugs can promote a

sort of projection of our internal beliefs onto reality, I believe it will be crucial to understand our beliefs about them in order to be able to disentangle the effects that may come from a potentiation of such beliefs versus the ones that might be inherent to these substances. In that regard, I want to close by quoting some important passages from Slavoj Žižek's *Sublime Object of Ideology,* which I believe can help set some important directions for the future of psychedelic research:

> From the Marxist point of view, the ideological procedure par excellence is that of *'false' eternalization and/or universalization*: a state which depends on a concrete historical conjunction appears as an eternal, universal feature of the human condition; the interest of a particular class disguises itself as universal human interest... and the aim of the 'criticism of ideology' is to denounce this false universality, to detect behind man in general the bourgeois individual; behind the universal rights of man the form which renders possible capitalist exploitation; behind the 'nuclear family' as a trans-historical constant the historically specified and limited form of kinship relations, and so on.[386]

In a sense, the analysis of our beliefs about psychedelics that I'm proposing here, could be thought of as a sort of Marxist-inspired critique of the ideology of psychedelics. Not only in the sense of uncovering the ways in which capitalist interests may influence psychedelic research,[387] but also simply in the sense of pointing out possible points where we are falling into the trap of 'over-universalization'. Do psychedelics really

[386] Žižek, *Sublime, pp 50*

[387] As mentioned before, portraying certain things as being inherent properties of these molecules does carry a certain economic relevance: if the therapeutic benefits are to be attributed simply to the chemical properties of a given molecule, they can be swiftly patented and commercialized. The idea that some fundamental therapeutic effects of these molecules have to do with our beliefs about them or with the sociocultural context where they are consumed, on the other hand, is much harder to profit from.

cause mystical experiences? Is the mystical experience even a valid construct to start with? Do psychedelics really alter metaphysical beliefs and promote less authoritarianism? Do they really universally increase empathy? Do they really increase a sense of connectedness with nature? Or are some of these ideas perhaps historically situated, and apparently confirmed by scientific experiments mainly because of the way in which psychedelics influence phenomenological control? These are real questions that will need to be addressed for the psychedelic field to move forward. Going back to Žižek:

> In the Lacanian perspective, we should change the terms and designate as the most 'cunning' ideological procedure the very opposite of externalization: an over-rapid historicization. Let us take one of the common places of the Marxist-feminist criticism of psychoanalysis, the idea that its insistence on the crucial role of the Oedipus complex and the nuclear family triangle transforms a historically conditioned form of patriarchal family into a feature of the universal human condition: is not this effort to historicize the family triangle precisely an attempt to elude the 'hard kernel' which announces itself through the 'patriarchal family' - the Real of the Law, the rock of castration? In other words, if over-rapid universalization produces a quasi-universal Image whose function is to make us blind to its historical, socio-symbolic determination, over-rapid historicization makes us blind to the real kernel which returns as the same through diverse historicizations/symbolizations.[388]
>
> It is the same with a phenomenon that designates most accurately the 'perverse' obverse of twentieth-century civilization: concentration camps. All the different attempts to attach this phenomenon to a concrete image ('Holocaust', 'Gulag' ...), to reduce it to a product of a concrete social order (Fascism, Stalinism ...) - what are they if not so many attempts to elude the fact that we are dealing

[388] Žižek, *Sublime, pp 51*

> here with the 'real' of our civilization which returns as the same traumatic kernel in all social systems? (We should not forget that concentration camps were an invention of 'liberal' England, dating from the Boer War; that they were also used in the US to isolate the Japanese population, and so on)

This Lacanian perspective, on the other hand, reminds us to not ‘throw the baby with the bathwater’. There are certainly some properties of these drugs that would remain unchanged even if our cultural beliefs about them were completely different. What are those effects? Is the modulation of phenomenological control a universal effect when psychedelics are consumed by humans? Of course most physiological responses such as effects on the cardiovascular system fall in this category, but are there other psychological effects that do so, too? And most importantly, to which extent are therapeutic effects in this category? Given the tight relationship that has been established in the past between the subjective effects of psychedelics and their image in public and political discourse,[389] it is entirely possible that some or all of the therapeutic effects might also be tightly connected to similar factors. This is reason for concern, since fluctuations in public opinion and in regulations are hard to control and could potentially lead to a termination of therapeutic effects. Thus, I believe it’s of utmost importance to stop thinking of extrapharmacological effects as technical problems to account for in our scientific investigations, and to prioritize studying exactly how psychedelic drugs interact with our ability to generate experiences for ourselves.

[389] Bunce, *Social*

Bibliography

1. Acunzo, David J., and Devin B. Terhune. “A Critical Review of Standardized Measures of Hypnotic Suggestibility, International Journal of Clinical and Experimental Hypnosis”, *International Journal of Clinical and Experimental Hypnosis* 69:1 (2021): 50-71. https://doi.org/10.1080/00207144.2021.1833209

2. Amidfar, Meysam, Yong-Ku Kim, Lejla Colic, et al. 2017. “Increased Levels of 5HT2A Receptor mRNA Expression in Peripheral Blood Mononuclear Cells of Patients with Major Depression: Correlations with Severity and Duration of Illness.” *Nordic Journal of Psychiatry* 71 (4): 282–88. https://doi.org/10.1080/08039488.2016.1276624.

3. Andrews, Paul W., Catherine Bosyj, Luke Brenton, Laura Green, Paul J. Gasser, Christopher A. Lowry, and Virginia M. Pickel. “All the Brain’s a Stage for Serotonin: The Forgotten Story of Serotonin Diffusion across Cell Membranes.” *Proceedings of the Royal Society B: Biological Sciences* 289, no. 1986 (November 9, 2022): 20221565. https://doi.org/10.1098/rspb.2022.1565.

4. Angluin, Dana, and Philip Laird. 1988. “Learning from Noisy Examples.” *Machine Learning* 2 (4): 343–70. https://doi.org/10.1007/BF00116829.

5. Arlandis Castro, Jaime. 2024. “Hypnosis, Aesthetics, and Sociality: On How Images Can Create Experiences.” *Open Philosophy* 7 (1): 20240052. https://doi.org/10.1515/opphil-2024-0052.

6. Atlas, Lauren Y. “A Social Affective Neuroscience Lens on Placebo Analgesia.” *Trends in Cognitive Sciences* 25, no. 11 (November 2021): 992–1005. https://doi.org/10.1016/j.tics.2021.07.016.

7. Avitan, Lilach, and Carsen Stringer. “Not so Spontaneous: Multi-Dimensional Representations of Behaviors and Context in Sensory Areas.” *Neuron* 110, no. 19 (October 2022): 3064–75. https://doi.org/10.1016/j.neuron.2022.06.019.

8. Balibar, Etienne, and Nicol A. Barria-Asenjo. “Sobre la política freudiana: la masa como formación inconsciente transindividual.” *Revista de Humanidades de Valparaíso*, no. 23 (December 26, 2023): 209–23. https://doi.org/10.22370/rhv2023iss23pp209-223

9. Barrett, F. S., Johnson, M. W., & Griffiths, R. R. (2015). *Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin.* Journal of Psychopharmacology, 29(11), 1182-1190. DOI:10.1177/0269881115609019.

10. Barth, Jürgen, Mathias Egli, Stefanie Maier, Patrick Meyenberger, and Claudia M. Witt. 2019. “Effectiveness of Hypnosis with the Dave

Elman Technique in Third Molar Extraction: Study Protocol for a Randomized Controlled Trial (HypMol).” *European Journal of Integrative Medicine* 26 (February): 18–23. https://doi.org/10.1016/j.eujim.2019.01.002.

11. Belcher AM, Ferré S, Martinez PE, Colloca L. Role of placebo effects in pain and neuropsychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Dec 20;87(Pt B):298-306. doi: 10.1016/j.pnpbp.2017.06.003.

12. Bellamy Foster, John. 2025. “The Trump Doctrine and the New MAGA Imperialism” *Monthly Review*, June 1, 27–47. https://doi.org/10.14452/MR-077-02-2025-06_2

13. Belle, D., & Doucet, J. (2003). Poverty, Inequality, and Discrimination as Sources of Depression Among U.S. Women. *Psychology of Women Quarterly*, *27*(2), 101-113. https://doi.org/10.1111/1471-6402.00090

14. Berman, Robert M, Angela Cappiello, Amit Anand, et al. 2000. “Antidepressant Effects of Ketamine in Depressed Patients.” *Biological Psychiatry* 47 (4): 351–54. https://doi.org/10.1016/S0006-3223(99)00230-9.

15. Bhatt, Umang, Sanyam Kapoor, Mihir Upadhyay, et al. 2025. “When Should We Orchestrate Multiple Agents?” arXiv:2503.13577. Preprint, arXiv, March 17. https://doi.org/10.48550/arXiv.2503.13577.

16. Bisbee, Cynthia Carson. “Psychedelic Prophets,” n.d.

17. Bisbee, Cynthia Carson. “Psychedelic Prophets,” n.d.

18. Bott, Antonia, Larissa Brockmann, Ivo Denneberg, et al. 2024. “Spontaneous Trait Inferences From Behavior: A Systematic Meta-Analysis.” *Personality and Social Psychology Bulletin* 50 (1): 78–102. https://doi.org/10.1177/01461672221100336.

19. Bottici, Chiara. 2021. *Anarchafeminism: An Introduction and Guide*. London and New York: Bloomsbury Academic. ISBN 9781350095878.

20. Bottici, Chiara. *Imaginal Politics: Images beyond Imagination and the Imaginary*. *New Directions in Critical Theory. Columbia University Press* (2014).

21. Boureau, Y.-L., and Dayan, P. (2011). Opponency revisited: competition and cooperation between dopamine and serotonin. Neuropsychopharmacology 36, 74–97. https://doi.org/10.1038/npp.2010.151.

22. Bowden K, Brown BG, Batty JE. 5-Hydroxytryptamine: its occurrence in cowhage. Nature 1954;174:925e6.

23. Brazil, Rachel. 2020. “Fighting Flat-Earth Theory.” *Physics World* 33 (7): 35–39. https://doi.org/10.1088/2058-7058/33/7/34.

24. Bredenberg, Colin, Fabrice Normandin, Blake Richards, and Guillaume Lajoie. “The Oneirogen Hypothesis: Modeling the Hallucinatory Effects of Classical Psychedelics in Terms of Replay-Dependent Plasticity Mechanisms,” September 30, 2024. https://doi.org/10.1101/2024.09.27.615483.

25. Brette, Romain. 2015. “Philosophy of the Spike: Rate-Based vs. Spike-Based Theories of the Brain.” *Frontiers in Systems Neuroscience* 9 (November). https://doi.org/10.3389/fnsys.2015.00151.

26. Breuer, Josef, and Sigmund Freud, *Studies on hysteria*, *Basic Books* (1957)

27. Browning, Michael, Philip J. Cowen, and Trevor Sharp, eds. 2024. *Emerging Neurobiology of Antidepressant Treatments*. Vol. 66. Current Topics in Behavioral Neurosciences. Springer International Publishing. https://doi.org/10.1007/978-3-031-66356-7

28. Bschor T, Nagel L, Unger J, Schwarzer G, Baethge C. Differential Outcomes of Placebo Treatment Across 9 Psychiatric Disorders: A Systematic Review and Meta-Analysis. *JAMA Psychiatry.* 2024;81(8):757–768. doi:10.1001/jamapsychiatry.2024.0994

29. Bunce, Richard. 1979. “Social and Political Sources of Drug Effects: The Case of Bad Trips on Psychedelics.” *Journal of Drug Issues* 9 (2): 213–33. https://doi.org/10.1177/002204267900900207.

30. Calder, A.E., Hase, A. & Hasler, G. Effects of psychoplastogens on blood levels of brain-derived neurotrophic factor (BDNF) in humans: a systematic review and meta-analysis. *Mol Psychiatry* 30, 763–776 (2025). https://doi.org/10.1038/s41380-024-02830-z

31. Canal, Clinton E., Tania Cordova-Sintjago, Yue Liu, Myong S. Kim, Drake Morgan, and Raymond G. Booth. “Molecular Pharmacology and Ligand Docking Studies Reveal a Single Amino Acid Difference between Mouse and Human Serotonin 5-HT2A Receptors That Impacts Behavioral Translation of Novel 4-Phenyl-2-Dimethylaminotetralin Ligands.” *The Journal of Pharmacology and Experimental Therapeutics* 347, no. 3 (December 2013): 705–16. https://doi.org/10.1124/jpet.113.208637.

32. Candy, Bridget, Louise Jones, Rachael Williams, Adrian Tookman, and Michael King. 2008. “Psychostimulants for Depression.” *Cochrane Database of Systematic Reviews*, ahead of print, April 23. https://doi.org/10.1002/14651858.CD006722.pub2.

33. Carandini, Matteo, Jonathan B. Demb, Valerio Mante, et al. 2005. “Do We Know What the Early Visual System Does?” *The Journal of*

Neuroscience 25 (46): 10577–97. https://doi.org/10.1523/JNEUROSCI.3726-05.2005.

34. Carhart-Harris, R.L., and K.J. Friston. “REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics.” *Pharmacological Reviews* 71, no. 3 (July 2019): 316–44. https://doi.org/10.1124/pr.118.017160.

35. Carhart-Harris, R. L., M. Kaelen, M. G. Whalley, M. Bolstridge, A. Feilding, and D. J. Nutt. “LSD Enhances Suggestibility in Healthy Volunteers.” *Psychopharmacology* 232, no. 4 (February 2015): 785–94. https://doi.org/10.1007/s00213-014-3714-z

36. Carhart-Harris, Robin L., Robert Leech, Peter J. Hellyer, Murray Shanahan, Amanda Feilding, Enzo Tagliazucchi, Dante R. Chialvo, and David Nutt. “The Entropic Brain: A Theory of Conscious States Informed by Neuroimaging Research with Psychedelic Drugs.” *Frontiers in Human Neuroscience* 8 (2014). https://doi.org/10.3389/fnhum.2014.00020.

37. Carhart-Harris RL, Erritzoe D, Williams T, et al. Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. Proc Natl Acad Sci USA. 2012;109:2138-2143.

38. Carhart-Harris RL, Murphy K, Leech R, et al. The effects of acutely administered 3,4-methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level-dependent resting state functional connectivity. Biol Psychiatry. 2015;78:554-562.

39. Carod-Artal, F. J. 2015. “Hallucinogenic Drugs in Pre-Columbian Mesoamerican Cultures.” *Neurología (English Edition)* 30 (1): 42–49. https://doi.org/10.1016/j.nrleng.2011.07.010.

40. Cavin, Jean‐Baptiste, Preedajit Wongkrasant, Joel B. Glover, Onesmo B. Balemba, Wallace K. MacNaughton, and Keith A. Sharkey. 2023. “Intestinal Distension Orchestrates Neuronal Activity in the Enteric Nervous System of Adult Mice.” *The Journal of Physiology* 601 (7): 1183–206. https://doi.org/10.1113/JP284171.

41. Charlton, Julie A., Wiktor F. Młynarski, Yoon H. Bai, Ann M. Hermundstad, and Robbe L. T. Goris. 2022. “Perceptual Decisions Exhibit Hallmarks of Dynamic Bayesian Inference.” Preprint, May 24. https://doi.org/10.1101/2022.05.23.493109.

42. Chen, Pin-Hao A., Jin Hyun Cheong, Eshin Jolly, Hirsh Elhence, Tor D. Wager, and Luke J. Chang. “Socially Transmitted Placebo Effects.” *Nature Human Behaviour* 3, no. 12 (October 21, 2019): 1295–1305. https://doi.org/10.1038/s41562-019-0749-5.

43. Chen, Yijing, Jinying Xu, and Yu Chen. “Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in

Neurological Disorders." *Nutrients* 13, no. 6 (June 19, 2021): 2099. https://doi.org/10.3390/nu13062099.

44. Chen PA, Cheong JH, Jolly E, Elhence H, Wager TD, Chang LJ. Socially transmitted placebo effects. Nat Hum Behav. 2019 Dec;3(12):1295-1305. doi: 10.1038/s41562-019-0749-5.

45. Cichon J,Wasilczuk AZ, Looger LL, Contreras D, Kelz MB, Proekt A. 2023. Ketamine triggers a switch in excitatory neuronal activity across neocortex. Nat. Neurosci. 26(1):39–52

46. Clarke, H. F., J. W. Dalley, H. S. Crofts, T. W. Robbins, and A. C. Roberts. "Cognitive Inflexibility After Prefrontal Serotonin Depletion." *Science* 304, no. 5672 (May 7, 2004): 878–80. https://doi.org/10.1126/science.1094987.

47. Cooper-Kazaz, Rena, Jeffrey T. Apter, Revital Cohen, et al. 2007. "Combined Treatment With Sertraline and Liothyronine in Major Depression: A Randomized, Double-Blind, Placebo-Controlled Trial." *Archives of General Psychiatry* 64 (6): 679. https://doi.org/10.1001/archpsyc.64.6.679.

48. Corlett, Philip R., Guillermo Horga, Paul C. Fletcher, Ben Alderson-Day, Katharina Schmack, and Albert R. Powers. 2019. "Hallucinations and Strong Priors." *Trends in Cognitive Sciences* 23 (2): 114–27. https://doi.org/10.1016/j.tics.2018.12.001.

49. Coughlin, B., Muñoz, W., Kfir, Y. *et al.* Modified Neuropixels probes for recording human neurophysiology in the operating room. *Nat Protoc* 18, 2927–2953 (2023). https://doi.org/10.1038/s41596-023-00871-2

50. Cummins, Benjamin R., Gerald B. Billac, David E. Nichols, and Charles D. Nichols. "5-HT2A Receptors: Pharmacology and Functional Selectivity." *Pharmacological Reviews* 77, no. 4 (July 2025): 100059. https://doi.org/10.1016/j.pharmr.2025.100059.

51. D. Elman, Hypnotherapy, Westwood Publishing Co., U.S. (1964), pp. 60–65.

52. D. W. Wooley, and E. Shaw. "A BIOCHEMICAL AND PHARMACOLOGICAL SUGGESTION ABOUT CERTAIN MENTAL DISORDERS" *Proceedings of the National Academy of Science* (1954)

53. Daunizeau, Jean, Hanneke E. M. Den Ouden, Matthias Pessiglione, Stefan J. Kiebel, Klaas E. Stephan, and Karl J. Friston. 2010. "Observing the Observer (I): Meta-Bayesian Models of Learning and Decision-Making." *PLoS ONE* 5 (12): e15554. https://doi.org/10.1371/journal.pone.0015554.

54. Davies, P. et al. (1982) An effective paradigm for conditioning visual perception in human subjects. Perception 11, 663–669

55. Dearnley, Bradley, Martynas Dervinis, Melissa Shaw, and Michael Okun. 2021. “Stretching and Squeezing of Neuronal Log Firing Rate Distribution by Psychedelic and Intrinsic Brain State Transitions.” Preprint, August 23. https://doi.org/10.1101/2021.08.22.457198.

56. Dearnley, Bradley, Melissa Jones, Martynas Dervinis, and Michael Okun. 2023. “Brain State Transitions Primarily Impact the Spontaneous Rate of Slow-Firing Neurons.” *Cell Reports* 42 (10): 113185. https://doi.org/10.1016/j.celrep.2023.113185.

57. Del Colle, Andrew, Narek Israelyan, and Kara Gross Margolis. “Novel Aspects of Enteric Serotonergic Signaling in Health and Brain-Gut Disease.” *American Journal of Physiology-Gastrointestinal and Liver Physiology* 318, no. 1 (January 1, 2020): G130–43. https://doi.org/10.1152/ajpgi.00173.2019.

58. de Marchi, John, 1947. “The True Story of Fatima: A complete account of the Fatima Apparitions” The Fatima Center.

59. Devenot, N., Conner, T. and Doyle, R. (2022), Dark Side of the Shroom: Erasing Indigenous and Counterculture Wisdoms with Psychedelic Capitalism, and the Open Source Alternative. Anthropol Conscious, 33: 476-505. https://doi.org/10.1111/anoc.12154

60. Devenot, Neşe; Hausfeld, Russell; Pace, Brian; and Normand, Brian. 2025. The Psychedelic Syndicate: How Silicon Valley Used Veterans to Hijack the Psychedelic Industry. *Psymposia. https://www.psymposia.com/psychedelic-syndicate-executive-summary-silicon-valley-maps-lykos-mdma-fda-billionaires/*

61. Devenot, Neşe. 2023. “TESCREAL Hallucinations: Psychedelic and AI Hype as Inequality Engines.” *Journal of Psychedelic Studies* 7 (S1): 22–39. https://doi.org/10.1556/2054.2023.00292.

62. Di Cyan E. The Biochemical Bases of Psychosis, or The Serotonin Hypothesis About Mental Diseases. *Arch Intern Med.* 1963;112(6):997–1000. 10.1001/archinte.1963.03860060209039

63. Dienes, Zoltan, and Peter Lush. “The Role of phenomenological Control in Experience.” *PsyArXiv* (April 25, 2022). https://doi.org/10.31234/osf.io/ndpbu.

64. Dienes, Zoltan, Pete Lush, Bence Palfi, Warrick Roseboom, Ryan Scott, Ben Parris, Anil Seth, and Max Lovell. “Phenomenological Control as Cold Control.” *Psychology of Consciousness: Theory, Research, and Practice* 9, no. 2 (June 2022): 101–16. https://doi.org/10.1037/cns0000230

65. Dienes, Zoltan, Pete Lush, Bence Palfi, Warrick Roseboom, Ryan Scott, Ben Parris, Anil Seth, and Max Lovell. “Phenomenological control as Cold Control.” *Psychology of Consciousness: Theory,*

Research, and Practice 9, no. 2 (June 2022): 101–16. https://doi.org/10.1037/cns0000230.

66. Doss, Manoj K, Maxwell B Madden, Andrew Gaddis, and Mary Beth Nebel. “Models of Psychedelic Drug Action: Modulation of Cortical-Subcortical Circuits,” n.d.

67. Drummond E-Wen McCulloch, Anders Stevnhoved Olsen, Brice Ozenne, Dea Siggard Stenbæk, Sophia Armand, Martin Korsbak Madsen, Gitte Moos Knudsen, Patrick MacDonald Fisher. 2023. Navigating the chaos of psychedelic neuroimaging: A multi-metric evaluation of acute psilocybin effects on brain entropy. medRxiv 2023.07.03.23292164; https://doi.org/10.1101/2023.07.03.23292164

68. Du, Yingjie, Yunfeng Li, Xiangting Zhao, Yishan Yao, Bin Wang, Liming Zhang, and Guyan Wang. “Psilocybin Facilitates Fear Extinction in Mice by Promoting Hippocampal Neuroplasticity.” *Chinese Medical Journal* 136, no. 24 (December 20, 2023): 2983–92. https://doi.org/10.1097/CM9.0000000000002647.

69. Dupuis, David, and Samuel Veissière. “Culture, Context, and Ethics in the Therapeutic Use of Hallucinogens: Psychedelics as Active Super-Placebos?” *Transcultural Psychiatry* 59, no. 5 (October 2022): 571–78. https://doi.org/10.1177/13634615221131465

70. Dupuis, David. “Psychedelics as Tools for Belief Transmission. Set, Setting, Suggestibility, and Persuasion in the Ritual Use of Hallucinogens.” *Frontiers in Psychology* 12 (November 23, 2021): 730031. https://doi.org/10.3389/fpsyg.2021.730031.

71. Dyck, Erika. “Flashback: Psychiatric Experimentation with LSD in Historical Perspective.” *The Canadian Journal of Psychiatry* 50, no. 7 (June 2005): 381–88. https://doi.org/10.1177/070674370505000703.

72. Eguíluz, Víctor M., Naoki Masuda, and Juan Fernández-Gracia. 2015. “Bayesian Decision Making in Human Collectives with Binary Choices.” *PLOS ONE* 10 (4): e0121332. https://doi.org/10.1371/journal.pone.0121332.

73. Ellson, D.G. (1941) Hallucinations produced by sensory conditioning. J. Exp. Psychol. 28, 1–20

74. Elsayed, Gamaleldin F., Antonio H. Lara, Matthew T. Kaufman, Mark M. Churchland, and John P. Cunningham. 2016. “Reorganization between Preparatory and Movement Population Responses in Motor Cortex.” *Nature Communications* 7 (1): 13239. https://doi.org/10.1038/ncomms13239.

75. Erickson, Milton H., and Ernest Lawrence Rossi. *Hypnotherapy: An Exploratory Casebook*. *Irvington Publishers* (1979).

76. Erland, Lauren A.E., Christina E. Turi, and Praveen K. Saxena. “Serotonin in Plants.” In *Serotonin*, 23–46. Elsevier, 2019. https://doi.org/10.1016/B978-0-12-800050-2.00002-4.

77. Erspamer V, Asero B. “Identification of enteramine, specific hormone of enterochromaffin cells, as 5-hydroxtryptamine.” *Nature* (1952) 169:800–801

78. Esdaile, James. 1852. “Natural and Mesmeric Clairvoyance, with the Practical Application of Mesmerism in Surgery and Medicine”

79. Evans, Jules, Marc Aixalà, Brian T. Anderson, et al. 2025. “On Minimizing Risk and Harm in the Use of Psychedelics.” *Psychiatric Research and Clinical Practice* 7 (1): 4–8. https://doi.org/10.1176/appi.prcp.20240128.

80. Evarts, Edward V., William Landau, Walter Freygang, and Wade H. Marshall. 1955. “Some Effects of Lysergic Acid Diethylamide and Bufotenine on Electrical Activity in the Cat’s Visual System.” *American Journal of Physiology-Legacy Content* 182 (3): 594–98. https://doi.org/10.1152/ajplegacy.1955.182.3.594.

81. Evers, E A T. “Serotonin and Cognitive Flexibility: Neuroimaging Studies into the Effect of Acute Tryptophan Depletion in Healthy Volunteers,” n.d.

82. Fage-Butler, Antoinette, Loni Ledderer, and Kristian H. Nielsen, eds. 2025. *Science Communication and Trust*. Springer Nature Singapore. https://doi.org/10.1007/978-981-96-1289-5.

83. Farnes N, Juel BE, Nilsen AS, Romundstad LG, Storm JF (2020) Increased signal diversity/complexity of spontaneous EEG, but not evoked EEG responses, in ketamine-induced psychedelic state in humans. PLoS ONE 15(11): e0242056. https://doi.org/10.1371/journal.pone.0242056

84. Feldberg, W., and C. C. Toh. “Distribution of 5‐hydroxytryptamine (Serotonin, Enteramine) in the Wall of the Digestive Tract.” *The Journal of Physiology* 119, no. 2–3 (February 27, 1953): 352–62. https://doi.org/10.1113/jphysiol.1953.sp004850.

85. Fernandes, Ana B., Joaquim Alves Da Silva, Joana Almeida, et al. 2020. “Postingestive Modulation of Food Seeking Depends on Vagus-Mediated Dopamine Neuron Activity.” *Neuron* 106 (5): 778-788.e6. https://doi.org/10.1016/j.neuron.2020.03.009.

86. Fernandes, Ana B. et al. (2020). Postingestive Modulation of Food Seeking Depends on Vagus-Mediated Dopamine Neuron Activity Neuron, Volume 106, Issue 5, 778 - 788.e6. 10.1016/j.neuron.2020.03.009

87. Fernbach, Philip M., and Jonathan E. Bogard. 2024. “Conspiracy Theory as Individual and Group Behavior: Observations from the Flat

Earth International Conference." *Topics in Cognitive Science* 16 (2): 187–205. https://doi.org/10.1111/tops.12662.

88. Figdor, Carrie. "The Fallacy of the Homuncular Fallacy." *Belgrade Philosophical Annual*, no. 31 (2018): 41–56. https://doi.org/10.5937/BPA1831041F.

89. Forli, Angelo, Wudi Fan, Kevin K. Qi, and Michael M. Yartsev. 2025. "Replay and Representation Dynamics in the Hippocampus of Freely Flying Bats." *Nature*, ahead of print, July 9. https://doi.org/10.1038/s41586-025-09341-z.

90. Fornaro, Michele, Annalisa Anastasia, Stefano Novello, Andrea Fusco, Riccardo Pariano, Domenico De Berardis, Marco Solmi, et al. "The Emergence of Loss of Efficacy during Antidepressant Drug Treatment for Major Depressive Disorder: An Integrative Review of Evidence, Mechanisms, and Clinical Implications." *Pharmacological Research* 139 (January 2019): 494–502. https://doi.org/10.1016/j.phrs.2018.10.025.

91. Freeman, Luke P., Rochelle E. Cox, and Amanda J. Barnier. "Transmitting Delusional Beliefs in a Hypnotic Model of Folie à Deux." *Consciousness and Cognition* 22, no. 4 (December 2013): 1285–97. https://doi.org/10.1016/j.concog.2013.07.011.

92. Freud, Sigmund. *The interpretation of dreams. Basic Books* (2010)

93. Freund, Yoav, and Robert E Schapire. 1997. "A Decision-Theoretic Generalization of On-Line Learning and an Application to Boosting." *Journal of Computer and System Sciences* 55 (1): 119–39. https://doi.org/10.1006/jcss.1997.1504.

94. Furukawa TA, Cipriani A, Leucht S, Atkinson LZ, Ogawa Y, Takeshima N, Hayasaka Y, Chaimani A, Salanti G. Is placebo response in antidepressant trials rising or not? A reanalysis of datasets to conclude this long-lasting controversy. Evid Based Ment Health. 2018 Feb;21(1):1-3. doi: 10.1136/eb-2017-102827. Epub 2018 Jan 12. PMID: 29330216; PMCID: PMC10270408.

95. Gandhi, Balaganesh, and David A. Oakley. 2005. "Does 'Hypnosis' by Any Other Name Smell as Sweet? The Efficacy of 'Hypnotic' Inductions Depends on the Label 'Hypnosis.'" *Consciousness and Cognition* 14 (2): 304–15. https://doi.org/10.1016/j.concog.2004.12.004.

96. Gandhi B, Oakley DA. "Does 'hypnosis' by any other name smell as sweet? The efficacy of 'hypnotic' inductions depends on the label 'hypnosis'." *Conscious Cogn* (2005).

97. Gattuso, James J, Daniel Perkins, Simon Ruffell, Andrew J Lawrence, Daniel Hoyer, Laura H Jacobson, Christopher Timmermann,

et al. “Default Mode Network Modulation by Psychedelics: A Systematic Review.” *International Journal of Neuropsychopharmacology* 26, no. 3 (March 22, 2023): 155–88. https://doi.org/10.1093/ijnp/pyac074.

98. Gershon, Michael D. 2013. “5-Hydroxytryptamine (Serotonin) in the Gastrointestinal Tract.” *Current Opinion in Endocrinology, Diabetes & Obesity* 20 (1): 14–21. https://doi.org/10.1097/MED.0b013e32835bc703.

99. Geyer, Mark A. “A Brief Historical Overview of Psychedelic Research.” *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 9, no. 5 (May 2024): 464–71. https://doi.org/10.1016/j.bpsc.2023.11.003.

100. Griffiths, R. R., Richards, W. A., McCann, U., & Jesse, R. (2006). *Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance.* Psychopharmacology, 187(3), 268-283. doi:10.1007/s00213-006-0457-5

101. Grof, Stanislav. 1975. “Realms of the Human Unconscious: Observations from LSD Research”. A Condor Book Souvenir Press (E & A) LTD.

102. Gross, Erica R., Michael D. Gershon, Kara G. Margolis, Zoya V. Gertsberg, and Robert A. Cowles. 2012. “Neuronal Serotonin Regulates Growth of the Intestinal Mucosa in Mice.” *Gastroenterology* 143 (2): 408-417.e2. https://doi.org/10.1053/j.gastro.2012.05.007.

103. Halberstadt, Adam L., Franz X. Vollenweider, and David E. Nichols, eds. *Behavioral Neurobiology of Psychedelic Drugs*. Vol. 36. Current Topics in Behavioral Neurosciences. Berlin, Heidelberg: Springer Berlin Heidelberg, 2018. https://doi.org/10.1007/978-3-662-55880-5.

104. Hargrave, Sara L., and Kimberly P. Kinzig. 2012. “Repeated Gastric Distension Alters Food Intake and Neuroendocrine Profiles in Rats.” *Physiology & Behavior* 105 (4): 975–81. https://doi.org/10.1016/j.physbeh.2011.11.006.

105. Harman, Graham. *Guerrilla Metaphysics: Phenomenology and the Carpentry of Things*, *Open Court* (2005).

106. Harman, Graham. *Object Oriented Ontology: A New Theory Of Everything*, *A Pelican Book* (2018).

107. Harman, Graham. *The Graham Harman Reader*, ch.20, *Nordic Journal of Aesthetics*, No. 47 (2014), pp. 94–110.

108. Hartogsohn, Ido. “Set and Setting, Psychedelics and the Placebo Response: An Extra-Pharmacological Perspective on Psychopharmacology.” *Journal of Psychopharmacology* 30, no. 12 (December 2016): 1259–67. https://doi.org/10.1177/0269881116677852

109. Hartogsohn, Ido. “The Meaning-Enhancing Properties of Psychedelics and Their Mediator Role in Psychedelic Therapy,

Spirituality, and Creativity." *Frontiers in Neuroscience* 12 (March 6, 2018): 129. https://doi.org/10.3389/fnins.2018.00129

110. Hatzipantelis, Cassandra J, and David E Olson. "The Effects of Psychedelics on Neuronal Physiology," n.d.

111. Hayes, Matthew R., Fiona M. Chory, Claire A. Gallagher, and Mihai Covasa. 2006. "Serotonin Type-3 Receptors Mediate Cholecystokinin-Induced Satiation through Gastric Distension." *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 291 (1): R115–23. https://doi.org/10.1152/ajpregu.00002.2006.

112. Hegel, G. W. F. *Phenomenology of Spirit.* Translated by A. V. Miller, with analysis of the text and foreword by J. N. Findlay. Oxford: Clarendon Press, 1977

113. Hieronymus F, López E, Werin Sjögren H, Lundberg J. Control Group Outcomes in Trials of Psilocybin, SSRIs, or Esketamine for Depression: A Meta-Analysis. *JAMA Netw Open.* 2025;8(7):e2524119. doi:10.1001/jamanetworkopen.2025.24119

114. Hoffman, Albert. 2022. *LSD My Problem Child (4th Edition): Reflections on Sacred Drugs, Mysticism and Science*. Multidisciplinary Association for Psychedelic Studies.

115. Holper, Lisa. 2020. "Raising Placebo Efficacy in Antidepressant Trials Across Decades Explained by Small-Study Effects: A Meta-Reanalysis." *Frontiers in Psychiatry* Volume 11-2020. https://doi.org/10.3389/fpsyt.2020.00633.

116. Holper, Lisa. "Raising Placebo Efficacy in Antidepressant Trials Across Decades Explained by Small-Study Effects: A Meta-Reanalysis." *Frontiers in Psychiatry* 11 (July 28, 2020): 633. https://doi.org/10.3389/fpsyt.2020.00633

117. Horrocks, Max, Jennifer L Mohn, and Santiago Jaramillo. "The Serotonergic Psychedelic DOI Impairs Deviance Detection in the Auditory Cortex," September 12, 2024. https://doi.org/10.1101/2024.09.06.611733.

118. Horsfall, Sara. 2000. "The Experience of Marian Apparitions and the Mary Cult." *The Social Science Journal* 37 (3): 375–84. https://doi.org/10.1016/S0362-3319(00)00075-6.

119. Hsu TW, Tsai CK, Kao YC, Thompson T, Carvalho AF, Yang FC, Tseng PT, Hsu CW, Yu CL, Tu YK, Liang CS. Comparative oral monotherapy of psilocybin, lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine, ayahuasca, and escitalopram for depressive symptoms: systematic review and Bayesian network meta-analysis. BMJ. 2024 Aug 21;386:e078607. doi: 10.1136/bmj-2023-078607. PMID: 39168500; PMCID: PMC11337322.

120. https://dictionary.apa.org/hypnosis

121. Huneke, N.T.M., Amin, J., Baldwin, D.S. *et al.* Placebo effects in randomized trials of pharmacological and neurostimulation interventions for mental disorders: An umbrella review. *Mol Psychiatry* 29, 3915–3925 (2024). https://doi.org/10.1038/s41380-024-02638-x

122. Hwang, Young Keun, and Jae Sang Oh. “Interaction of the Vagus Nerve and Serotonin in the Gut–Brain Axis.” *International Journal of Molecular Sciences* 26, no. 3 (January 29, 2025): 1160. https://doi.org/10.3390/ijms26031160.

123. Inserra A, De Gregorio D, Rezai T, Lopez-Canul MG, Comai S, Gobbi G. Lysergic acid diethylamide differentially modulates the reticular thalamus, mediodorsal thalamus, and infralimbic prefrontal cortex: An in vivo electrophysiology study in male mice. J Psychopharmacol. Published online March 1, 2021; 35(4):469–482.doi:10.1177/0269881121991569

124. International Brain Laboratory (2021). Standardized and reproducible measurement of decision-making in mice *eLife* 10:e63711. https://doi.org/10.7554/eLife.63711

125. International Brain Laboratory (2022). Spike sorting pipeline for the International Brain Laboratory. figshare. Online resource. https://doi.org/10.6084/m9.figshare.19705522.v4

126. International Brain Laboratory (2022). Video hardware and software for the International Brain Laboratory. figshare. Online resource. https://doi.org/10.6084/m9.figshare.19694452.v1

127. International Brain Laboratory (2025) Reproducibility of in vivo electrophysiological measurements in mice eLife 13:RP100840 https://doi.org/10.7554/eLife.100840.3

128. Ioannidis JPA (2022) Why Most Published Research Findings Are False. PLOS Medicine 19(8): e1004085. https://doi.org/10.1371/journal.pmed.0020124

129. Ionescu, Tudor M., Mario Amend, Tadashi Watabe, et al. 2023. “Neurovascular Uncoupling: Multimodal Imaging Delineates the Acute Effects of 3,4-Methylenedioxymethamphetamine.” *Journal of Nuclear Medicine* 64 (3): 466–71. https://doi.org/10.2967/jnumed.122.264391.

130. Janice Hopkins Tanne. “Humphry Osmond: Psychiatrist who investigated LSD, “turned on” Aldous Huxley, and coined the word “psychedelic” ” *Obituaries.* (March 2004)

131. Javadzadeh, Mitra, and Sonja B. Hofer. “Dynamic Causal Communication Channels between Neocortical Areas.” *Neuron* 110, no. 15 (August 2022): 2470-2483.e7. https://doi.org/10.1016/j.neuron.2022.05.011.

132. Jensen JS, Bielefeldt AØ, Hróbjartsson A. Active placebo control groups of pharmacological interventions were rarely used but merited serious consideration: a methodological overview. J Clin Epidemiol. 2017 Jul;87:35-46. doi: 10.1016/j.jclinepi.2017.03.001. Epub 2017 Mar 22. PMID: 28342907

133. Hidalgo Jiménez, Javier ; Kristjan Kaup, Jaan Aru. 2025. "Electrophysiological Mechanisms of Psychedelic Drugs: A Systematic Review". bioRxiv 2025.07.05.663289; doi: https://doi.org/10.1101/2025.07.05.663289

134. Johnson MW, Yaden DB. There's no good evidence that psychedelics can change your politics or religion. 2020.

135. Jones, Melissa. "Structure of Modulation of Neuronal Firing Rates across Different Brain State Transitions.," n.d.

136. Juczewski, Konrad, Jonathan A. Koussa, Andrew J. Kesner, Jeong O. Lee, and David M. Lovinger. 2020a. "Stress and Behavioral Correlates in the Head-Fixed Method: Stress Measurements, Habituation Dynamics, Locomotion, and Motor-Skill Learning in Mice." *Scientific Reports* 10 (1): 12245. https://doi.org/10.1038/s41598-020-69132-6.

137. Kadriu, Bashkim, Maximillian Greenwald, Ioline D Henter, Jessica R Gilbert, Christoph Kraus, Lawrence T Park, and Carlos A Zarate. "Ketamine and Serotonergic Psychedelics: Common Mechanisms Underlying the Effects of Rapid-Acting Antidepressants." *International Journal of Neuropsychopharmacology* 24, no. 1 (January 20, 2021): 8–21. https://doi.org/10.1093/ijnp/pyaa087.

138. Kaptchuk, Ted J. 1998. "Powerful Placebo: The Dark Side of the Randomised Controlled Trial." *The Lancet* 351 (9117): 1722–25. https://doi.org/10.1016/S0140-6736(97)10111-8.

139. Kato, Kosuke, Jennifer M. Kleinhenz, Yoon-Joo Shin, Cristian Coarfa, Ali J. Zarrabi, and Louise Hecker. 2025. "Psilocybin Treatment Extends Cellular Lifespan and Improves Survival of Aged Mice." *Npj Aging* 11 (1): 55. https://doi.org/10.1038/s41514-025-00244-x.

140. Kato, Shiro, Hideo Kumamoto, Masahiko Hirano, Hideo Akiyama, and Noboru Kaneko. n.d. *Expression of 5-HT2A and 5-HT1B Receptor mRNA in Blood Vessels*.

141. Keller, Doris L., and Wayne W. Umbreit. 1956. "'Permanent' Alteration of Behavior in Mice by Chemical and Psychological Means." *Science* 124 (3225): 723–24. https://doi.org/10.1126/science.124.3225.723.

142. Kelly SF, Fisher S, Kelly RJ. Effects of cannabis intoxication on primary suggestibility. Psychopharmacology (Berl). 1978 Mar 1;56(2):217-9. doi: 10.1007/BF00431853. PMID: 417375.

143. Kelmendi, Benjamin, Alfred P. Kaye, Christopher Pittenger, and Alex C. Kwan. “Psychedelics.” *Current Biology* 32, no. 2 (January 2022): R63–67. https://doi.org/10.1016/j.cub.2021.12.009.

144. Kenneth D. Harris. 2020. Nonsense correlations in neuroscience. bioRxiv 2020.11.29.402719; https://doi.org/10.1101/2020.11.29.402719

145. Kirsch, Irving. “The Emperor’s New Drugs: Medication and Placebo in the Treatment of Depression.” In *Placebo*, edited by Fabrizio Benedetti, Paul Enck, Elisa Frisaldi, and Manfred Schedlowski, 225:291–303. Handbook of Experimental Pharmacology. Berlin, Heidelberg: Springer Berlin Heidelberg, 2014. https://doi.org/10.1007/978-3-662-44519-8_16.

146. Köhler, Ole, Michael E. Benros, Merete Nordentoft, et al. 2014. “Effect of Anti-Inflammatory Treatment on Depression, Depressive Symptoms, and Adverse Effects: A Systematic Review and Meta-Analysis of Randomized Clinical Trials.” *JAMA Psychiatry* 71 (12): 1381. https://doi.org/10.1001/jamapsychiatry.2014.1611.

147. Korenbrot, Juan I. 2012. “Speed, Sensitivity, and Stability of the Light Response in Rod and Cone Photoreceptors: Facts and Models.” *Progress in Retinal and Eye Research* 31 (5): 442–66. https://doi.org/10.1016/j.preteyeres.2012.05.002.

148. Kot, T. and Serper, M. (2002) Increased susceptibility to auditory conditioning in hallucinating schizophrenic patients: a preliminary investigation. J. Nerv. Ment. Dis. 190, 282–288

149. Krippner, Stanley. “The Hypnotic Trance, the Psychedelic Experience, and the Creative Act.” *American Journal of Clinical Hypnosis* 7, no. 2 (October 1964): 140–47. https://doi.org/10.1080/00029157.1964.10402408

150. Krystal, J.H., Kavalali, E.T. & Monteggia, L.M. Ketamine and rapid antidepressant action: new treatments and novel synaptic signaling mechanisms. *Neuropsychopharmacol.* 49, 41–50 (2024). https://doi.org/10.1038/s41386-023-01629-w

151. Kwan, Alex C., David E. Olson, Katrin H. Preller, and Bryan L. Roth. “The Neural Basis of Psychedelic Action.” *Nature Neuroscience* 25, no. 11 (November 2022): 1407–19. https://doi.org/10.1038/s41593-022-01177-4.

152. Lamberti, Claudia, Alessandra Ipponi, Alessandro Bartolini, Walter Schunack, and Petra Malmberg-Aiello. n.d. “*Antidepressant-like Eff ects of Endogenous Histamine and of Two Histamine H1 Receptor Agonists in the Mouse Forced Swim Test*.”

153. Laursen, David RT *et al.* 2023. Impact of active placebo controls on estimated drug effects in randomised trials a systematic review of trials with both active placebo and standard placebo. Cochrane

Database of Systematic Reviews
https://doi.org/10.1002/14651858.MR000055.pub2

154. Lee, Martin A., and Bruce Shlain. 1992. *Acid Dreams: The Complete Social History of LSD: The CIA, the Sixties, and Beyond*. Rev. Evergreen ed. Grove Weidenfeld.

155. Leichsenring F, Steinert C, Rabung S, Ioannidis JPA. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses. World Psychiatry. 2022 Feb;21(1):133-145. doi: 10.1002/wps.20941.

156. Lemercier, Clément E, and Devin B Terhune. “Psychedelics and Hypnosis: Commonalities and Therapeutic Implications.” *Journal of Psychopharmacology* 32, no. 7 (July 2018): 732–40. https://doi.org/10.1177/0269881118780714

157. Lempel, A., Ziv, J., 1976. On the Complexity of Finite Sequences. IEEE Trans. Inf. Theory 22,75–81. https://doi.org/10.1109/TIT.1976.1055501

158. Levine, Jerome, Arnold M. Ludwig, and William H. Lyle. “The Controlled Psychedelic State.” *American Journal of Clinical Hypnosis* 6, no. 2 (October 1963): 163–64. https://doi.org/10.1080/00029157.1963.10402334

159. Levine J, Ludwig AM. Alterations in consciousness produced by combinations of LSD, hypnosis and psychotherapy. Psychopharmacologia. 1965 Feb 15;7(2):123-37. doi: 10.1007/BF00403635. PMID: 5830970.

160. Levine J., Ludwig A. “Alterations in Consciousness Produced by Combinations of LSD, Hypnosis and Psychotherapy.” *Psychopharmacologia* 7, no. 2 (1965): 123–37. https://doi.org/10.1007/BF00403635

161. Levine J., Ludwig A. “The Hypnodelic Treatment Technique.” *International Journal of Clinical and Experimental Hypnosis* 14, no. 3 (July 1966): 207–15. https://doi.org/10.1080/00207146608412963

162. Levy, J V, J Tollman, J A King, et al. forthcoming. *Lysergic Acid Diethylamide: Sensitive Neuronal Units in the Midbrain Raphe Abstract. Units in Areas of the Mid-*. 161.

163. Libby, Alexandra, and Timothy J. Buschman. 2021. “Rotational Dynamics Reduce Interference between Sensory and Memory Representations.” *Nature Neuroscience* 24 (5): 715–26. https://doi.org/10.1038/s41593-021-00821-9.

164. Ligneul, Romain, and Zachary F. Mainen. “Serotonin.” *Current Biology* 33, no. 23 (December 2023): R1216–21. https://doi.org/10.1016/j.cub.2023.09.068.

165. Lima da Cruz, R.V., Leão, R.N. & Moulin, T.C. Effects of psychedelics on neurogenesis and broader neuroplasticity: a systematic review. *Mol Med* 30, 244 (2024). https://doi.org/10.1186/s10020-024-01013-4

166. Lladó-Pelfort, L., P. Celada, M. S. Riga, E. Troyano-Rodríguez, N. Santana, and F. Artigas. “Effects of Hallucinogens on Neuronal Activity.” In *Behavioral Neurobiology of Psychedelic Drugs*, edited by Adam L. Halberstadt, Franz X. Vollenweider, and David E. Nichols, 36:75–105. Current Topics in Behavioral Neurosciences. Berlin, Heidelberg: Springer Berlin Heidelberg, 2017. https://doi.org/10.1007/7854_2017_473.

167. Losos, Jonathan B. 2014. *The Princeton Guide to Evolution*. Princeton Reference. Princeton university press.

168. Ludwig, Arnold M., and Jerome Levine. “A Controlled Comparison of Five Brief Treatment Techniques Employing LSD, Hypnosis, and Psychotherapy.” *American Journal of Psychotherapy* 19, no. 3 (July 1965): 417–35.

169. Lush, P, G Moga, N McLatchie, and Z Dienes. “The Sussex-Waterloo Scale of Hypnotizability (SWASH): Measuring Capacity for Altering Conscious Experience.” *Neuroscience of Consciousness* 2018, no. 1 (January 1, 2018). https://doi.org/10.1093/nc/niy006

170. Lush, Peter, Gyorgy Moga, Neil McLatchie, and Zoltan Dienes. “The Sussex-Waterloo Scale of Hypnotizability (SWASH): Measuring Capacity for Altering Conscious Experience.” *Neuroscience of Consciousness* 2018, no. 1 (January 1, 2018). https://doi.org/10.1093/nc/niy006.

171. Lush, Peter, Ryan B. Scott, Anil K. Seth, and Zoltan Dienes. “The Phenomenological Control Scale: Measuring the Capacity for Creating Illusory Nonvolition, Hallucination and Delusion.” *Collabra: Psychology* 7, no. 1 (November 15, 2021): 29542. https://doi.org/10.1525/collabra.29542

172. Lush, Peter. 2023. “Expectancies and the Generation of Perceptual Experience: Predictive Processing and Phenomenological Control” In: Cheng, Tony, Ryoji Sato, and Jakob Hohwy. *Expected Experiences: The Predictive Mind in an Uncertain World*. (pp.47) 1st ed. New York: Routledge, 2023. https://doi.org/10.4324/9781003084082

173. Lynn, Steven J., and Judith Rhue, eds. 1991. *Theories of Hypnosis: Current Models and Perspectives*. The Guilford Clinical and Experimental Hypnosis Series. Guilford Press.

174. Lyons T, Carhart-Harris RL. Increased nature relatedness and decreased authoritarian political views after psilocybin for

treatment-resistant depression. *Journal of Psychopharmacology*. 2018;32(7):811-819. doi:10.1177/0269881117748902

175. MacDowell, Camden J., Alexandra Libby, Caroline I. Jahn, Sina Tafazoli, and Timothy J. Buschman. “Multiplexed Subspaces Route Neural Activity Across Brain-Wide Networks” Nature, February 12, 2023. https://doi.org/10.1038/s41467-025-58698-2

176. March, Sebastià *et al*. 2025. Potential Global Effects of the Rise of the Far Right on Public Health American Journal of Public Health 115, 873_882, https://doi.org/10.2105/AJPH.2025.308016

177. Marshall, Jonathan W. *Performing Neurology: The Dramaturgy of Dr Jean-Martin Charcot*. *Palgrave Macmillan* (2016). https://doi.org/10.1057/978-1-137-51762-3.

178. Mashour, George A. “From LSD to the IRB: Henry Beecher’s Psychedelic Research and the Foundation of Clinical Ethics.” *International Anesthesiology Clinics* 45, no. 4 (2007): 105–11. https://doi.org/10.1097/AIA.0b013e31811f4613.

179. Mason, Oliver J., and Francesca Brady. 2009. “The Psychotomimetic Effects of Short-Term Sensory Deprivation.” *Journal of Nervous & Mental Disease* 197 (10): 783–85. https://doi.org/10.1097/NMD.0b013e3181b9760b.

180. Matias, Sara, Eran Lottem, Guillaume P Dugué, and Zachary F Mainen. “Activity Patterns of Serotonin Neurons Underlying Cognitive Flexibility.” *eLife* 6 (March 21, 2017): e20552. https://doi.org/10.7554/eLife.20552.

181. Mawe, Gary M., and Jill M. Hoffman. 2013. “Serotonin Signaling in the Gastrointestinal Tract—Functions, Dysfunctions and Therapeutic Targets.” *Nature Reviews Gastroenterology & Hepatology* 10 (8): 473–86. https://doi.org/10.1038/nrgastro.2013.105.

182. McClure-Begley, Tristan D., and Bryan L. Roth. “The Promises and Perils of Psychedelic Pharmacology for Psychiatry.” *Nature Reviews Drug Discovery* 21, no. 6 (June 2022): 463–73. https://doi.org/10.1038/s41573-022-00421-7.

183. McGovern, H. T., H. J. Grimmer, M. K. Doss, B. T. Hutchinson, C. Timmermann, A. Lyon, P. R. Corlett, and R. E. Laukkonen. “An Integrated Theory of False Insights and Beliefs under Psychedelics.” *Communications Psychology* 2, no. 1 (August 1, 2024): 69. https://doi.org/10.1038/s44271-024-00120-6.

184. Mediano PAM, Rosas FE, Timmermann C, Roseman L, Nutt DJ, Feilding A, Kaelen M, Kringelbach ML, Barrett AB, Seth AK, Muthukumaraswamy S, Bor D, Carhart-Harris RL. Effects of External Stimulation on Psychedelic State Neurodynamics. ACS Chem Neurosci.

2024 Feb 7;15(3):462-471. doi: 10.1021/acschemneuro.3c00289. Epub 2024 Jan 12. PMID: 38214686; PMCID: PMC10853937.

185. Meijer, Guido. 2021. “Neurons in the Mouse Brain Correlate with Cryptocurrency Price: A Cautionary Tale.” *Peer Community Journal* 1 (November): e29. https://doi.org/10.24072/pcjournal.30.

186. Meling, Daniel, Rebecca Ehrenkranz, Sandeep M. Nayak, Helena D. Aicher, Xaver Funk, Michiel Van Elk, Marianna Graziosi, Prisca R. Bauer, Milan Scheidegger, and David B. Yaden. “Mind the Psychedelic Hype: Characterizing the Risks and Benefits of Psychedelics for Depression.” *Psychoactives* 3, no. 2 (April 16, 2024): 215–34. https://doi.org/10.3390/psychoactives3020014

187. Meltzer-Brody, Samantha, Helen Colquhoun, Robert Riesenberg, et al. 2018. “Brexanolone Injection in Post-Partum Depression: Two Multicentre, Double-Blind, Randomised, Placebo-Controlled, Phase 3 Trials.” *The Lancet* 392 (10152): 1058–70. https://doi.org/10.1016/S0140-6736(18)31551-4.

188. Metaxa A, Clarke M. Efficacy of psilocybin for treating symptoms of depression: systematic review and meta-analysis BMJ 2024; 385 :e078084 doi:10.1136/bmj-2023-078084

189. Michaiel, Angie M., Philip R.L. Parker, and Cristopher M. Niell. 2019. “A Hallucinogenic Serotonin-2A Receptor Agonist Reduces Visual Response Gain and Alters Temporal Dynamics in Mouse V1.” *Cell Reports* 26 (13): 3475-3483.e4. https://doi.org/10.1016/j.celrep.2019.02.104.

190. Michaiel, Angie M. et al. 2019. A Hallucinogenic Serotonin-2A Receptor Agonist Reduces Visual Response Gain and Alters Temporal Dynamics in Mouse V1. Cell Reports, Volume 26, Issue 13, 3475 - 3483.e4 https://doi.org/10.1016/j.celrep.2019.02.104

191. Miller, Cory T., David Gire, Kim Hoke, et al. 2022. “Natural Behavior Is the Language of the Brain.” *Current Biology* 32 (10): R482–93. https://doi.org/10.1016/j.cub.2022.03.031.

192. Milling, Leonard S., Keara E. Valentine, Hannah S. McCarley, and Lindsey M. LoStimolo. “A Meta-Analysis of Hypnotic Interventions for Depression Symptoms: High Hopes for Hypnosis?” *American Journal of Clinical Hypnosis* 61, no. 3 (January 1, 2019): 227–43. https://doi.org/10.1080/00029157.2018.1489777.

193. Miyazaki, K., Miyazaki, K.W. & Doya, K. The Role of Serotonin in the Regulation of Patience and Impulsivity. *Mol Neurobiol* 45, 213–224 (2012). https://doi.org/10.1007/s12035-012-8232-6

194. Moerman, D. (2002). Meaning, Medicine and the “Placebo Effect.” Cambridge; New York, NY: Cambridge University Press.

195. Möller HJ, Falkai P. 2023. Is the serotonin hypothesis/theory of depression still relevant? Methodological reflections motivated by a recently published umbrella review. Eur Arch Psychiatry Clin Neurosci.;273(1):1-3. doi: 10.1007/s00406-022-01549-8.

196. Moncrieff, J. 2018. “What Does the Latest Meta-Analysis Really Tell Us about Antidepressants?” *Epidemiology and Psychiatric Sciences* 27 (5): 430–32. https://doi.org/10.1017/S2045796018000240.

197. Moncrieff, Joanna, Ruth E. Cooper, Tom Stockmann, Simone Amendola, Michael P. Hengartner, and Mark A. Horowitz. “The Serotonin Theory of Depression: A Systematic Umbrella Review of the Evidence.” *Molecular Psychiatry* 28, no. 8 (August 2023): 3243–56. https://doi.org/10.1038/s41380-022-01661-0.

198. Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. Cochrane Database of Systematic Reviews 1998, Issue 3. Art. No.: CD003012. DOI: 10.1002/14651858.CD003012. Accessed 18 October 2025.

199. Moore, James W. “What Is the Sense of Agency and Why Does It Matter?” *Frontiers in Psychology* 7 (August 29, 2016). https://doi.org/10.3389/fpsyg.2016.01272.

200. Moreno, Jonathan D. “Acid Brothers: Henry Beecher, Timothy Leary, and the Psychedelic of the Century.” *Perspectives in Biology and Medicine* 59, no. 1 (2016): 107–21. https://doi.org/10.1353/pbm.2016.0019.

201. Nabers, Dirk, and Frank A. Stengel. 2024. “Discourse, Fantasy and Anxiety in Trump’s America.” *SSRN Electronic Journal*, ahead of print. https://doi.org/10.2139/ssrn.5016416.

202. Nagpurkar, Krutika, Pratik Ghive, Mayur Kale, et al. 2025. “Neurosteroids as Emerging Therapeutics for Treatment-Resistant Depression: Mechanisms and Clinical Potential.” *Neuroscience* 577 (June): 300–314. https://doi.org/10.1016/j.neuroscience.2025.05.022.

203. Nelson, J Craig, and George I Papakostas. n.d. “*Atypical Antipsychotic Augmentation in Major Depressive Disorder: A Meta-Analysis of Placebo-Controlled Randomized Trials*.”

204. Nichols, David E., and Hannes Walter. “The History of Psychedelics in Psychiatry.” *Pharmacopsychiatry* 54, no. 04 (July 2021): 151–66. https://doi.org/10.1055/a-1310-3990.

205. Nichols, David E. “Psychedelics” *Pharmacological Reviews* 68, no. 2 (April 2016): 264–355. https://doi.org/10.1124/pr.115.011478.

206. Oakley, David A., and Peter W. Halligan. “Hypnotic Suggestion: Opportunities for Cognitive Neuroscience.” *Nature Reviews Neuroscience* 14, no. 8 (August 2013): 565–76. https://doi.org/10.1038/nrn3538.

207. Odilia D. Lu *et al.* 2025. “A multi-institutional investigation of psilocybin’s effects on mouse behavior” bioRxiv 2025.04.08.647810; doi: https://doi.org/10.1101/2025.04.08.647810

208. Okaty, B.W., Commons, K.G. & Dymecki, S.M. Embracing diversity in the 5-HT neuronal system. *Nat Rev Neurosci* 20, 397–424 (2019). https://doi.org/10.1038/s41583-019-0151-3

209. Okaty, Benjamin W., Kathryn G. Commons, and Susan M. Dymecki. 2019. “Embracing Diversity in the 5-HT Neuronal System.” *Nature Reviews Neuroscience* 20 (7): 397–424. https://doi.org/10.1038/s41583-019-0151-3.

210. Okaty, Benjamin W., Kathryn G. Commons, and Susan M. Dymecki. “Embracing Diversity in the 5-HT Neuronal System.” *Nature Reviews Neuroscience* 20, no. 7 (July 2019): 397–424. https://doi.org/10.1038/s41583-019-0151-3.

211. Olbrich, Sebastian, Katrin H. Preller, and Franz X. Vollenweider. 2021. “LSD and Ketanserin and Their Impact on the Human Autonomic Nervous System.” *Psychophysiology* 58 (6): e13822. https://doi.org/10.1111/psyp.13822.

212. Oliphant, Stephen N., Zainab Hans, Anna E. Austin, and Rebeccah L. Sokol. 2025. “The Evolving Impact of Medicaid Expansion on Suicide Mortality: Demographic and Method-Specific Effects.” *American Journal of Preventive Medicine*, 108130. https://doi.org/10.1016/j.amepre.2025.108130.

213. Oliver, Alison, Alice Wong, Emma Chen, and Amir Raz. 2024. “Suggestibility and Psychedelics: From Therapeutics to Social Context.” *Psychology of Consciousness: Theory, Research, and Practice*, ahead of print, December 12. https://doi.org/10.1037/cns0000412.

214. Olson, J.A., Suissa-Rocheleau, L., Lifshitz, M. *et al.* Tripping on nothing: placebo psychedelics and contextual factors. *Psychopharmacology* 237, 1371–1382 (2020). https://doi.org/10.1007/s00213-020-05464-5

215. Olson, Randall J., Lowell Bartlett, Alex Sonneborn, Zachary Bretton-Granatoor, Ayesha Firdous, Alexander Z. Harris, and Atheir I. Abbas. “The Classic Psychedelic DOI Induces a Persistent Desynchronized State in Medial Prefrontal Cortex,” February 27, 2023. https://doi.org/10.1101/2023.02.26.529963.

216. Orne, M. T. “On the social psychology of the psychological experiment: With particular reference to demand characteristics and their implications.” *American Psychologist* 17 (1962), 776–783. http://dx.doi.org/10.1037/h0043424

217. Ortega y Gasset, José. *La deshumanización del arte y otros ensayos de estética. Espasa Libros*, (2017). 150-175.

218. Pabayo R, Kawachi I, Gilman SE. 2014. Income inequality among American states and the incidence of major depression. J Epidemiol Community Health 2014;68:110-115.

219. Pace BA and Devenot N (2021) Right-Wing Psychedelia: Case Studies in Cultural Plasticity and Political Pluripotency. *Front. Psychol.* 12:733185. doi: 10.3389/fpsyg.2021.733185

220. Padawer-Curry, Jonah A. *et al.* 2023. “Psychedelic 5-HT_{2A} receptor agonism: neuronal signatures and altered neurovascular coupling” bioRxiv 2023.09.23.559145; doi: https://doi.org/10.1101/2023.09.23.559145

221. Padawer-Curry, Jonah Aryeh, "Investigating neural, neurovascular, and vascular function: insights from imaging 5-HT2AR compounds, optogenetic motor mapping, and cross-modal functional mapping" (2025). McKelvey School of Engineering Theses & Dissertations. 1241. https://openscholarship.wustl.edu/eng_etds/1241

222. Palamar JJ, Kumar S, Yang KH, Han BH. Ketamine use in relation to depressive symptoms among high school seniors. Am J Addict. 2022 Mar;31(2):100-107. doi: 10.1111/ajad.13259.

223. Pang, Jolene Wan Vun, Ponnusamy Subramaniam, Noh Amit, Suzaily Wahab, and Ahmed A. Moustafa. “Hypnotherapy as Treatment for Depression: A Scoping Review.” *International Journal of Clinical and Experimental Hypnosis* 72, no. 2 (April 2, 2024): 155–88. https://doi.org/10.1080/00207144.2024.2317193.

224. Paskov, M., & Richards, L. (2021). Social status inequality and depression in Europe. *International Journal of Comparative Sociology*, *62*(2), 93-114. https://doi.org/10.1177/00207152211022419

225. Patel, V., Burns, J.K., Dhingra, M., Tarver, L., Kohrt, B.A. and Lund, C. (2018), Income inequality and depression: a systematic review and meta-analysis of the association and a scoping review of mechanisms. World Psychiatry, 17: 76-89. https://doi.org/10.1002/wps.20492

226. Patterson DR, Hoffer C, Jensen MP, Wiechman SA, Sharar SR. Ketamine as a possible moderator of hypnotizability: a feasibility study. Int J Clin Exp Hypn. 2018 Jul-Sep;66(3):298-307. doi: 10.1080/00207144.2018.1460559. PMID: 29856288; PMCID: PMC6181123.

227. Paulk, Angelique C., Yoav Kfir, Arjun R. Khanna, et al. 2022. “Large-Scale Neural Recordings with Single Neuron Resolution Using Neuropixels Probes in Human Cortex.” *Nature Neuroscience* 25 (2): 252–63. https://doi.org/10.1038/s41593-021-00997-0.

228. Pekala, Rronald J., Kumar, V. K., and Marcano, G. . “Anomalous/paranormal experiences, hypnotic susceptibility, and

dissociation". *Journal of the American Society for Psychical Research*, 89(4) (1995), 313–332.

229. Pereira-Obilinovic, Ulises; Froudist-Walsh, Sean; Wang, Xiao-Jing. 2024. Cognitive network interactions through communication subspaces in large-scale models of the neocortex. bioRxiv 2024.11.01.621513; https://doi.org/10.1101/2024.11.01.621513

230. Pintar, Judith, and Steven J. Lynn. *Hypnosis: A Brief History*. *Blackwell Brief Histories of Psychology* (2008).

231. Pokorny T, Preller KH, Kometer M, Dziobek I, Vollenweider FX. Effect of Psilocybin on Empathy and Moral Decision-Making. Int J Neuropsychopharmacol. 2017 Sep 1;20(9):747-757. doi: 10.1093/ijnp/pyx047. PMID: 28637246; PMCID: PMC5581487.

232. Powers, A. R., C. Mathys, and P. R. Corlett. 2017. "Pavlovian Conditioning–Induced Hallucinations Result from Overweighting of Perceptual Priors." *Science* 357 (6351): 596–600. https://doi.org/10.1126/science.aan3458.

233. Purple, Ross J., Rahul Gupta, Christopher W. Thomas, Caroline T. Golden, Seán Froudist-Walsh, and Matthew W. Jones. 2024. "Short- and Long-Term Reconfiguration of Rat Prefrontal Cortical Networks Following Single Doses of Psilocybin." Preprint, December 13. https://doi.org/10.1101/2024.12.10.627734.

234. Rapport, Maurice M., Arda.Alden. Green, and Irvine H. Page. "SERUM VASOCONSTRICTOR (SEROTONIN)." *Journal of Biological Chemistry* 176, no. 3 (December 1948): 1243–51. https://doi.org/10.1016/S0021-9258(18)57137-4.

235. Rapport, Maurice M. "SERUM VASOCONSTRICTOR (SEROTONIN)." *Journal of Biological Chemistry* 180, no. 3 (October 1949): 961–69. https://doi.org/10.1016/S0021-9258(19)51208-X.

236. Rensch, Bernhard, and Bernhard Rensch. 1970. *Evolution above the Species Level*. 2. print. Columbia Biological Series 19. Columbia University Press.

237. Román-Aso, J.A., Bellido, H. & Olmos, L. When government's economic ideology shapes income redistribution. Empirical evidence from the OECD. J Econ Inequal 23, 177–204 (2025). https://doi.org/10.1007/s10888-024-09634-9

238. Sagi, Yotam, Lucian Medrihan, Katia George, Miles Barney, Kathryn A. McCabe, and Paul Greengard. 2020. "Emergence of 5-HT5A Signaling in Parvalbumin Neurons Mediates Delayed Antidepressant Action." *Molecular Psychiatry* 25 (6): 1191–201. https://doi.org/10.1038/s41380-019-0379-3.

239. Schartner, M., Carhart-Harris, R., Barrett, A. *et al.* Increased spontaneous MEG signal diversity for psychoactive doses of ketamine,

LSD and psilocybin. *Sci Rep* 7, 46421 (2017). https://doi.org/10.1038/srep46421

240. Schmack K, Bosc M, Ott T, Sturgill JF, Kepecs A. Striatal dopamine mediates hallucination-like perception in mice. Science. 2021 Apr 2;372(6537):eabf4740. doi: 10.1126/science.abf4740. PMID: 33795430.

241. Schmid, Yasmin, Florian Enzler, Peter Gasser, Eric Grouzmann, Katrin H. Preller, Franz X. Vollenweider, Rudolf Brenneisen, Felix Müller, Stefan Borgwardt, and Matthias E. Liechti. “Acute Effects of Lysergic Acid Diethylamide in Healthy Subjects.” *Biological Psychiatry* 78, no. 8 (October 2015): 544–53. https://doi.org/10.1016/j.biopsych.2014.11.015.

242. Schultz, W., Dayan, P. & Montague, P. R. A neural substrate of prediction and reward. *Science* 275, 1593–1599 (1997).

243. Shao, LX., Liao, C., Davoudian, P.A. *et al.* Psilocybin’s lasting action requires pyramidal cell types and 5-HT_{2A} receptors. *Nature* 642, 411–420 (2025). https://doi.org/10.1038/s41586-025-08813-6

244. Sheldrake, Kevin. 2025. “The Experience of Responding to Imaginative Suggestions: A Micro-phenomenological Interview Exploratory Study”

245. Sherif, Muzafer. 1937. “An Experimental Approach to the Study of Attitudes.” *Sociometry* 1 (1/2): 90. https://doi.org/10.2307/2785261.

246. Shih, Miaozun, Yuan-Han Yang, and Malcolm Koo. “A Meta-Analysis of Hypnosis in the Treatment of Depressive Symptoms: *A Brief Communication*.” *International Journal of Clinical and Experimental Hypnosis* 57, no. 4 (August 31, 2009): 431–42. https://doi.org/10.1080/00207140903099039.

247. Siegel, Joshua S., Subha Subramanian, Demetrius Perry, Benjamin P. Kay, Evan M. Gordon, Timothy O. Laumann, T. Rick Reneau, et al. “Psilocybin Desynchronizes the Human Brain.” *Nature* 632, no. 8023 (August 1, 2024): 131–38. https://doi.org/10.1038/s41586-024-07624-5.

248. Sjoberg, B.M., Hollister, L.E. The effects of psychotomimetic drugs on primary suggestibility. *Psychopharmacologia* 8, 251–262 (1965). https://doi.org/10.1007/BF00407857

249. Sjoberg, B. M., Jr., & Hollister, L. E. 1965. “The effects of psychotomimetic drugs on primary suggestibility.” Psychopharmacology, 8(4), 251–262. https://doi.org/10.1007/BF00407857

250. Smausz, Rebecca, Joanna Neill, and John Gigg. “Neural Mechanisms Underlying Psilocybin’s Therapeutic Potential – the Need for Preclinical in Vivo Electrophysiology.” *Journal of Psychopharmacology* 36, no. 7 (July 2022): 781–93. https://doi.org/10.1177/02698811221092508.

251. Snyder, Madeleine C., Kevin K. Qi, and Michael M. Yartsev. 2024. “Neural Representation of Human Experimenters in the Bat Hippocampus.” *Nature Neuroscience* 27 (9): 1675–79. https://doi.org/10.1038/s41593-024-01690-8.

252. Sodhi, Monsheel S.K, and Elaine Sanders-Bush. 2004. “Serotonin and Brain Development.” In *International Review of Neurobiology*, vol. 59. Elsevier. https://doi.org/10.1016/S0074-7742(04)59006-2.

253. Solursh LP, Rae JM. LSD, suggestion and hypnosis. Int J Neuropsychiatry. 1966 Feb;2(1):60-4. PMID: 5907815.

254. Souza, Filipe Luis, Murilo Schiefler Moura, Juliana Vieira Almeida Silva, and Gary Elkins. “Hypnosis for Depression: Systematic Review of Randomized Clinical Trials with Meta-Analysis.” *Complementary Therapies in Clinical Practice* 57 (November 2024): 101913. https://doi.org/10.1016/j.ctcp.2024.101913.

255. Steinmetz *et al*. Neuropixels 2.0: A miniaturized high-density probe for stable, long-term brain recordings. Science. 2021 Apr 16;372(6539):eabf4588. doi: 10.1126/science.abf4588

256. Stone M B, Yaseen Z S, Miller B J, Richardville K, Kalaria S N, Kirsch I et al. Response to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration: individual participant data analysis BMJ 2022; 378 :e067606 doi:10.1136/bmj-2021-067606

257. Stringer, Carsen, Marius Pachitariu, Nicholas Steinmetz, Charu Bai Reddy, Matteo Carandini, and Kenneth D. Harris. “Spontaneous Behaviors Drive Multidimensional, Brainwide Activity.” *Science* 364, no. 6437 (April 19, 2019): eaav7893. https://doi.org/10.1126/science.aav7893.

258. Subramanian, Subha, Travis Rick Reneau, Demetrius Perry, et al. 2025. “Psilocybin’s Acute and Persistent Brain Effects: A Precision Imaging Drug Trial.” *Scientific Data* 12 (1): 941. https://doi.org/10.1038/s41597-025-05189-0.

259. Syed, Adnan, and Michael S. Jacob. “Languaging Psychopathology: Neurobiology and Metaphor.” *Frontiers in Psychiatry* 15 (February 5, 2024): 1320771. https://doi.org/10.3389/fpsyt.2024.1320771.

260. Szigeti B, Heifets B. Expectancy effects in psychedelic trials. Biol Psychiatry Cogn Neurosci Neuroimaging 2024;9(5):512–521; doi: 10.1016/j.bpsc.2024.02.004

261. Tillmann, Arne. 2025. “Literature Review Of Multi-Agent Debate For Problem-Solving.” arXiv:2506.00066. Preprint, arXiv, May 29. https://doi.org/10.48550/arXiv.2506.00066.

262. Tourish, Dennis. 2024. “It Is Time to Use the F Word about Trump: Fascism, Populism and the Rebirth of History.” *Leadership* 20 (1): 9–32. https://doi.org/10.1177/17427150231210732.

263. Tozzi, Arturo, Marzieh Zare, and April A. Benasich. 2016. “New Perspectives on Spontaneous Brain Activity: Dynamic Networks and Energy Matter.” *Frontiers in Human Neuroscience* 10 (May). https://doi.org/10.3389/fnhum.2016.00247.

264. Turner, Eric H. *et al.* 2008. Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. *The New England Journal of Medicine.* https://doi.org/10.1056/NEJMsa065779

265. Twarog BM, Page IH (1953): Serotonin content of some mammalian tissues and urine and a method for its determination. Am J Physiol 175:157–161

266. Uddin, Lucina Q. “Cognitive and Behavioural Flexibility: Neural Mechanisms and Clinical Considerations.” *Nature Reviews Neuroscience* 22, no. 3 (March 2021): 167–79. https://doi.org/10.1038/s41583-021-00428-w.

267. Ueno, Akiko, Raul Lazaro, Ping-Yen Wang, Reiichi Higashiyama, Keigo Machida, and Hidekazu Tsukamoto. 2012. “Mouse Intragastric Infusion (iG) Model.” *Nature Protocols* 7 (4): 771–81. https://doi.org/10.1038/nprot.2012.014.

268. Ueno, Takato, and Keito Inoshita. 2025. “A Multi-Agent Probabilistic Inference Framework Inspired by Kairanban-Style CoT System with IdoBata Conversation for Debiasing.” arXiv:2506.21565. Preprint, arXiv, June 12. https://doi.org/10.48550/arXiv.2506.21565.

269. Ulett, George A. *et al.* 1972. Hypnosis: Physiological, Pharmacological Reality. The American Journal of Psychiatry. https://doi.org/10.1176/ajp.128.7.799

270. United States Senate, Select Committee on Intelligence, and the Subcommittee on Health and Scientific Research of the Committee on Human Resources. *1977. Project MKULTRA: The CIA’s Program of Research in Behavioral Modification: Joint Hearing before the Select Committee on Intelligence and the Subcommittee on Health and Scientific Research of the Committee on Human Resources, United States Senate, Ninety-Fifth Congress, First Session,* Washington: U.S. Government Printing Office.

271. Vahora, Ilmaben S, Nicholas Tsouklidis, Rajat Kumar, Ravi Soni, and Safeera Khan. 2020. “How Serotonin Level Fluctuation Affects the Effectiveness of Treatment in Irritable Bowel Syndrome.” *Cureus*, ahead of print, August 19. https://doi.org/10.7759/cureus.9871.

272. Van De Schoot, Rens, Sarah Depaoli, Ruth King, Bianca Kramer, Kaspar Märtens, Mahlet G. Tadesse, Marina Vannucci, et al. “Bayesian

Statistics and Modelling." *Nature Reviews Methods Primers* 1, no. 1 (January 14, 2021): 1. https://doi.org/10.1038/s43586-020-00001-2.

273. van Leeuwen, E.J.C., DeTroy, S.E., Haun, D.B.M. *et al.* Chimpanzees use social information to acquire a skill they fail to innovate. *Nat Hum Behav* 8, 891–902 (2024). https://doi.org/10.1038/s41562-024-01836-5

274. Van Nuys, D. W. (1972). Drug use and hypnotic susceptibility. *International Journal of Clinical and Experimental Hypnosis*, *20*(1), 31–37. https://doi.org/10.1080/00207147208409273

275. Varshney, Kush R. 2024. "Decolonial AI Alignment: Openness, Visesa-Dharma, and Including Excluded Knowledges." *Proceedings of the AAAI/ACM Conference on AI, Ethics, and Society* 7 (October): 1467–81. https://doi.org/10.1609/aies.v7i1.31739.

276. Vejmola, Čestmír, Filip Tylš, Václava Piorecká, Vlastimil Koudelka, Lukáš Kadeřábek, Tomáš Novák, and Tomáš Páleníček. "Psilocin, LSD, Mescaline, and DOB All Induce Broadband Desynchronization of EEG and Disconnection in Rats with Robust Translational Validity." *Translational Psychiatry* 11, no. 1 (October 2, 2021): 506. https://doi.org/10.1038/s41398-021-01603-4.

277. Vernon, Jack. *et al.* 1961 "Sensory Deprivation and Hallucinations" Science, Vol. 133

278. Vigo, Daniel V., and Ross J. Baldessarini. 2009. "Anticonvulsants in the Treatment of Major Depressive Disorder: An Overview." *Harvard Review of Psychiatry* 17 (4): 231–41. https://doi.org/10.1080/10673220903129814.

279. Vollenweider, Franz X., and Katrin H. Preller. "Psychedelic Drugs: Neurobiology and Potential for Treatment of Psychiatric Disorders." *Nature Reviews Neuroscience* 21, no. 11 (November 2020): 611–24. https://doi.org/10.1038/s41583-020-0367-2.

280. Wallach, J., Cao, A.B., Calkins, M.M. *et al.* Identification of 5-HT_{2A} receptor signaling pathways associated with psychedelic potential. *Nat Commun* 14, 8221 (2023). https://doi.org/10.1038/s41467-023-44016-1

281. Wallach, Jason, Andrew B. Cao, Maggie M. Calkins, et al. 2023. "Identification of 5-HT2A Receptor Signaling Pathways Associated with Psychedelic Potential." *Nature Communications* 14 (1): 8221. https://doi.org/10.1038/s41467-023-44016-1.

282. Walsh, B. Timothy, Stuart N. Seidman, Robyn Sysko, and Madelyn Gould. "Placebo Response in Studies of Major Depression: Variable, Substantial, and Growing." *JAMA* 287, no. 14 (April 10, 2002): 1840. https://doi.org/10.1001/jama.287.14.1840.

283. Wan, Jinpeng, Ping Zhang, Liangliang Sun, et al. 2018. "Involvement of Reactive Oxygen Species and Auxin in

Serotonin-Induced Inhibition of Primary Root Elongation.” *Journal of Plant Physiology* 229 (October): 89–99. https://doi.org/10.1016/j.jplph.2018.07.004.

284. Weitzenhoffer AM, Sjoberg BM Jr. Suggestibility with and without "induction of hypnosis". J Nerv Ment Dis. 1961 Mar;132:204-20. doi: 10.1097/00005053-196103000-00002. PMID: 13784157.

285. Whalley MG, Brooks GB. Enhancement of suggestibility and imaginative ability with nitrous oxide. Psychopharmacology (Berl). 2009 May;203(4):745-52. doi: https://doi.org/10.1007/s00213-008-1424-0

286. Whitaker-Azmitia, Patricia Mack. “The Discovery of Serotonin and Its Role in Neuroscience” 21, no. 2 (n.d.).

287. Winter, L. *et al* (1984). When are social judgments made? Evidence for the spontaneousness of trait inferences. Journal of Personality and Social Psychology, 47, 237–252. https://doi.org/10.1037/0022-3514.47.2.237

288. Woody, Erik, and Pamela Sadler. 2016. “What Can a Hypnotic Induction Do?” *American Journal of Clinical Hypnosis* 59 (2): 138–54. https://doi.org/10.1080/00029157.2016.1185004.

289. Yaden paper A Field-Wide Review and Analysis of Study Materials Used in Psilocybin Trials: Assessment of Two Decades of Research

290. Yakovlev, D. S., A. A. Spasov, D. V. Mal’tsev, and V. A. Anisimova. 2014b. “Effect of 5-HT2A Receptor Antagonists on Blood Flow in the Carotid Vessels upon Elevation of Serotonin Level.” *Bulletin of Experimental Biology and Medicine* 157 (3): 350–52. https://doi.org/10.1007/s10517-014-2563-4.

291. Yapko, Michael D. *Trancework: An Introduction to the Practice of Clinical Hypnosis.* 4th ed. Routledge (2012).

292. Yovell, Yoram, Gali Bar, Moti Mashiah, et al. 2016. “Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation: A Randomized Controlled Trial.” *American Journal of Psychiatry* 173 (5): 491–98. https://doi.org/10.1176/appi.ajp.2015.15040535.

293. Zeifman, Richard J., Meg J. Spriggs, Hannes Kettner, et al. 2025. “From Relaxed Beliefs under Psychedelics (REBUS) to Revised Beliefs after Psychedelics (REBAS).” *Scientific Reports* 15 (1): 3651. https://doi.org/10.1038/s41598-023-28111-3.

294. Zhang, Fu-Chao, Rui-Xia Weng, Di Li, et al. 2024. “A Vagus Nerve Dominant Tetra-Synaptic Ascending Pathway for Gastric Pain Processing.” *Nature Communications* 15 (1): 9824. https://doi.org/10.1038/s41467-024-54056-w.

295. Zhao, Xiangting, Yingjie Du, Yishan Yao, Wei Dai, Yongyu Yin, Guyan Wang, Yunfeng Li, and Liming Zhang. “Psilocybin Promotes Neuroplasticity and Induces Rapid and Sustained Antidepressant-like Effects in Mice.” *Journal of Psychopharmacology* 38, no. 5 (May 2024): 489–99. https://doi.org/10.1177/02698811241249436.

296. Zhu, Chen, Nate Tsz-kit Kwok, Tracey Chi-wan Chan, Gloria Hoi-kei Chan, and Suzanne Ho-wai So. “Inflexibility in Reasoning: Comparisons of Cognitive Flexibility, Explanatory Flexibility, and Belief Flexibility Between Schizophrenia and Major Depressive Disorder.” *Frontiers in Psychiatry* 11 (January 18, 2021): 609569. https://doi.org/10.3389/fpsyt.2020.609569.

297. Zimmermann, Marie-Claire, and Anne Charlon. *Actes del dotzè Colloqui Internacional de Llengua i Literatura Catalanes, Universitat de Paris IV – Sorbonne 4-10 de setembre de 2000*, vol I

298. Žižek, Slavoj. 1989. *The Sublime Object of Ideology*. The Essential Žižek. Verso.